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Feature Review

# Dietary interventions and precision nutrition in cancer therapy

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**In recent years dietary interventions have become a promising tool in cancer treatment and have demonstrated a powerful ability to alter metabolism and tumor growth, development, and therapeutic response. However, because the mechanisms underlying dietary therapeutics are poorly understood, they are frequently ignored as a potential line of treatment for cancer. We discuss the proposed mechanisms behind the anticancer effects of various diets and their development for clinical use. This review aims to provide researchers and clinicians in the field of oncology with a complete overview of the contemporary landscape of nutritional interventions and precision nutrition as cancer therapeutics, and offers a perspective on the steps necessary to establish nutritional interventions as a standard line of treatment.**

## Highlights

Although the link between dietary intake and cancer has been studied for decades, the data on the anticancer effects of dietary interventions remain inconsistent.

Recent studies have demonstrated the powerful potential of particular diets in preventing tumorigenesis, delaying tumor growth, and improving the effectiveness of existing cancer treatments.

Understanding the interactions between cancer and diet is crucial for establishing diet as a line of treatment, and can uncover new mechanisms to target in the design of anticancer therapies.

Given the heterogeneous nature of cancer and host metabolism, several diets have been designed to target specific vulnerabilities. The approach of precision nutrition aims to design diets tailored to each individual and their condition, with the goal of maximizing effectiveness while limiting adverse effects.

## Dietary interventions as a promising approach to cancer therapy

Despite large strides taken over the past century in the fight against cancer, it remains a major source of death and public health costs, and an estimated one in five people are diagnosed with cancer before the age of 75 years, and half of those diagnosed die from the disease [1]. Contemporary prevention, diagnosis, and treatment tools have revolutionized cancer treatment, and have reversed the upward trend of cancer deaths over the past century [2]. Despite this, there remain many cancers with a poor prognosis owing to the lack of effective treatment options; therefore, new approaches to treat cancer or improve current therapies will be crucial for reducing cancer mortality.

The physiological adaptations to dietary intake have widespread effects that can influence cancer incidence, growth, and development (Figure 1), and current estimates suggest that a third of the most common cancers are preventable, at least in part, through changes in diet [3–5]. In recent years evidence from preclinical models and early clinical studies has shown that some dietary patterns have a powerful role in the prevention and treatment of cancer by preventing tumorigenesis, delaying tumor growth, and synergizing with a variety of anticancer therapies [5–7].

Despite promising results, the lack of robust mechanistic evidence and the limitations of large-scale clinical trials of nutritional therapeutics has resulted in **dietary interventions** (see Glossary) being largely overlooked in the clinic, particularly in the context of cancer treatment. The lack of well-controlled studies to evaluate diet in patients, as well as complications in current studies owing to ambiguous criteria for the enrolment and grouping of patients with heterogeneous metabolic and tumor profiles, have likely obscured the efficacy of nutritional therapeutics in patients who can benefit from them. Nevertheless, the push toward nutritional therapeutics in oncology has been set in motion, and an increased scientific effort is underway to characterize the mechanisms underlying the effects of dietary interventions in cancer. The resulting knowledge is being used to inform extensive randomized clinical trials to evaluate the effects of diet on tumor growth, progression, and therapy, with the goal of applying specific personalized dietary regimes to improve cancer outcomes through **precision nutrition** (see Outstanding questions).

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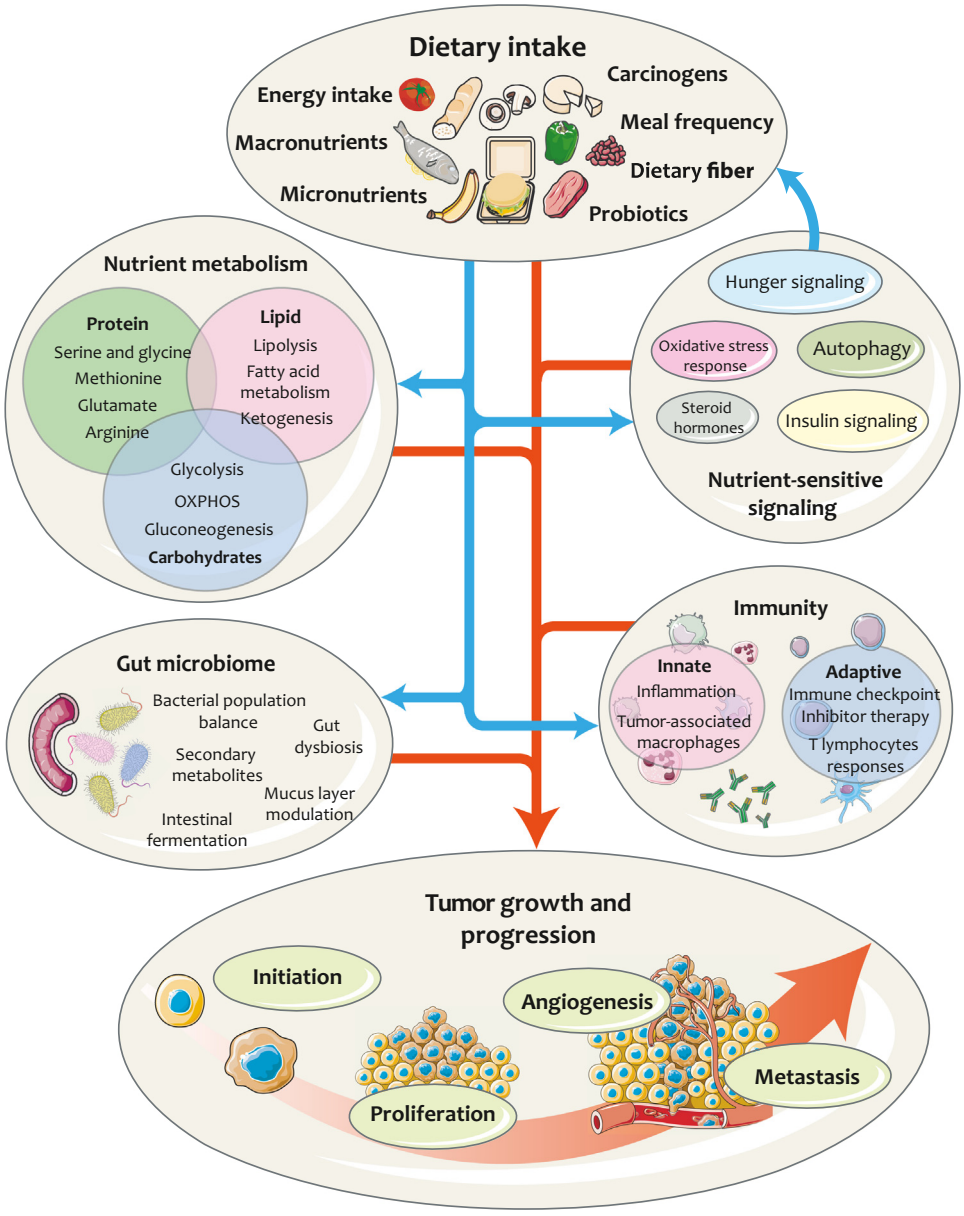


Figure 1. Multiple axes of diet–cancer interactions. Different aspects of dietary intake (e.g., energy intake, macro- and micro-nutrients, meal frequency) influence (blue) a variety of body systems, including nutrient metabolism (nutrient availability, breakdown of macronutrients, metabolite synthesis), nutrient-sensitive signaling (insulin signaling, steroid hormone production, oxidative stress responses), and the gut microbiome and immunity, and can self-regulate through hunger and satiety signaling. These systems are highly integrated and can influence cancer (red) at essentially all stages, altering incidence in the population and disease outcomes in affected individuals. Abbreviation: OXPHOS, oxidative phosphorylation.

In this review we provide an overview of state-of-the-art nutritional therapeutics in translational oncology. We outline the current evidence for diet–cancer interactions and describe the known axes through which dietary interventions can influence the process of tumorigenesis, including nutrient metabolism, growth signaling, antitumor immunity, diet–microbiota interactions, and

## Glossary

**Anaplerotic reactions:** compensatory chemical reactions that can lead to the production of metabolites from the citric acid cycle when these are not available through canonical processes.
**Atkins diet:** a dietary intervention developed by cardiologist Robert C. Atkins to promote weight loss and cardiovascular health. A variation of the KD, this approach aims to limit carbohydrates, but promotes high-protein as well as high-fat intake.
**Caloric restriction (CR):** a dietary regimen aimed at reducing average daily energy intake by 20–40% without causing malnutrition.
**Cancer metabolism:** modifications to nutritional homeostasis in tumors that promote and satisfy the energy demands of unregulated growth.
**Dietary intervention:** modifications to food intake with a planned goal – it is usually applied in the context of metabolic disease or to improve the general health of a subject.
**Dietary restriction:** partial or absolute avoidance of specific nutrients or food products.
**Dysbiosis:** imbalance, functional changes, or shifts in the distribution of the gut microbial community that are associated with disease.
**Fasting:** severe (>50%) or complete abstinence from caloric intake for a period of time.
**Fasting-mimicking diet (FMD):** a regimen aimed at reproducing the metabolic adaptations to fasting without abstaining from food intake; the most common approaches combine a high-fat diet with at least 50% reduction in caloric intake over a period of 5 days.
**Intermittent fasting (IF):** periodic abstinence from caloric intake, which can involve using multiple approaches, including time-restricted eating, twice-a-week fasting, or alternate day fasting.
**Ketogenic diet (KD):** a fasting-mimicking intervention based on maximal restriction of carbohydrate intake, with very high fat and adequate protein content. This approach aims to reduce circulating glucose levels to induce energy production through fatty acid oxidation and ketogenesis.
**Mediterranean diet:** a regimen based on the regional eating habits of individuals living around the Mediterranean Sea. Prompted by observational studies showing reductions in all-cause mortality, this diet

inflammation (Figure 1). We also provide insight into the main dietary regimes proposed to have anticancer effects, such as **caloric restriction (CR)**, the **ketogenic diet (KD)**, and **intermittent fasting (IF)**, and explore the rationale behind their selection and the preclinical data supporting their therapeutic value. Finally, we give our perspective on the current state of nutritional therapeutics in clinical usage by reviewing recent trials exploring the safety and feasibility of dietary interventions, as well as ongoing and future trials that aim to determine the effects of these interventions on the clinical outcomes of patients with cancer.

Through this work we aim to provide researchers and clinicians in the field of oncology with a complete overview of the contemporary landscape of nutritional interventions as cancer therapeutics, and we offer a perspective on the steps necessary to establish them as a standard line of treatment. This information has the potential to inform and aid in the design and progress of future translational and clinical studies, thus advancing the development of a novel and promising approach to the treatment of cancer.

## Current evidence for diet–cancer interactions

The widespread effects of diet on health and physiology suggest that there are many axes through which dietary interventions can mediate antitumor effects. Diets can directly target **cancer metabolism** by depriving tumors of their preferred nutrients, or they can modulate other relevant elements of cancer survival and progression such as growth signaling, oxidative stress, and immunity. In this section we describe the main proposed mechanisms that mediate diet–cancer interactions.

### Nutrient metabolism

First observed by Otto Warburg in the early 20th century, the importance of metabolic reprogramming as one of the defining hallmarks of cancer is now undeniable [8–10]. This phenomenon enables tumors to maximize energy and nutrient availability to facilitate their growth and migration. The genetic heterogeneity of tumors and the different metabolic profiles of their tissues of origin cause cancer cells to favor particular nutrients, making them vulnerable to changes in nutrient intake as a therapeutic intervention.

Under normal conditions, tissues utilize glucose to generate ATP by coupling glycolysis and oxidative phosphorylation. Cancer cells typically metabolize glucose through aerobic glycolysis and ferment glucose to lactate regardless of oxygen availability and mitochondrial function. This is an inefficient way to obtain ATP per unit of glucose compared to mitochondrial respiration; however, it allows a much faster rate of glucose metabolism. Glycolysis also generates waste products such as lactate which contribute to cancer growth and progression and can be incorporated into tricarboxylic acid cycle intermediates to fuel tumors [11]. Consequently, cancer cells commonly favor glucose as a primary nutrient for energy production, making glucose metabolism a fundamental element of cancer progression and a promising therapeutic target [12].

Fructose is another monosaccharide associated with cancer growth. Genes of the polyol pathway are known to be strongly correlated with epithelial-to-mesenchymal transition (EMT) in human lung cancer samples and EMT-driven colon cancer models in mice [13]. Fructose has also been found to be a potent inducer of transketolase in pancreatic cancer cells and induces cell proliferation through the phosphate pentose pathway [14]. Overall, there is a link between dietary intake of simple carbohydrates and tumor incidence and growth, both through directly fueling existing tumors and through metabolic reprogramming to facilitate unregulated cellular growth [15].

Amino acids are another nutrient related to tumorigenesis because cancer cells have high demands for protein synthesis to satisfy growth and proliferation. In addition, because some

is based on fish and lean meats, legumes, olive oil, fruits, and vegetables, and has been studied thoroughly for its health benefits.
**Precision nutrition:** a therapeutic approach aiming to combine data from high-throughput screening strategies with nutritional therapeutics to design and implement highly specific and individualized dietary regimes to improve overall health and therapeutic effectiveness in specific disease states.
**Time-restricted feeding:** an intermittent fasting approach aimed at limiting dietary intake to a specific time-window, typically consisting of 12–16 h of fasting and 8–12 h of feeding.
**Vegan diet:** a dietary approach that involves completely abstaining from the consumption of animal-derived products.
**Vegetarian diet: a** dietary approach focused on abstaining from meat, poultry, and seafood, and that focuses on the consumption of plant-based foods.

cancers are dependent on exogenous sources of non-essential amino acids to fuel growth, they can be considered to be conditionally essential. The Hoffman effect describes the common phenomenon by which cancer cells are often unable to synthesize methionine from its metabolic precursor, homocysteine, and instead rely on exogenous intake of methionine for growth [16,17]. Similarly, argininosuccinate synthetase, an enzyme essential for arginine synthesis, is often not expressed in high-grade neuroendocrine carcinoma of the urinary bladder [18]. Serine and glycine metabolism has also been shown to be important in cancer proliferation, and **dietary restrictions** inhibit tumor growth and extend survival in mouse models of intestinal cancer and lymphoma [19]. Furthermore, inhibition of the glutamate transporter ASCT2 has been shown to reduce the growth of gastric cancer, triple-negative breast cancer, and prostate cancer in various mouse models [20–22]. These data suggest that some cancers may strongly rely on dietary sources of specific amino acids to maintain growth. In addition, there is evidence to suggest that some metabolites obtained from amino acid catabolism, such as polyamines and kynurenine derived from arginine and tryptophan, respectively, support cancer growth and migration [23,24].

Lipids are the main component of biological membranes, serve as the main energy stores of the body, and are influential in metabolism and hormone synthesis. Therefore, it is not surprising that altered lipid metabolism is another commonly observed feature in cancer [25]. Cancer cells often display upregulated expression of lipid receptors and transporters. Indeed, increased expression of CD36, a fatty acid receptor, correlates strongly with poor prognosis in squamous cell lung carcinoma and in bladder and breast cancers. CD36 also appears to boost cancer progression and metastatic potential in oral squamous cell carcinoma and ovarian cancer in response to lipids provided through adipocytes, making it an attractive target for cancer treatment and prevention [26–28]. Some dietary lipids, such as palmitic acid, have been shown to stimulate long-term metastasis in a CD36-dependent manner through transcriptional and chromatin changes that lead to intratumoral Schwann cell activation [26,29]. Increased lipid uptake through CD36 has also been reported to drive $CD8^+$ T cell dysfunction in multiple models, thus creating an immunosuppressive tumor microenvironment and enhancing metastasis initiation [28]. High expression of low-density lipoprotein receptor (LDLR) in human breast cancers is associated with shorter recurrence-free and overall survival, and mouse models of breast cancer display LDLR upregulation to generate resistance against endocrine therapy and chemotherapy [30]. In addition, lipid trafficking through fatty acid-binding proteins (FABPs) favors ovarian cancer metastasis to the omentum, where cancer cells can use adipocyte-derived lipids for tumor growth through FABP4 upregulation [31].

### Hormone signaling and oxidative stress

Dietary interventions can produce adaptations that are antagonistic to tumor formation and development that extend beyond cellular nutrition. Dietary patterns can produce systemic changes in growth signaling that promote a more proliferative or conservative state so as to optimize energy and nutrient availability. Many of the pathways involved in cancer proliferation and survival are modulated through nutrient-sensitive hormones such as leptin, insulin, insulin-like growth factor 1 (IGF-1), and steroid hormones, which play a significant role in the anticancer effects of dietary interventions.

Increased circulating levels of glucose and amino acids increase growth factor signaling through insulin and IGF-1. Their downstream cascades (the PI3K/AKT/mTOR and Ras/MAPK pathways) are major modulators of survival and proliferation, and are some of the most commonly overexpressed pathways in cancer [32,33]. Dietary interventions can also regulate the tumor-suppressor p53 through modulation of aldolase A and its downstream effector, DNA-dependent protein kinase (Figure 2) [33,34].

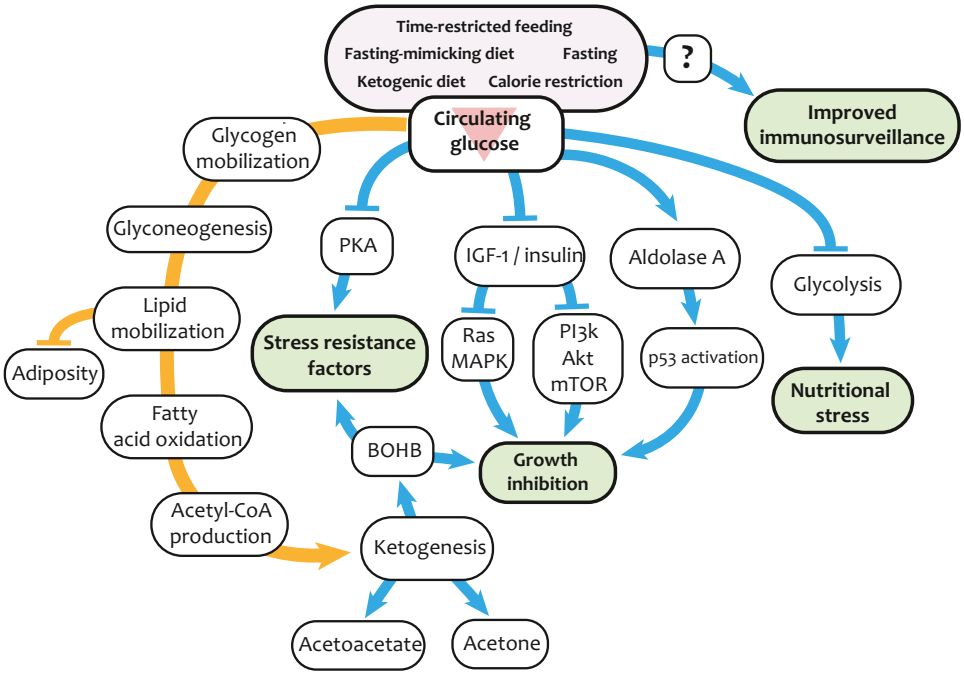


Figure 2. Low circulating glucose mediates the effects of caloric restriction (CR), fasting, and fasting-mimicking diets. Many of the most effective dietary interventions aim to reduce circulating glucose, which leads to mobilization and catabolism of glycogen, and subsequent lipid mobilization and catabolism following depletion of glycogen stores. This results in the accumulation of acetyl-CoA and the production of ketone bodies [e.g., β-hydroxybutyrate (BOHB), acetone, acetoacetate] through ketogenesis. Lowered circulating glucose mediates some of the mechanisms observed in these diets through reduced insulin signaling, activation of tumor-suppressor genes, and inhibition of glycolysis; however, ketone bodies can induce stress-resistance factors and inhibit the growth of some cancers regardless of glucose levels. Moreover, many observed effects, such as improvements in immunosurveillance, remain mechanistically unknown and may be associated with a metabolic shift towards more energy-conserving states during nutrient or caloric restriction.

Steroid hormones such as estrogens and androgens are known to connect cancer incidence to metabolic disease. Adipose tissue is involved in the conversion of androgens to estrogen in men and postmenopausal women through the production of aromatase in adipocytes. Increased estrogen signaling is thought to be one of the mechanisms linking obesity to cancer because it promotes tumor growth by enhancing proliferation signaling and inducing angiogenesis [35].

Modulation of oxidative stress signaling is another factor that plays a role in the effect of dietary interventions. AKT is an inhibitor of FOXO transcription factors which transactivate oxidative stress resistance programs through enzymes such as heme oxygenase 1 (HO1), superoxide dismutase (SOD), and catalase [36,37]. High blood glucose levels negatively regulate AMPK through protein kinase A signaling, thereby preventing the expression of early growth response protein 1, a stress-resistance factor (Figure 2) [38]. β-Hydroxybutyrate (βOHB), a product of ketogenesis, inhibits histone deacetylases, thus increasing the acetylation of oxidative stress-resistance factors FOXO3A and MT2 [39] (Figure 2). In addition, βOHB can suppress tumor growth directly through the induction of *Hopx* in mouse models of colorectal cancer (CRC) [40].

## The gut microbiome and its derived metabolites

The large population of microbes in the intestinal tract, termed the gut microbiome, is one of the major players in the interaction between dietary intake and health. The microbiome is one of the

first points of contact for orally ingested substances such as nutrients and drugs, and interacts with these in a profound manner. The gut microbiome maintains the homeostasis of body energy, intestinal development and mucosal barrier, and immunity, and **dysbiosis** of the intestinal microbiota has strong links with many disorders including metabolic syndrome, neurological, and cardiovascular disorders, and some types of cancer [41–44].

Many of the oncogenic effects attributed to the gut microbiome are consequences of its importance in inflammation of the digestive tract and other related tissues. Indeed, populations of specific bacterial strains are linked to chronic inflammation associated with cancers of the gallbladder, bile duct, and stomach [45–47], and some can act as genotoxic agents that directly alter genomic integrity and growth signaling in gut cells [47]. General gut dysbiosis through partial depletion of microbiota during recurrent use of antibiotics has also been associated with an increased risk of various cancers, including colon, gastric, and lung cancer [48–50], highlighting the close relationship between the microbiome and health (Box 1).

Over the past decade the gut microbiota has emerged as a powerful mediator of tumor immunosurveillance, and the gut microbiome can modulate the efficacy of immunotherapy [51–53]. Although most of these effects have been demonstrated through fecal microbial transplantation, dietary modulation of the microbiome appears to be another effective approach for improving antitumor immunity. A microbiome-dependent boost in immunosurveillance via the production of acetate has been shown to be one of the main mechanisms for the antitumor effects of CR, but not of other energy-restricted interventions such as IF [54]. In addition, supplementation with inosine, a microbiome-derived nucleoside, has been shown to improve the effectiveness of anti-PD-L1 and anti-CTLA-4 therapeutics in mice by enhancing T cell function

### Box 1. The microbiome as a mediator of diet-driven disease

The microbiome is a major driving force in metabolism because it can signal to cells within the intestinal mucosa, which can then relay these signals to the rest of the body through synthesis of metabolic hormones. Through this system, the ecology of the microbiome can affect key processes such as insulin and glucose metabolism, hunger and satiety signaling, and adipose tissue dynamics, thus contributing to the metabolic phenotype of an individual, including obesity and associated metabolic disorders [147]. Dysbiosis can therefore link the gut microbiome to several diseases.

The microbiota modifies dietary components as they travel through our digestive tract and produces metabolites that can influence cancer. The production of short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, through the digestion of dietary fiber by colonic microorganisms has been linked to the induction of apoptosis by cancer cells, expression of tumor-suppressor genes, and improved regulation of glucose metabolism [148,149]. Fiber–microbiota interactions have also been shown to modulate the mucus layer of the intestine in a SCFA-independent manner in animal models, and can alter mucous production and the immune state towards a tumor-suppressive profiles through reduction of chronic inflammation [42,149]. However, studies have suggested that dietary intake of soluble fiber can induce several liver diseases [150] such as cirrhosis, cholestasis, and hepatocellular carcinoma (HCC) in dysbiotic mice through an increase in fermentation metabolites and bile acids [151,152]. The gut microbiota may be a key mediator in the cancer-related effect of nutrients such as ω3 fatty acids and many plant-derived secondary metabolites [149], and is likely to contribute to inflammation-driven cancers in dysbiotic environments.

Malnutrition can alter the intestinal flora to induce HCC [153] and, conversely, some gut microbes can drive HCC formation through malnutrition, affecting nutrient metabolism during dysbiosis, and leading to liver disease and cancer. Degradation of tryptophan by gut bacteria can limit its availability in the kynurenine pathway, leading to insufficient $NAD^+$ synthesis. Insufficient $NAD^+$ production increases cancer risk, which can be reversed through daily supplementation with $NAD^+$ precursors in populations with tryptophan deficiency [154]. Moreover, non-alcoholic steatohepatitis (NASH)-induced HCC as well as pancreatic cancer can be prevented and abolished in preclinical mouse models treated with nicotinamide riboside, a $NAD^+$ booster [58,155]. In line with these findings, a recent study reported that indole-3-acetic acid (3-IAA), a microbiota-derived tryptophan metabolite, is enriched in pancreatic ductal adenocarcinoma (PDAC) chemotherapy responders, and that increases in 3-IAA through dietary manipulation boosts the effectiveness of PDAC chemotherapy in mouse models [156].

[55], and dietary intake of the prebiotics mucin and inulin appears to control tumor growth through a microbiome-dependent enhancement of antitumor immunity [56].

Given the notable importance of the microbiome in health and disease, and the ecological variability observed between individuals, it is evident that mapping the gut microbiome of patients, characterizing dysbiosis, and identifying specific detrimental bacteria implicated in disease development or therapeutic responses would be of assistance in precision nutrition.

### The immune system and tumor immunosurveillance

One of the main determinants of tumor growth and therapeutic response is the interaction between cancer cells and immunity. Immunosurveillance is a key mechanism in preventing cancer growth, and when tumors develop mechanisms to avoid it, or when immune dysregulation compromises surveillance, tumors are more likely to arise and/or be resistant to therapy. Nutrition is a known modulator of immune function by supporting the energy and metabolic requirements needed for optimal immune function, as illustrated by the clear connection between malnutrition and poor immune function during famines in developing countries. The lion's share of immune cells in the body are present throughout the gut-associated lymphoid tissue as a defensive barrier against orally ingested compounds and invasive pathogens. Some dietary components can elicit significant immune responses, and overnutrition has been shown to lead to adipocyte-induced chronic low-grade inflammation through the interleukin 17 (IL-17) axis [57], which can lead to poor immune function and drive the formation of tumors [58].

Specific micronutrients and metabolites are of also particular importance to immune function. For example, arginine metabolism is crucial for M1/M2 macrophage polarization and the production of nitric oxide; selenium is an important regulator of T cell immunity through its selenoprotein-mediated role in redox homeostasis [59,60]. Many vitamins have been shown to support immune function and boost immunity: vitamins A and D can induce anti-inflammatory IL-10 production by regulatory T cells in the gut to prevent inflammation after feeding, while vitamin C has shown to accumulate in B and T lymphocytes through sodium-dependent vitamin C transporters to support T cell maturation and B cell expansion [61–63]. Overall, immunity has strong links to dietary intake, and adequate nutrition is crucial to ensure that pro- and anti-inflammatory signaling is tightly regulated. Dietary interventions have also been shown to boost immunity through metabolic adaptations to specific dietary regimens in a microbiome-independent manner, thus enhancing disease outcomes [64]. Enhanced antitumor immunity has been shown to be a significant factor in the effects of dietary interventions, particularly those focused on energy restriction approaches; however, the underlying mechanisms of their interaction and the degree of microbiota involvement remain unclear [65–68].

## Dietary interventions in cancer treatment: what works?

The study of dietary interventions in cancer has led to numerous philosophies regarding their design. Interventions can focus on restrictions to overall dietary intake, caloric content, and/or the timing of meals, with limited focus on the content of the diet itself, such as in CR, **fasting**, and **time-restricted feeding**. Others prioritize nutrient content, favoring specific ratios of different macronutrients to achieve specific metabolic states that promote health. Some strategies focus on dietary supplementation or restriction of micronutrients to achieve antitumor effects, whereas others are based on regional and cultural dietary patterns associated with longevity and health, such as plant-based diets and **Mediterranean diets**. In this section we discuss the main dietary interventions that are currently proposed to promote health and therapeutic outcomes in cancer, their observed effects in preclinical models and early clinical data, and the mechanisms proposed to be responsible for their anticancer effects. A summary of the evidence can be found in Table 1.

Table 1. Preclinical studies supporting dietary interventions in cancer[a]

| Intervention(s) | Year | Cancer model(s) | Reported results | Refs |
|---|---|---|---|---|
| Serine and glycine restriction | 2017 | Genetic-driven CRC (loss of APC), lymphoma (Myc activation), pancreatic and intestinal cancer (Kras-driven) | ↑ Survival | [19] |
| KD, BOHB supplement | 2022 | Carcinogen-induced CRC (AOM/DSS) and genetic-driven CRC (loss of APC) | ↓ Tumor burden | [40] |
| CR, fasting, acetate supplement | 2023 | Syngeneic CRC (MC38) and BC (4T1) xenografts | ↓ Tumor burden (all)<br>↓ Metastasis (CR) | [54] |
| Inosine supplement | 2020 | Genetic-driven intestinal cancer (Msh2 loss), bladder cancer (MB49) and melanoma (B16_F10) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ ICI efficacy | [55] |
| Prebiotic supplement | 2020 | Genetic-driven melanoma (BRAF) and melanoma (YUMM1.5) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity | [56] |
| KD, BOHB supplement | 2022 | Syngeneic CRC (MC38 and CT26) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ ICI efficacy | [66] |
| KD, BOHB supplement | 2021 | Genetic-driven melanoma (RET) | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ ICI efficacy | [67] |
| CR | 2017 | Carcinogen-induced HCC (DEN) | ∅ Tumor formation<br>↓ Steatosis and inflammation | [74] |
| CR, FMD | 2021 | Syngeneic BC (4T1) xenografts | ↓ Tumor burden<br>↓ Metastasis<br>↑ Antitumor immunity | [75] |
| CR | 2018 | Syngeneic CRC (CT26) xenografts | ↓ Tumor burden<br>↓ Cachexia | [76] |
| FMD | 2020 | Syngeneic CRC (HCT116 and CT26) xenografts | ↓ Tumor burden<br>↑ Chemotherapy efficacy | [82] |
| FMD | 2021 | Syngeneic BC (4T1) xenografts | ↓ Tumor burden<br>↓ Metastasis | [83] |
| Fasting | 2012 | Syngeneic BC (4T1), melanoma (B16), and glioma (GL26) xenografts | ↓ Tumor burden<br>↓ Metastasis<br>↑ Survival<br>↑ Chemotherapy efficacy | [84] |
| Fasting | 2020 | Syngeneic lung cancer (393P, LLC, Lacun3) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ ICI efficacy | [85] |
| Fasting | 2016 | Syngeneic fibrosarcoma (MCA205) xenograft | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ Chemotherapy efficacy | [86] |
| FMD, fasting | 2020 | Syngeneic BC (MCF7, ZR-75-1, T47D) xenografts | ↓ Tumor burden<br>↑ Hormone therapy efficacy | [88] |
| FMD, fasting | 2016 | Syngeneic BC (4T1) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ Chemotherapy | [89] |

Table 1. (continued)

| Intervention(s) | Year | Cancer model(s) | Reported results | Refs |
|---|---|---|---|---|
| | | | efficacy | |
| KD | 2015 | Carcinogen-induced HCC (DEN) | ↓ Tumor burden<br>↓ Steatosis and inflammation | [93] |
| KD | 2018 | Syngeneic CRC (CT26) xenografts | ↓ Tumor burden<br>↓ Cachexia | [94] |
| KD | 2018 | Syngeneic pancreatic cancer (K8484) xenografts | ↓ Tumor burden<br>↑ PI3Ki efficacy | [95] |
| KD, CR | 2015 | Syngeneic neuroblastoma (SH-SY5Y, SK-N-BE) xenografts | ↓ Tumor burden<br>↑ Survival | [96] |
| KD | 2017 | Syngeneic neuroblastoma (SH-SY5Y, SK-N-BE) xenografts | ↓ Tumor burden<br>↑ Chemotherapy efficacy | [97] |
| KD | 2016 | Syngeneic glioblastoma (GL261–luc2) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity | [98] |
| KD | 2015 | Syngeneic glioblastoma (GL261–luc2) xenografts | ↓ Tumor burden | [100] |
| KD | 2010 | Syngeneic glioblastoma (GL261–luc2) xenografts | ↓ Tumor burden<br>↑ Survival<br>↓ Reactive oxygen species | [101] |
| Protein restriction | 2013 | Syngeneic prostate (LuCaP23.1) and breast (WHIM16) xenografts | ↓ Tumor burden | [106] |
| Protein restriction, fasting | 2015 | BC (WHIM16) xenografts | ↓ Tumor burden<br>↓ IGF/mTORC1 | [107] |
| Protein restriction | 2018 | Syngeneic prostate (LRP-B6–Myc) and kidney (RENCA) cancer xenografts | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ ICI efficacy | [108] |
| Protein restriction | 2018 | Syngeneic lymphoma (Eμ–Myc), CRC (CT26) and melanoma (B16) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity | [109] |
| Low CHO and high protein | 2011 | Syngeneic SCC (SCCVII) and human CRC (HCT-116) xenografts, genetically driven BC (HER2/Neu–ovalbumin) | ↓ Tumor burden<br>∅ Tumor formation | [110] |
| Whey supplement | 2018 | Carcinogen-induced CRC (AOM/DSS) | ↓ Tumor burden<br>↑ mTORC1 | [111] |
| Methionine restriction | 2023 | Syngeneic CRC (CT26, MC38) xenografts | ↓ Tumor burden<br>↑ Antitumor immunity<br>↑ ICI efficacy | [112] |
| Methionine restriction | 2019 | Human CRC (CRC119, CRC240) xenografts, genetically driven (*KrasG12*$^{D/+}$; *Tp53*$^{-/-}$) soft-tissue sarcoma | ↓ Tumor burden<br>↑ Chemotherapy efficacy<br>↑ Radiotherapy efficacy | [113] |
| Methionine restriction | 2016 | Human BC (MCF10AT1) xenografts | ↓ Tumor burden | [114] |
| Serine restriction | 2013 | Human CRC (HCT-116) xenografts | ↓ Tumor burden<br>metabolic remodeling | [115] |
| Serine and glycine restriction | 2014 | Syngeneic CRC (MC38) xenografts | ↓ Tumor burden<br>↑ Biguanides efficacy | [116] |
| Leucine restriction | 2016 | Syngeneic BC (MDA-MV-231, MCF-7) xenografts | ↓ Tumor burden | [117] |

*(continued on next page)*

Table 1. (continued)

| Intervention(s) | Year | Cancer model(s) | Reported results | Refs |
|---|---|---|---|---|
| Asparagine restriction | 2018 | Syngeneic BC (4T1, MDA-MB-231) xenografts | ↓ Tumor burden<br>↓ Metastasis | [118] |
| 3-IAA supplement | 2023 | Syngeneic PDAC (KPC) xenografts | ↓ Tumor burden<br>↑ Chemotherapy efficacy | [156] |
| CR | 2013 | Syngeneic lymphoma (Eμ–Myc) xenografts | ↓ Tumor burden<br>↑ Chemotherapy efficacy | [163] |
| Fasting | 2015 | Human lung adenocarcinoma (H3122), CRC (HCT116) xenografts | ↓ Tumor burden<br>↑ TKI efficacy | [164] |
| Fasting | 2015 | Syngeneic pancreatic cancer (BxPC-3, MiaPaca-2, Panc-1) xenografts | ↓ Tumor burden<br>↑ Chemotherapy efficacy | [165] |
| Mannose supplement | 2018 | Human osteosarcoma (U2OS), pancreatic cancer (KP-4) xenografts | ↓ Tumor burden<br>↑ Chemotherapy efficacy | [168] |

[a]Symbols and abbreviations: ↑, increased; ↓, decreased; ∅, arrest of the process; BC, breast cancer; BOHB, β-hydroxybutyrate; CHO, carbohydrate; CR, caloric restriction; CRC, colorectal cancer; FMD, fasting-mimicking diet; HCC, hepatocellular carcinoma; HER2/Neu-ovalbumin, human epidermal growth factor receptor 2/Neu-ovalbumin; 3-IAA, indole-3-acetic acid; ICI, immune checkpoint inhibitor; KD, ketogenic diet; PDAC, pancreatic ductal adenocarcinoma; PI3Ki, phosphoinositide 3-kinase inhibitor; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

## CR, fasting, and fasting-mimicking approaches

CR interventions aim to restrict caloric intake by~10–40% while maintaining a balanced nutrient intake to prevent malnutrition. CR has been shown to extend lifespan and health span in many model organisms [69–72], and to prevent or reduce the onset of many inflammation- and age-related diseases such as type 2 diabetes, neurodegenerative disease, and cancer. CR leads to reductions in blood glucose and a consequent mobilization of glycogen stores. When carbohydrate stores are depleted, the body relies on catabolism of lipids through fatty acid oxidation (FAO) in hepatocytes to obtain energy. This leads to the generation of large amounts of acetyl-CoA and ketone bodies, mainly acetoacetate, acetone, and βOHB, which tissues such as the heart, brain, and muscle can utilize as fuel (Figure 2).

The positive effects of CR as an anticancer intervention in preclinical models are very clear. First observed more than 100 years ago [73], CR has been shown to prevent cancer incidence, slow tumor growth [74], inhibit metastasis, improve antitumor immunity [75], attenuate symptoms such as cachexia [76], and can even completely block tumor growth in models where chemical carcinogens normally induce 100% cancer penetrance.

The benefits of CR appear to occur through a series of metabolic adaptations related to lower levels of blood glucose; these include a decrease in growth factor signaling through reduced IGF-1 and insulin signaling, upregulation of antioxidant programs leading to decreased DNA damage, reduction in inflammation through reduced circulation of proinflammatory cytokines, and improved host immunosurveillance [77]. Despite considerable evidence that CR is one of the most effective treatments against cancer in mice, it remains largely ignored by clinicians, and no currently established lines of treatment prescribe a CR diet as a means to combat cancer.

Fasting aims to cut caloric intake entirely for shorter periods, leading to depletion of circulating glucose and glycogen stores after~24 h and consequent lipid mobilization and FAO in the liver. This process leads to many of the same adaptations observed with CR, including reductions in glucose, insulin, and leptin, and increases in glucagon, adiponectin, and ketone bodies, as well as reductions in IGF-1 signaling and improvements in resistance to reactive oxygen species

[36]. Despite its apparent safety [78,79], prolonged abstinence from caloric intake (also known as 'water fasting') as a therapeutic intervention is difficult to implement because it is often challenging for patients to comply with and may lead to adverse events and malnutrition in diseased patients. For these reasons many current approaches utilize dietary strategies to reproduce fasting and trigger matching metabolic adaptations.

IF is a widely used approach to mimic the effects of fasting. The goal of these approaches is to sustain a fasted state for long enough to induce the metabolic switch towards FAO and ketosis, thus triggering the same positive adaptations observed in fasting but in a more conservative manner to aid with compliance and prolong feasibility [36,80]. A cyclical IF approach was found to inhibit tumor initiation and delay growth, and synergized with therapy in settings with different caloric intakes, diet compositions, and bodyweights [81–86]. The IF approach used depends on the length and periodicity of the fasting window, and these include time-restricted feeding, 5:2 or twice per week fasting, and alternate day fasting.

**Fasting-mimicking diets (FMDs)** are another means to exploit the benefits of fasting via a more feasible regimen. FMDs are diets that have very strong CR (>50%), are high in fat and low in proteins, and are typically supplemented with micronutrients to prevent malnutrition. These diets are typically applied for 5 consecutive days every 3–4 weeks. Treatment with a FMD promotes healthy aging and metabolic health [87], has antitumor effects in a variety of cancer models, and synergizes with various cancer therapies [82,88,89].

KDs, or very low carbohydrate diets, are one of the most promising interventions in the current landscape of cancer treatment. KDs are an alternative to FMDs, with a focus on maximally limiting the intake of carbohydrates to ensure chronic limitation of glucose availability to trigger many of the same adaptations observed in CR and fasting. Maintaining isocaloric intake while strongly restricting carbohydrates is a promising concept to capitalize on the metabolic adaptations of cancer and to maximize the benefits of FAO and ketosis over longer periods of time, which may not be achievable through CR or fasting. The premise of the KD lies largely on the restriction of carbohydrates; however, there are different formulations based on fat and protein contents. The standard KD is based on intake of~80% fat, 10% protein, and <1% of carbohydrates by weight (95% of calories derived from fats), supplemented with a mix of vitamins and minerals to avoid malnutrition [90,91]. However, variations such as the high-fat/high-protein and **Atkins diet**-like KDs typically have higher amounts of protein, accounting for 30–40% of the total caloric intake [91,92]. The composition of non-carbohydrate macronutrients in a KD is important because adaptations to carbohydrate-restricted diets can trigger a series of compensatory **anaplerotic reactions** and *de novo* synthesis of glucose from glucogenic amino acids. Therefore, the amino acid composition of these diets must be carefully considered to ensure the induction of a glucose-restricted physiological state.

Standard KDs have been extensively studied in preclinical models of cancer, and produce anticancer effects in models of hepatocellular carcinoma (HCC) [93], CRC [40,66,94], and pancreatic cancer [95], and have shown particularly promising results in models of malignant glioma [96–102].

The evidence for these approaches as anticancer interventions in preclinical models is solid; however, the mechanisms underlying the effects of CR, fasting, and FMDs remain largely unknown, and this has limited their applicability (Box 2).

Box 2. How do fasting-related diets work against cancer?

It was widely believed that these approaches target the nutritional dependency of tumor cells, particularly their reliance on glucose and other metabolites to fuel energy production and biosynthesis. However, cancer cells are known to activate protective functions and survival mechanisms under selective pressure and metabolic stress, particularly when reduced and defective vasculature leads to compromised nutrient delivery [157], to ensure that their metabolic demands are satisfied through anaplerosis. Therefore, it is likely that there are many mechanisms beyond glucose starvation that influence the observed pathological response following adherence to fasting-related diets.

Many studies implicate ketones, mainly βOHB, as the agents behind the antitumor effects of these diets, particularly the KD [67,93,99]. Ketone catabolism varies across tissues because the liver lacks the rate-limiting enzyme SCOT (succinyl-CoA-3-oxaloacid CoA transferase) and is unable to use ketones as fuel [158]. Tumors can also display different levels of enzymes involved in ketone catabolism such as SCOT and *O*-hydroxy-butyrate dehydrogenase (3-HBDH) [67,159]. This heterogeneity in the ability of tissues to catabolize ketone bodies may explain why approaches such as the KD are not effective for all tumor types [95,160] and, even if they are effective, their mechanisms of action might extend beyond βOHB. Overall, it is unlikely that ketone bodies alone play a causal role in the antitumor effects of dietary interventions because there is evidence that other factors, such as growth signaling, inflammation, immunosurveillance, mitochondrial metabolism, and angiogenesis, are modified during these approaches [5,36,158,161] (Figure 2).

It is worth noting that, despite their mechanistic commonalities, these approaches have unique features which may make them more suitable to treat specific tumors, be more effective in combination with specific therapies, or improve their feasibility and effectiveness in different patient scenarios. In addition, the protective effect of CR and fasting-related diets against DNA damage in healthy cells [162] has made them an attractive subject to study to improve quality of life and the effectiveness of chemotherapy during treatment.

In preclinical mouse models, various forms of CR, fasting, and fasting-mimicking diets sensitize cancer cells to chemotherapeutic interventions such as gemcitabine, tyrosine kinase inhibitors, βOHB, mimetics, tamoxifen, and fulvestrant, and also reduce side effects caused by toxicity to healthy tissues, thus improving overall treatment performance [86,88,163–165]. These results have accelerated the push for these diets to be implemented as adjuvant therapies that synergize with established treatments and perhaps overcome therapeutic resistance, which is currently one of the biggest obstacles in cancer therapy.

## Dietary restriction approaches

Evidence that amino acids can enable cancer biosynthesis and growth has generated interest in protein-restricted diets. However, the role of protein intake in the context of cancer initiation and development remains controversial. Evidence from population studies suggests that protein restriction has a positive influence on longevity and healthspan; however, these benefits appear to be exclusive to the population under 65 years of age [103,104]. The findings of a recent study suggested that protein intake of >20% of total calories leads to major increases in cancer risk and mortality compared to a diet with <10% of calories gained from proteins [105]. However, there is a lack of robust evidence linking protein consumption to cancer, and protein consumption has been hypothesized to act as a 'double-edged sword" by fueling established tumors through amino acids but having a preventative role in the formation of tumors by sustaining tissue homeostasis.

Research in preclinical mouse models has also provided controversial results. Some studies suggest that low-protein diets inhibit tumor growth by downregulating the IGF/mTOR pathway [106,107] and by enhancing immunosurveillance through reprogramming of tumor-associated macrophages [108] and inositol-requiring transmembrane kinase/endoribonuclease 1α (IRE1α)-dependent activation of the unfolded protein response [109]. Other studies have shown that protein-rich diets protect against tumor growth and initiation [110] and can prevent colitis-induced CRC through amino acid-mediated activation of mTOR [111]. Therefore, it is likely that tumors have heterogeneous responses to protein restriction, driving growth signaling and tissue biosynthesis in some cases, but supporting tissue homeostasis to disrupt tumor growth in others.

Diets that restrict specific amino acids have also been studied for their anticancer effects, with a focus on commonly found amino acid synthesis deficiencies. Indeed, inhibition of one-carbon metabolism through depletion of dietary methionine, serine, cysteine, and glycine was shown to reduce tumor growth in various preclinical models [19,112–116]. Restriction of other amino acids, such as leucine and asparagine, also produced antitumor effects in preclinical models [117,118]. Amino acid composition may be a powerful element in the context of nutritional interventions because cancers could be evaluated for their specific amino acid metabolism, and diets that restrict particular amino acids could then be used to target specific tumor types.

Low-fat diets (LFDs) are a commonly used interventions to reduce adiposity and improve metabolic health. LFDs typically restrict fat intake to <30% of daily calorie intake and promote the intake of plant-based foods and fiber. LFDs do not produce reductions in glycemic load or increases in ketone bodies; however, they are effective at promoting loss of body weight and body fat [119,120]. Dietary and adipocyte-derived lipids have been shown to contribute to tumor progression and facilitate metastasis [26,29], and it has been proposed that limiting lipid consumption might have antitumor effects, although there are currently no conclusive data from preclinical models.

The beneficial effects of LFDs are largely due to the low caloric density of carbohydrates and proteins compared to lipids (4 kcal/g for proteins and carbohydrates vs. 9 kcal/g for fats), leading to a passive form of CR, reduced adiposity, improvements in metabolic health, and consequently improved cancer outcomes. Studies comparing LFDs to diets higher in fat have found that patients undergoing a LFD have a spontaneous reduction in caloric intake of up to 800 kcal/day [120,121].

### Alternative dietary approaches

An array of dietary patterns are being studied for their role in aging and cancer. These include approaches based on adding key supplements to otherwise normal diets (Box 3), regional diets such as Mediterranean diets, which focus on intake of fruits and vegetables, whole grains, and fish and plant-sourced protein and unsaturated fats; and **vegetarian diets** or **vegan**

#### Box 3. Supplementation: the optimal approach to nutritional therapy?

Supplementation with specific micronutrients or metabolites is a promising approach to dietary interventions because it requires a much reduced commitment from patients than altering their diet in a strict and specific manner. With our increasing knowledge on cancer and metabolism, we are uncovering a series of key metabolites that can act as antitumoral agents, and supplementing an otherwise unrestricted diet with these metabolites may be a viable option to improve cancer outcomes. Many of these metabolites have been characterized through mechanistic studies on diet–cancer interactions, as is the case in SCFAs that are produced during fermentation of dietary fibers by microbiota, and β-hydroxybutyrate produced during ketogenesis. These have both been shown to be effective in reducing CRC growth and may be viable supplements in the treatment and management of colon cancer [40,166]. Microbiota-derived acetate has been shown to be an anticancer agent in caloric restriction and can delay tumor growth when supplemented into an otherwise regular diet [54]. Supplements to improve the efficacy of existing therapies are also being explored because increases in different metabolites through dietary manipulation, such as tryptophan, 3-IAA, histidine, and mannose, have been shown to improve the effectiveness of chemotherapy in a variety of cancer models [156,167,168]. Interestingly, boosting $NAD^+$ levels by nicotinamide riboside can improve cancer therapeutic treatment and protect from chemotherapy-induced toxicity [169]. Diets aimed at improving microbial health in the digestive tract through supplementation represent another research area of interest. This can be achieved in multiple ways, including the intake of prebiotics (e.g., dietary fibers) to nourish beneficial bacteria growth, or probiotics – microorganisms taken through the diet that can colonize the digestive tract. Our increasing knowledge of how the microbiota interacts with immunity, and how it can modulate immunity to enhance the effect of immunotherapies, makes these approaches an attractive strategy to treat cancers that are unresponsive to immunotherapy. Because the interactions underlying these effects remain to be fully characterized, we do not yet have a clear pattern of 'anticancer microbiota' that could be promoted through dietary interventions.

**diets,** which exclude meat and other animal products in favor of plant-based foods. These diets generally promote healthy body compositions to improve cardiovascular and metabolic health, although their effects on cancer remain to be explored, largely because of the difficulty in implementing these 'ingredient-based' diets in preclinical models [122–124].

## Development of dietary interventions for clinical use

Despite gaps in our mechanistic knowledge of dietary interventions in the context of cancer treatment, the results of preclinical studies have advanced clinical research using dietary interventions as a cancer treatment, particularly as adjuvant therapies, with the goal of improving the effectiveness of current treatments. Ongoing clinical trials using dietary interventions as a cancer treatment are outlined in Table 2.

The focus on dietary interventions in cancer is largely based on 'nutrient-restricted' approaches that combine CR, fasting, and glucose restriction, and which aim to provide relatively simple and easy-to-follow guidelines while maximizing the benefits of fasting/CR. However, other dietary interventions are also being explored in smaller trials. These include essential amino acid restriction, Mediterranean diet-based KD variants, and dietary supplements which may widen the arsenal of tools to implement nutritional therapeutics in the clinic. Although data from trials applying these interventions to larger populations of patients with cancer remain limited, they have provided a solid base to develop these interventions in larger clinical trials.

### Completed clinical trials

Most completed clinical trials have aimed to establish feasible and safe protocols for dietary interventions. Because dietary habits are strongly rooted in the personal and cultural preferences and education of each individual, drastically changing the diet of an individual to a treatment is very difficult, and dropout rates from clinical trials usually account for one in three participants enrolled, even when the participants are well-informed and motivated [125–128]. To encourage adherence to the treatment, many trials offer added assistance such as preformulated meals, which are often provided by the institution itself, as well as dietary counseling and frequent follow-ups with a dietician to maintain communication and keep participants engaged. Despite the typically high dropout rates, dietary interventions have showed sufficient safety and feasibility, and side effects such as low-grade fatigue, digestive issues, hypoglycemia, and acidosis have been relatively common as a result of adaptations to the diet, but severe side effects were rare and were usually associated with older patients and comorbidities.

Short-term fasting trials have produced improvements in quality of life and cancer risk factors such as decreased adiposity, fasting glucose, insulin, IGF-1, and leptin levels, as well as successful induction of ketogenesis by fasting [129,130], FMD [87], and KD interventions [131–134]. Pilot studies for short-term fasting in combination with chemotherapy have reported improved quality of life, reduced fatigue, and decreased frequency and severity of chemotherapy-related side effects [135,136], albeit with no conclusive evidence pointing to improved therapeutic responses.

Notably, FMDs have been shown to modulate immunity towards signatures that are typically associated with improved clinical outcomes [65]. However, 'DIRECT', a multicenter, open-label, randomized Phase 2 trial for FMD in combination with chemotherapy for patients with stage II–III human epidermal growth factor receptor 2 (HER2)-negative breast cancer, assessed the percentage of patients with grade III/IV toxicity, as well as the percentage of pathological complete responses over 4 years, and reported a lack of strong clinical improvements in patients who used an FMD before chemotherapy. However, it also reported that the FMD-

Table 2. Clinical trials evaluating dietary interventions in cancer[a,b]

| Dietary intervention class | Dietary intervention | Therapeutic intervention | Cancer type | Identifier |
|---|---|---|---|---|
| Fasting | Fasting 48 h before and 24 h after immunotherapy | Immunotherapy | Advanced and metastatic malignant skin neoplasm | NCT04387084 |
| Caloric restriction and fasting | TRE (feeding 12:00 pm – 8:00 pm) vs. 25% CR | None | Colorectal cancer | NCT05114798 |
| Fasting | TRE (16 h fast) for 12 weeks | None | Colorectal cancer | NCT04722341 |
| Fast-mimicking diet | FMD, 5 days in 3-week cycles + metformin | Chemotherapy | Breast cancer | NCT04248998 |
| Caloric restriction | Short-term CR (4 weeks) | Chemotherapy | Non-Hodgkin lymphoma | NCT05376709 |
| Fasting | TRE (14 h fast) | Chemotherapy | Breast cancer | NCT05327608 |
| Caloric restriction | 75% CR | Surgery | Breast, endometrial, and prostate cancer | NCT02983279 |
| Caloric restriction | 6–12 weeks 75% CR | Radiotherapy | Breast cancer | NCT04959474 |
| Fasting | TRE (16 h fast) for 12 weeks | Chemotherapy | Breast cancer | NCT05259410 |
| Fasting | TRE (16 h fast) for 6 weeks | None | Endometrial cancer | NCT04783467 |
| Fast-mimicking diet | Postoperative FMD (800–1000 kcal high-fat diet) for four cycles | None | Colorectal cancer | NCT05384444 |
| Fasting | TRE (14–16 h fast) for 8 weeks | None | Endometrial cancer | NCT04763902 |
| Caloric restriction | 50% CR and aerobic exercise 48 h before chemotherapy | Chemotherapy | Breast cancer | NCT03131024 |
| Caloric restriction | CR 3 days pre- and 2 days post-chemotherapy for 12 weeks | Chemotherapy | Breast cancer and prostate cancer | NCT01802346 |
| Caloric restriction | 15% CR with~25/55/20% kcal in fat/carbohydrates/protein and moderate exercise | Chemotherapy | Hematological cancers | NCT05082519 |
| Ketogenic diet | 75% Fat KD for 12 weeks | Chemotherapy | Breast cancer | NCT05234502 |
| Ketogenic diet | Two-week KD | Aromatase inhibitor | $ER^+$ breast cancer | NCT03962647 |
| Ketogenic diet | Isocaloric 3:1 KD | None | Endometrial cancer | NCT03285152 |
| Ketogenic diet | Calorie-unrestricted 3:1 KD | Chemotherapy | Pediatric brain tumor | NCT03591861 |
| Ketogenic diet | KD 7 days before the first treatment cycle and continuous after the second cycle | PI3K inhibitors | Follicular lymphoma and endometrial cancer | NCT04750941 |
| Ketogenic diet | Macronutrient intake: <30 g/day carbohydrates and 1.5 g/kg/day protein | Chemotherapy | Pancreatic ductal adenocarcinoma | NCT04631445 |
| Ketogenic diet | KD for 12 weeks during PI3K inhibitor treatment | PI3K inhibitors | Breast cancer | NCT05090358 |
| Ketogenic diet | Isocaloric or protein-restricted KD for~10 days before surgery | Surgery | Breast cancer | NCT04469296 |
| Ketogenic diet | Energy restricted KD (20–25 kcal/kg/day) for 6 weeks after radiotherapy | Radiotherapy | Glioblastoma | NCT01535911 |
| Ketogenic diet | Classic KD for 3+ months | None | Brain cancer | NCT05564949 |
| Ketogenic diet | KD through prepared meals for 12 weeks | None | Mantle cell lymphoma | NCT04231734 |
| Ketogenic diet | Standard of care procedure with or without an adjuvant KD up to 16 weeks | Not specified | Brain metastases | NCT05428852 |
| Fasting | 72 h fasting cycle before biopsy/resection | Surgery | Brain cancer | NCT04461938 |
| Ketogenic diet | Modified Atkins KD (>20 g carbohydrates/day) | Radiotherapy | Glioblastoma | NCT03278249 |
| Ketogenic diet | Carbohydrate-restricted diet (>20 g carbohydrates/day) for 6 months | None | Prostate cancer | NCT03679260 |
| Ketogenic diet | KD for 4 months | Radiotherapy and chemotherapy | Glioblastoma | NCT03451799 |

(continued on next page)

Table 2. (continued)

| Dietary intervention class | Dietary intervention | Therapeutic intervention | Cancer type | Identifier |
|---|---|---|---|---|
| Ketogenic diet | Continuous or cyclical (15 days on/15 days off) KD (<40 g/day CHO)/βOHB supplementation | Immunotherapy | Renal cell carcinoma | NCT05119010 |
| Ketogenic diet | KD + metformin | PI3K inhibitor | Glioblastoma | NCT05183204 |
| Ketogenic diet | Isocaloric 2:1 KD for six 4-week cycles | None | Glioma | NCT05373381 |
| Fast-mimicking diet | 4-day low-calorie, low-protein, vegetarian diet 3 days before chemotherapy | Chemotherapy | Breast cancer ($HR^+$, $HER2^-$) | NCT05503108 |
| Fast-mimicking diet | FMD, 5 days in 3 week cycles + metformin | Chemotherapy | Lung adenocarcinoma | NCT03709147 |
| Low protein diet | 10% Protein intake vs. a 20% protein intake control | Immunotherapy | General | NCT05356182 |
| Ketogenic and low-protein diet | Isocaloric KD (65% lipids) vs. 20% protein reduction from usual intake | Surgery | Breast cancer | NCT04469296 |
| Mediterranean diet | Low-carbohydrate Mediterranean diet (35% CHO) vs. low-fat Mediterranean diet (10% fat) | None | Prostate cancer | NCT05590624 |
| Amino acid restriction | Nonessential amino acid restriction | Chemotherapy | Metastatic pancreatic cancer | NCT05078775 |
| Amino acid restriction | Nonessential amino acid restriction | Chemotherapy | Metastatic colorectal cancer | NCT05183295 |
| Mediterranean diet and low-fat diet | Mediterranean diet supplemented with extra-virgin olive oil or low-fat diet | None | Breast cancer | NCT04174391 |

[a]Trials listed at clinicaltrials.gov as of April 2023.
[b]Abbreviations: βOHB, β-hydroxybutyrate; CR, caloric restriction; FMD, fasting-mimicking diet; KD, ketogenic diet; PI3K, phosphoinositide 3-kinase; TRE, time-restricted eating.

treated group had no more grade III/IV adverse events than those who did not follow the diet, despite not being prescribed dexamethasone alongside chemotherapy [137]. Nevertheless, more recent reports have shown exceptional tumor responses in patients undergoing FMD cycles alongside standard therapy, and advanced tumors with a typically poor prognosis showed complete and long-lasting responses to therapy [138].

Past trials of KDs in patients with cancer have mostly consisted of pilot studies focusing on safety and tolerance to the diet, and there have been few randomized controlled trials [139–143]. The ERGO2 randomized pilot trial applied 3-day cycles of fasting followed by 3 days of a calorie-restricted KD combined with re-irradiation for patients with recurrent glioblastoma or gliosarcoma, and measured the rate of progression-free survival over 6 months as well as secondary measures related to safety, tolerability, and patient quality of life. The study showed good adherence and safety, no adverse effects were attributable to the diet, and successful reduction in blood glucose and induction of ketosis were reported after 6 days of treatment. However, no significant differences in progression-free or overall survival were observed, partly owing to the short length of the schedule reported in the trial [144]. Moreover, a randomized, controlled open-label pilot trial for patients with locally advanced and metastatic breast cancer studied the safety and tolerability of a medium-chain triglyceride-based KD on breast cancer treated-patients, as well as body composition changes and overall survival rates. This trial reported similarly good patient involvement, lack of adverse effects, and improvement in physiological parameters, as well as improved survival rate in the intervention group, although the study was conducted in a small and highly heterogeneous group of patients, which compromises the veracity of the results [134].

Studies on CR and LFDs in cancer have mostly targeted lifestyle changes to mitigate the incidence and recurrence of cancers associated with obesity, such as breast cancer and CRC, rather than as a direct therapeutic approach. The Women's Health Initiative randomized controlled trial conducted a thorough investigation into the use of LFDs as an intervention to improve the

outcomes of women suffering from breast cancer. The results showed similar rates of breast cancer incidence but an overall lower incidence of death in the intervention group [145].

Previous clinical studies have highlighted the feasibility and safety of dietary interventions, but patients with cancer are not typically given specific dietary advice and are encouraged to consume a caloric excess to maintain their bodyweight through treatment cycles. However, the data on improved disease outcomes as a direct consequence of dietary interventions are inconsistent. Extracting valid and reproducible results will require greater effort, and current and upcoming studies are aiming to use large-scale, controlled randomized trials to evaluate disease progression and survival in cancer after applying diets in combination with specific therapeutic interventions.

## Current and future clinical trials

Owing to the efforts of early trials, most ongoing studies focus on the effect that dietary interventions have on specific physiological parameters and, most importantly, on pathologic responses (Table 1).

Ongoing and upcoming trials largely focus on fasting, fasting-mimicking, and CR approaches applied to cancers with poor prognosis. This is highlighted by the notable focus on the KD as a treatment for glioblastoma and other brain cancers (NCT01535911[i], NCT03278249[ii], NCT05373381[iii], and NCT03451799[iv]). These cancers have a dismal prognosis owing to their aggressiveness and the lack of effective lines of treatment, and promising preclinical results for a KD on brain tumor development have prompted clinicians to promote ketogenic and fasting approaches as a means to enhance therapy and extend lifespan (Table 1).

Other dietary approaches being studied include the implementation of nonessential amino acid-restricted diets for the management of metastatic pancreatic and CRC alongside chemotherapy (NCT05078775[v] and NCT05183295[vi]), or Mediterranean diet variations to prevent the recurrence of breast cancer (NCT04174391[vii]).

Furthermore, the principles of precision nutrition are being used to identify specific diet/drug combinations that would boost the effectiveness of existing drugs and overcome resistance. One of the most promising combinations is that of KDs and phosphoinositide 3-kinase (PI3K) inhibitors. PI3K inhibitors target hyperactivation of the PI3K pathway which is a frequent metabolic driver of cancer in humans. However, this therapeutic approach is inconsistent owing to insulin feedback-mediated resistance mechanisms. Suppression of insulin feedback through carbohydrate-restricted diets such as the KD has been shown to improve PI3K inhibitor efficacy in preclinical models [95], and ongoing trials are aiming to establish the KD as an effective adjuvant therapy for PI3K inhibitors in various tumors (NCT04750941[viii], NCT05090358[ix], and NCT05183204[x]) (Table 1). The positive effects of fasting and a KD on anticancer immune responsiveness has also led clinicians to begin to evaluate dietary interventions to boost the effects of immune checkpoint inhibitors (NCT05356182[xi] and NCT04387084[xii]) given that many cancers fail to respond to this powerful therapeutic approach [146]. Given the heterogeneity between different types of cancers, further exploration of specific cancer–drug–diet synergies will be essential for the further development of the field, and establishing specific lines of treatment for each cancer and patient will be crucial to improve therapeutic effectiveness.

Overall, dietary interventions have been well studied in the context of cardiovascular disease, cancer, and metabolic diseases, and have shown sufficient safety and feasibility when applied to humans. Despite this, effective anticancer effects are often inconsistent, and current and upcoming clinical trials will be essential to evaluate the efficacy of these interventions alongside

## Clinician's corner

Diet is one of the most significant risk factors for cancer, and a substantial proportion of preventable cancer incidence can be attributed to poor and toxic dietary habits. Animal models have demonstrated that diet plays a crucial role not only in cancer prevention but also in cancer progression and treatment.

Several types of dietary interventions have shown promising therapeutic effects in preclinical mouse models of cancers. Despite ongoing trials to determine the clinical utility of dietary interventions, these are rarely prescribed by clinicians for treating cancer, partly because of the lack of mechanistic insights and precise, well-controlled studies in humans.

Dietary interventions are a holistic approach to cancer treatment that is affordable, highly customizable, and generally associated with few or modest adverse effects. Although there are currently insufficient data from large-scale clinical studies to support widespread implementation of these diets as a primary treatment for cancer, there is a growing effort to characterize their effects on cancer and incorporate them into clinical practice.

Dietary interventions require drastic behavioral changes, which may severely compromise adherence to treatment, and their effects in cancer treatment may depend on the health status (diabetes, obesity etc.), disposition, and cancer type of each patient. Moreover, many people find prolonged caloric restriction or fasting difficult to maintain because of diverse side effects (e.g., fatigue, headache, nausea, constipation, hypoglycemia). Finding metabolites that can prevent cancer would be a solution to circumvent these difficulties.

Precision nutrition approaches tailored to specific patient and cancer scenarios, such as dietary interventions or supplementation with key micronutrients and metabolites, are a promising strategy in the current oncology landscape. These approaches may

established therapies. Furthermore, commonly observed adverse effects, such as low-grade fatigue, digestive issues, hypoglycemia, and acidosis, which occur as a result of adaptation to a new dietary regimen, can result in inflammation of the liver and pancreas and excessive circulating triglycerides and cholesterol [5]. Therefore, these adverse effects require careful and personalized approaches to ensure that dietary interventions do not deteriorate the condition of a patient or disrupt their treatment.

soon become a new pillar in cancer treatment, given their apparent effectiveness, flexibility, and synergy with existing therapies.

The precision nutrition approach aims to employ specific dietary regimens informed by specific tumor profiles and patient considerations to maximize treatment efficacy while limiting toxicity and possible complications. In addition, introducing dietary interventions into the clinic requires the establishment of consistent and effective protocols to determine dietary content in terms of caloric intake, macronutrient shares of calories, micronutrients, and possible supplements. The periodicity and duration of these interventions, as well as their combination with other treatments, are other important aspects that remain to be defined. Creating uniform and streamlined guidelines for dietary therapeutics will aid in designing powerful and productive large-scale clinical trials that will help to refine and accelerate their development.

## The future of dietary interventions in the treatment of cancer

As we have highlighted throughout this review, diet is a powerful modulator of many of the axes involved in cancer, including growth signaling, immunity, and the microbiome. The study of dietary interventions in the context of disease is a mechanistically young and rapidly expanding field. However, over the coming years the information obtained from these studies will contribute to an in-depth characterization of cancer–nutrient interactions, and will help to refine the methodology and approaches to cancer treatment through dietary interventions.

Given the broad-spanning impact of nutrition on health, there are many considerations regarding the applicability of nutritional therapies to individuals; it is therefore essential to apply specific regimes based on the unique scenario of each patient. For example, high lipid density diets such as KDs may be unsuitable for patients with atherosclerosis, carbohydrate-rich diets may be unsuitable for diabetic patients, and CR or fasting may be unsuitable for underweight patients. Tumor nutritional preferences, inflammatory status, and microbiota interactions are also key considerations when aiming to optimize antitumor effects. Indeed, 'glucose hungry' tumors, which have undergone a major shift towards glycolysis, will suffer more from carbohydrate restriction, whereas those that rely on lipids (e.g., triple-negative breast cancers and ovarian cancers) may be more effectively treated with a LFD. The same could be applied to cancers with deficiencies in specific pathways of amino acid metabolism – where restriction of foods containing specific amino acids may be a valid strategy during treatment. Synergies between specific treatments and diets are another important factor to consider because tumors that develop weak responses to immunotherapy may benefit most from diets that improve immunosurveillance.

Implementing lifestyle changes at a societal level is a difficult task. Dietary intervention trials suffer from relatively high dropout rates, typically in the range of 20–40% of participants [125–128]. In addition, the feasibility of some of these diets can be a strong limiting factor because interventions such as strong CR, fasting, or KD are difficult to implement for long periods. It is therefore crucial to understand the mechanisms of action of each diet (although they may have similarities) to establish personalized treatments through precision nutrition, and transform cancer treatment from a one-size-fits-all approach to bespoke interventions for specific cancer types and patients. It is also essential to identify small molecules and therapeutic targets to establish novel lines of treatment that could circumvent the need for dietary interventions.

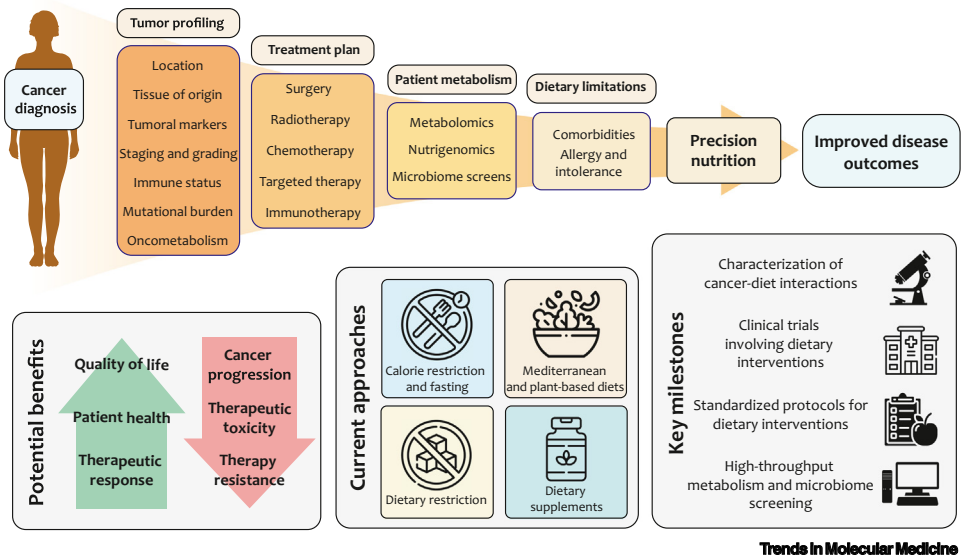


Figure 3. The pipeline for precision nutrition in cancer therapy. Precision nutrition is an approach to personalized nutrition that takes into account the unique genetic, physiological, and lifestyle factors of an individual to develop customized dietary plans and interventions that optimize health outcomes. This approach uses a combination of advanced technologies, including genomics, metabolomics, and microbiomics, to better understand the unique nutritional needs of an individual and to provide targeted recommendations for dietary changes, nutrient supplementation, and other lifestyle modifications. The goal of precision nutrition is to provide individuals with a more personalized and effective approach to improving their health and well-being, while also helping to prevent or manage chronic diseases such as obesity, diabetes, and heart disease.

## Concluding remarks

The advent of molecular oncology – the ability to analyze tumors in depth and classify them based on their molecular profile – has shifted the philosophy of treatment from generalized treatments for most cancer types towards specific approaches tailored to each cancer type and stage. This approach has not only led to major improvements in the outcomes of patients suffering from cancer but can also be applied to nutrition, combining clinical data with microbiome screens, nutrigenomics, molecular diagnostics, and metabolomics to develop dietary regimes aimed at targeting specific cancer abnormalities while maintaining or improving patient metabolic health (Figure 3).

This approach will require a more thorough characterization of cancer–nutrition interactions, combined with clinical data to validate these observations and standardized high-throughput metabolic and microbiome screens. Owing to the promising potential of precision nutrition as a future therapeutic approach, it will be crucial to further study dietary interventions to understand how they affect host health and disease states. In-depth understanding of dietary interventions will allow us to produce more refined treatments by designing specific diets for individuals based not only on their disease state but also on their metabolism and pre-existing conditions, to maximize tolerability and safety and improve patient health. Given the powerful effects that dietary interventions have shown in preclinical data and early clinical trials, this approach represents the advent of a new era in cancer therapy which has the potential to treat many difficult cancers by embracing metabolic interventions alongside existing treatment (see Outstanding questions).

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## Outstanding questions

Are dietary interventions a viable strategy for the treatment of cancer? How can dietary interventions improve cancer outcomes?

What are the mechanisms underlying the positive effects of dietary interventions in preclinical and early clinical data? How does diet impact on metabolism, microbiota, immunity, and other aspects of health?

Which patients could benefit from dietary interventions, and how can these interventions be tailored based on the health and status, cancer type, and metabolic profile of each patient? Precision nutrition is a crucial aspect of developing nutritional therapeutics.

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## Declaration of interests

The authors declare no conflicts of interest.

## Resources

[i] https://clinicaltrials.gov/ct2/show/NCT01535911
[ii] https://clinicaltrials.gov/ct2/show/NCT03278249
[iii] https://clinicaltrials.gov/ct2/show/NCT05373381
[iv] https://clinicaltrials.gov/ct2/show/NCT03451799
[v] https://clinicaltrials.gov/ct2/show/NCT05078775
[vi] https://clinicaltrials.gov/ct2/show/NCT05183295
[vii] https://clinicaltrials.gov/ct2/show/NCT04174391
[viii] https://clinicaltrials.gov/ct2/show/NCT04750941
[ix] https://clinicaltrials.gov/ct2/show/NCT05090358
[x] https://clinicaltrials.gov/ct2/show/NCT05183204
[xi] https://clinicaltrials.gov/ct2/show/NCT05356182
[xii] https://clinicaltrials.gov/ct2/show/NCT04387084

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