Engineered diets to improve cancer outcomes.

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Abstract

Cancer cells acquire a diverse range of metabolic adaptations that support their enhanced rates of growth and proliferation. While these adaptations help tune metabolism to support higher anabolic output and bolster antioxidant defenses, they can also decrease metabolic flexibility and increase dependence on nutrient uptake versus de novo synthesis. Diet is the major source of nutrients that ultimately support tumor growth, yet the potential impact of diet is currently underutilized during the treatment of cancer. Here, we review several forms of dietary augmentation therapy including those that alter the content of food, such as energy or macronutrient restriction, and those that alter the timing of food consumption, like intermittent fasting regimens. We discuss how these dietary strategies can be combined with pharmacologic therapies to exaggerate the metabolic liabilities of different cancer types.

Cancer Metabolism

Cancer cells can acquire a diverse range of metabolic adaptations that support their enhanced rates of growth and proliferation, and changes to cellular metabolism are recognized as a key hallmark of cancer [1]. These metabolic changes are driven directly and indirectly by gene mutations which activate a variety of cellular metabolic pathways. While these adaptations help tune metabolism to support higher anabolic output and bolster antioxidant defenses, they can also decrease metabolic flexibility and increase dependence on nutrient uptake versus *de novo* synthesis. Cancer cells consume a wide range of nutrients, including sugars, amino acids and fatty acids. An adequate supply of exogenous nutrients is critical to provide for energy production, macromolecule precursors – both of which support anabolism – and the ability to combat stresses such as reactive oxygen species. Diet is the major source of nutrients that ultimately support tumor growth [2,3], yet dietary interventions are currently underutilized during the treatment of cancer.

Dietary Augmentation Therapy

Estimates suggest that 10-35% of cancer initiation can be attributed to diet [4,5]. There are three primary ways in which diet promotes tumor development and progression. (1) Diet may introduce nutrients like sugars and lipids that can be used by tumor cells for anabolic growth [6]. (2) Diet may strongly impact systemic signaling factors like leptin, insulin, insulin-like growth factor 1 (IGF1), and estradiol, which stimulate tumor cell growth and survival [7]. (3) Diet may predispose to obesity, which creates a milieu that favors tumor initiation and growth. All three mechanisms are innately intertwined so dietary strategies that focus on one approach may broadly benefit the host.

The manipulation of foods in order to exaggerate the metabolic liabilities of cancer cells is called dietary augmentation therapy. Currently, several forms exist. Some focus on *content,* such as energy or macronutrient restriction (e.g. calorie restriction or low carbohydrate diets), while others are defined by *timing,* like intermittent fasting regimens that involve intervals of complete or partial energy restriction, regardless of meal composition. There are even hybrid models that alter both content and timing by delivering protein- and carbohydrate-restricted meals in-between periods of fasting [8]. Most of these interventions impose a caloric deficiency, which

induces a standard physiologic response including weight loss, a reduction in leptin, fatty acid mobilization, and reduced blood glucose variability. Other dietary approaches impact metabolism and systemic hormone levels without changing weight. Ultimately, the best approach depends on the biology of the host and metabolism of the tumor.

Modulating Dietary Content

Calorie-restriction (CR) is the most commonly used dietary augmentation strategy. CR reduces the total daily energy intake while maintaining a well-balanced macronutrient ratio. In a prospective, randomized, controlled trial of healthy, sedentary men and women (n=48), a 6 month exposure to a 25% CR diet reduced weight, fasting insulin, core temperature, and total energy expenditure [9] without affecting the somatotropic axis (GH and IGF1) [10]. These metabolic benefits persist through 2-years of intervention [11], and similar results have been observed in trials where CR is added to additional lifestyle interventions in obese subjects with pre-existing metabolic dysfunction (~40% of the adult population in Western countries) [12,13]. The effects of CR in subjects with cancer has not been robustly studied because of concerns regarding cachexia, quality of life, and compliance.

Some effects of CR can be recapitulated by eucaloric feeding of diets with altered macronutrient ratios. Diets with large proportions of fat and carbohydrate influence tumor development and progression in large, observational clinical studies [6]. Therefore, dietary interventions that restrict these macronutrients may improve anti-cancer therapy (Figure 1). Low fat (less than 30% kcal per day, LFD) and very low fat (less than 10% kcal per day, VLFD) diets are popular clinical interventions, and there are various iterations of this style of eating including the Ornish, Plant-based whole food (PBWF), Dietary Approaches to Stop Hypertension (DASH), and American Heart Association (AHA) diets. Carbohydrate restricted diets also come in a variety of options including those low (less than 100g per day, LCD) and very low (less than 30-40g per day, VLCD) in carbohydrate. VLCDs potently induce ketosis by suppressing insulin so are referred to as ketogenic diets. However, this term encapsulates a wide variety of dietary eating patterns that vary in fat content, fat composition, and protein content [14].

Although most dietary interventions fail to demonstrate superiority of one diet over another for weight loss[14–17], the different *content* approaches may have unique metabolic effects that can be utilized for specific cancer types. For example, carbohydrate restriction using a VLCD lowers insulin quickly especially when insulin resistance is present [18–20]. Therefore, these diets may be best in the setting of breast and endometrial tumors with an amplified insulin-PI3K pathway [21,22], but should be avoided in metastatic ovarian and prostate cancers that appear to feed on lipid [23,24]. Dietary protein also impacts circulating mitogens. Protein intake is a key determinant of circulating levels of IGF1[25,26] so diets including a protein restriction (e.g. CR, "classic" 3:1 ketogenic, and the Well-Formulated Ketogenic (WFKD) diet) may be more effective against IGF1-sensitive tumors such as those in the prostate and colon [27–30]. Furthermore, LFDs reduce circulating estrogens and/or progestins, which may explain the reduced deaths observed in the Women's Health Initiative Dietary Modification trial, a prospective, randomized, controlled study in postmenopausal women designed to examine the long-term benefits and risks of a LFD on breast and colorectal cancers and cardiovascular disease [31–33].

Modulating Dietary Timing

Intermittent fasting is a broad term that encompasses a variety of *timing* regimens that restrict energy intake for distinct periods. The five most common are time-restricted feeding (TRF), alternate-day fasting (ADF), alternate-day modified fasting (ADMF), the 5:2 schedule, and the fasting mimicking diet (FMD) (Figure 2)[34]. TRF prolongs the daily nocturnal fast by restricting intake to a pre-defined interval per day (*e.g.* 8 consecutive hours). ADF increases the fasting period further by requiring a complete fast every other day. ADMF is like ADF except that a small amount of food (about 25% of the daily kcal requirement) is allowed during the fasting day. The 5:2 program and FMD also utilize these days with minimal calorie intake occurring 2 days per week and 5 days per month, respectively.

The estimated degree of calorie restriction and the associated weight loss varies among the *timing* approaches, but the effects of systemic growth factors appear consistent. ADF and ADMF both show similar amounts of weight loss as compared to CR[35], but with better insulin suppression [36–39]. TRF has no effect on weight loss over

12 months[40] despite rapid changes to insulin sensitivity [41]. FMD did not reduce body weight in women with breast cancer, however still reduced insulin, IGF1, and leptin [42,43].

Engineering Diets to Improve Cancer Outcomes

While many agree that dietary factors can contribute to the development of certain tumors types[44], it is unlikely that diet alone will combat tumor progression. In this setting, diet should be combined with pharmacologic approaches to enhance anti-cancer therapy. There are several promising strategies that show efficacy in pre-clinical models. For example, a VLCD enhanced the effects of multiple PI3K inhibitors against 12 different tumor models, including genetically engineered mouse models, traditional xenografts, and patient-derived xenografts [21]. FMD led to durable remission of breast tumors in mice for over 160 days when combined with fulvestrant and CDK4/6 inhibition [43]. Other approaches like CR[2] and depletion of specific sugars[45] or amino acids such as serine & glycine [46,47], cysteine [48], methionine [49–51] from the diet show prominent effects alone and are likely to enhance standard of care treatment[2,46]. Supplementing the diet with certain sugars (e.g. mannose [52]), vitamins[53,54], or amino acids (e.g. histidine [55]) also have anti-tumour properties in pre-clinical models.

These dietary augmentation strategies are now being translated to humans with cancer. This process should be treated with the same care and rigor that we use in developing pharmacologic therapies including proper adjustment for the differences between mouse and human metabolism. We need well-designed and adequately powered phase I safety and feasibility studies, phase II therapeutic exploration trials, and, if needed, larger phase III studies for therapeutic confirmation. The first step is to design menus that are safe, cost-effective, tolerable, and efficacious. The best formulations arise from multidisciplinary collaboration amongst dieticians, chefs, food industry experts, and medical professionals familiar with patient behavior and potential side effects of medication that in some cases could alter food consumption and absorption (i.e. dysgeusia, anorexia, nausea, vomiting, stomatitis, dysphagia, autonomic dysfunction, pancreatic insufficiency, diarrhea, constipation, abdominal pain). For diets being prescribed for long periods of time, we recommend starting with a base of 25-30 kcal/kg of energy, 4 kcal/kg of protein, and splitting the rest of the energy using a 2.5 to 1 proportion carbohydrate to fat by kcal [56]. For a 70 kg subject, this formulation yields about 1900 kcal, 70g protein, 50g fat, and 290g carbohydrate.

This base can then be modified to meet the prescribed energy and macronutrient content. The menu should not contain simple sugars, processed meat, or ultra-processed foods [44]. Thought should be given to the composition of saturated to unsaturated fats and the total fiber content as these factors may alter the growth of specific tumor types[6]. When it is not possible to provide a well-formulated diet, the missing vitamins, minerals, and other components should be supplemented. In addition to designing an effective intervention diet, care should be taken where possible to use an appropriate control arm, which could be relatively 'normal' diet (but within defined macronutrient & caloric ranges), or potentially a calorie matched defined diet.

Compliance with diet – as with any therapeutic agent – is an important consideration. While many cancer patients have high motivation to comply, the quality and taste of the food should be optimized. Preferably, the menu contains both fresh and frozen options and caters to a range of individual patient preferences. The use of ingredients like garlic, hot sauce, and curry powder can help make meals more appealing and acceptable to different cultural backgrounds. Having a wide range of meal options has helped compliance with commercial CR programs for weight loss [57]. In addition to tasty food, dietary augmentation programs can be supported by dietary counseling and communication. Subject interaction through telephone follow up and video improves adherence to dietary interventions for chronic conditions such as diabetes and cardiovascular disease [58]. Providing similar contact through smart phone apps has been shown to improve adherence to diet in healthy volunteers [59]. Food is a source of joy for many people, and the emotional journey through cancer therapy is not easy. Counselors help to motivate and counsel patients through difficult times and teach subjects how to modify the dietary menu during special events and trips that inevitably arise.

Metabolic monitoring is the third core component to an effective dietary intervention. Metabolic monitoring is typically performed using metabolite or hormone measures in biofluids like venous and capillary blood, urine, saliva, or subcutaneous interstitial fluid. These measures ensure the efficacy of the intervention and the safety of the subject. For example, levels of capillary β-hydroxybutyrate are a reliable readout for the VLCD-induced suppression of insulin and safety monitoring for ketoacidosis when levels are too high [60]. It is important to note that hormonal and metabolic changes that occur in biofluids do not always translate to tissue level effects [61,62].

However, we lack convenient methods to easily access tissue level biomarkers. This may be possible using cells from freshly plucked hair or mucosal surfaces.

We are already quite advanced in the process to bring CR, VLCD, and FMD approaches to phase II and III clinical trials in cancer patients. In addition to being safe and feasible in subjects with cancer [63], a recent randomized, controlled trial provided evidence that a VLCD reduces tumor size in patients with locally advanced breast cancer[22]. Also, FMD also has very strong feasibility and safety data with hints of therapeutic efficacy when combined with CDK4/6 inhibition [43]. With these data in mind, we have started to outline an approach for Precision Nutrition in cancer (Figure 3). In this algorithm, tumor tissue types are further delineated using histologic and molecular features that have data supporting their use in animal models. The dietary interventions are then prescribed and monitored for efficacy. One limitation of this approach is that we are currently ignoring host factors (obesity, insulin resistance, pre-menopause, etc) that are known to influence tumor progression. We look forward to designing more advanced designs that account for this issue.

We are on the verge of a revolution in way we implement diet in patients during cancer therapy. Several rigorous preclinical studies have demonstrated that multiple forms of dietary augmentation therapy can improve cancer outcomes. Over the next 5 years, we will learn if these beneficial effects persist in prospective, controlled, randomized clinical trials[64]. It has become clear that a one-sized-fits-all approach is not appropriate, and we need to clarify the algorithms we use to implement dietary interventions.

Figure Legends

Figure 1 Dietary Interventions that Modify Content

A principle component analysis (PCA) was performed using the average macronutrient content (% carbohydrate, fat, and protein) of various dietary interventions. PC-1 (x-axis) accounted for 65% of the variation and segregated the diets based on carbohydrate and fat content, whereas PC-2 (y-axis, 35% of the variation) separated based on protein content. Ketogenic diets are found on the right side of the y-axis. Abbreviations: Plant-based whole food (PBWF), Dietary Approaches to Stop Hypertension (DASH), the average American diet from The Third

National Health and Nutrition Examination Survey (NHANES III), WFKD (Well-formulated ketogenic diet), 3:1 classic ketogenic diet (3:1 Keto).

Figure 2 Dietary Interventions that Modify Timing

The schedule of different intermittent fasting approaches as compared to a daily 25% calorie restriction (CR). Time-restricted feeding (TRF*) does not restrict energy intake. Instead, food consumption is limited to certain hours per day to create an extended period of daily fasting. As its name implies, alternate-day fasting (ADF) alternates between unrestricted access and no food intake every other day. Alternate-day modified fasting (ADMF) is a version of ADF that allows a small amount (~25% of normal daily intake) of food on the fasting days. The 5:2 schedule is a less stringent version of ADMF where the low calorie days occur 2 days per week. The fasting mimicking diet (FMD) is a program where the low calorie days occur for 5 consecutive days each month and food is not restricted the remainder of the time (#). The shaded areas represent the daily % intake of total caloric needs, e.g. the fully shaded circles represent daily consumption of 100% of total caloric needs.

Figure 3 Precision Nutrition Algorithm for Cancer

In this algorithm, tumor tissue types are further delineated using histologic and molecular features that have data supporting their use in animal models and early phase clinical studies. Breast cancer is first delineated by the presence of alterations in the PI3K pathway, which are predicted to grow in response to systemic insulin. The treatment of these tumors, and endometroid subtypes of endometrial cancer that also have high PI3K activity, should be paired with a very low carbohydrate diet (VLCD). Other types of breast cancer may respond best to combination therapies using the fasting mimicking diet (FMD) or low fat diets (LFD). We speculate that this paradigm can also be used for prostate cancer and glioblastoma, however the specific subtypes that respond well to each diet have not been demonstrated. APC-mutated colorectal cancers develop and progress in response to a variety of dietary components like red meat, processed meat, fructose-containing sugars, and low fiber diets so a plant-based whole food (PBWF) approach may be best in this setting. PIK3CA: gene for phosphatidylinositol 3-kinase p110 alpha; PTEN: gene for Phosphatase and tensin homolog; APC: gene for

adenomatous polyposis coli; FMD: fasting mimicking diet; LFD: low fat diet; VLCD: very low carbohydrate diet; PBWF: plant-based whole food diet.

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Conflict of interest

M.D.G. is a co-founder, shareholder, and consultant of Faeth Therapeutics Inc., which is developing nutritional therapies for cancer. M.D.G. has received speaking and/or consulting fees from Pfizer Inc., Novartis AG, Petra Pharmaceuticals, and TruMacro nutrition. M.D.G.'s laboratory receives financial support from Pfizer, Inc. O.D.K.M. is a co-founder and shareholder of Faeth Therapeutics Inc.

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Ref 3: A more comprehensive review of cancer cell metabolism and the promise of dietary augmentation therapy.

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Ref 11: CALERIE was a phase 2, multicenter, randomized controlled trial in 218 young and middle-aged, healthy non-obese men and women that were randomly assigned (2:1) to a 25% calorie restriction (CR) diet or an ad libitum control diet. CR reduced all measured conventional cardiometabolic risk factors. Although not in a cancer population, CALERIE is the first systematic investigation of CR in nonobese humans and it serves to define the long-term physiologic effects of this dietary approach.

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Ref 21: This is a mouse study showcasing an improvement in efficacy when PI3K inhibitors are paired with very low carbohydrate diets.

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Ref 32: This is a secondary analysis of the Women's Health Initiative randomized clinical trial where 48 835 postmenopausal women were randomized to a dietary intervention (N = 19 541) with goals to reduce fat intake to 20% of energy and increase fruit, vegetable, and grain intake as compared to a usual-diet group (N = 29 294). In the dietary intervention group, breast cancer overall survival was significantly greater (HR 0.78; 95% CI, 0.65-0.94; P = .01), and there were fewer deaths from breast cancer, other cancers, and cardiovascular disease.

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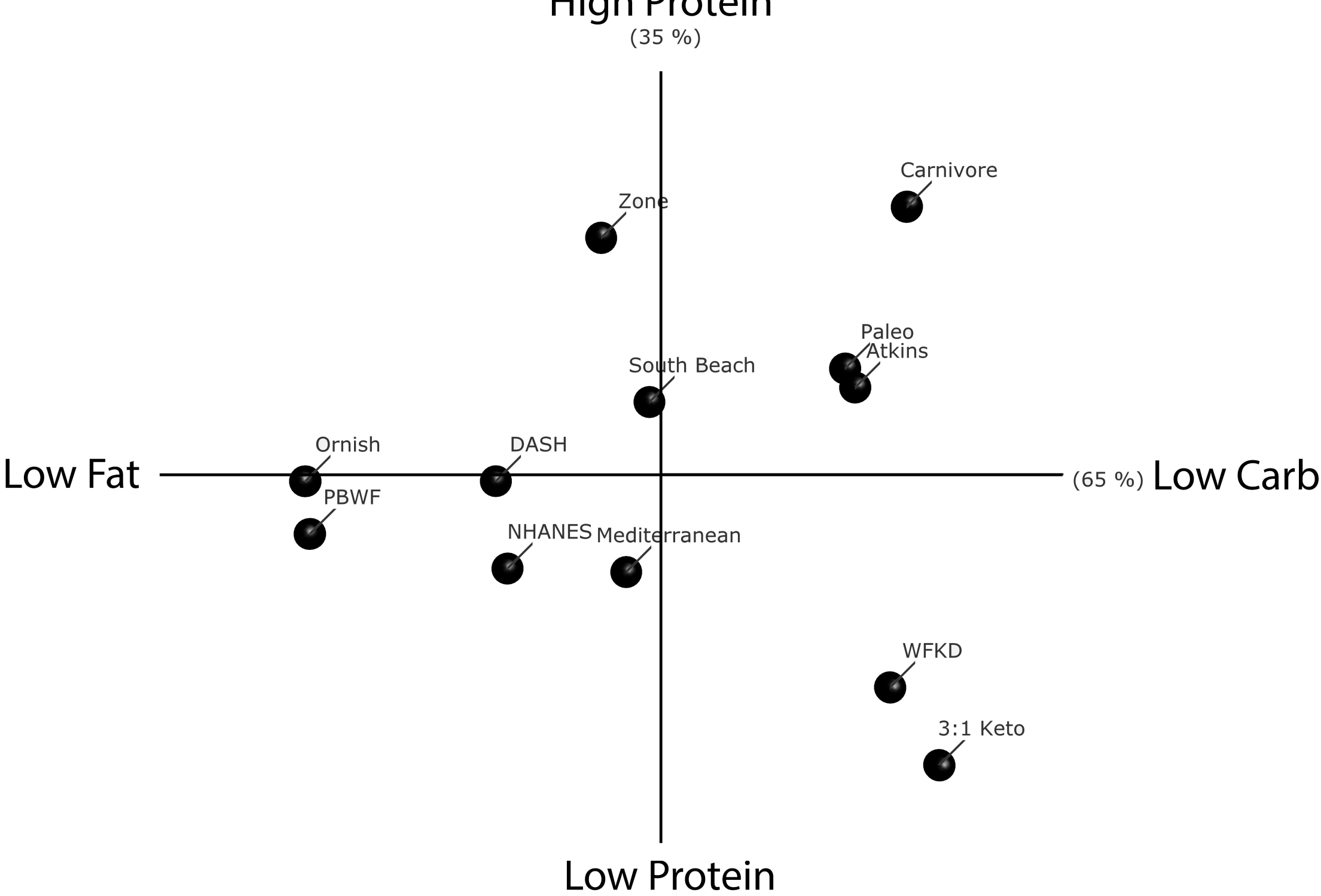
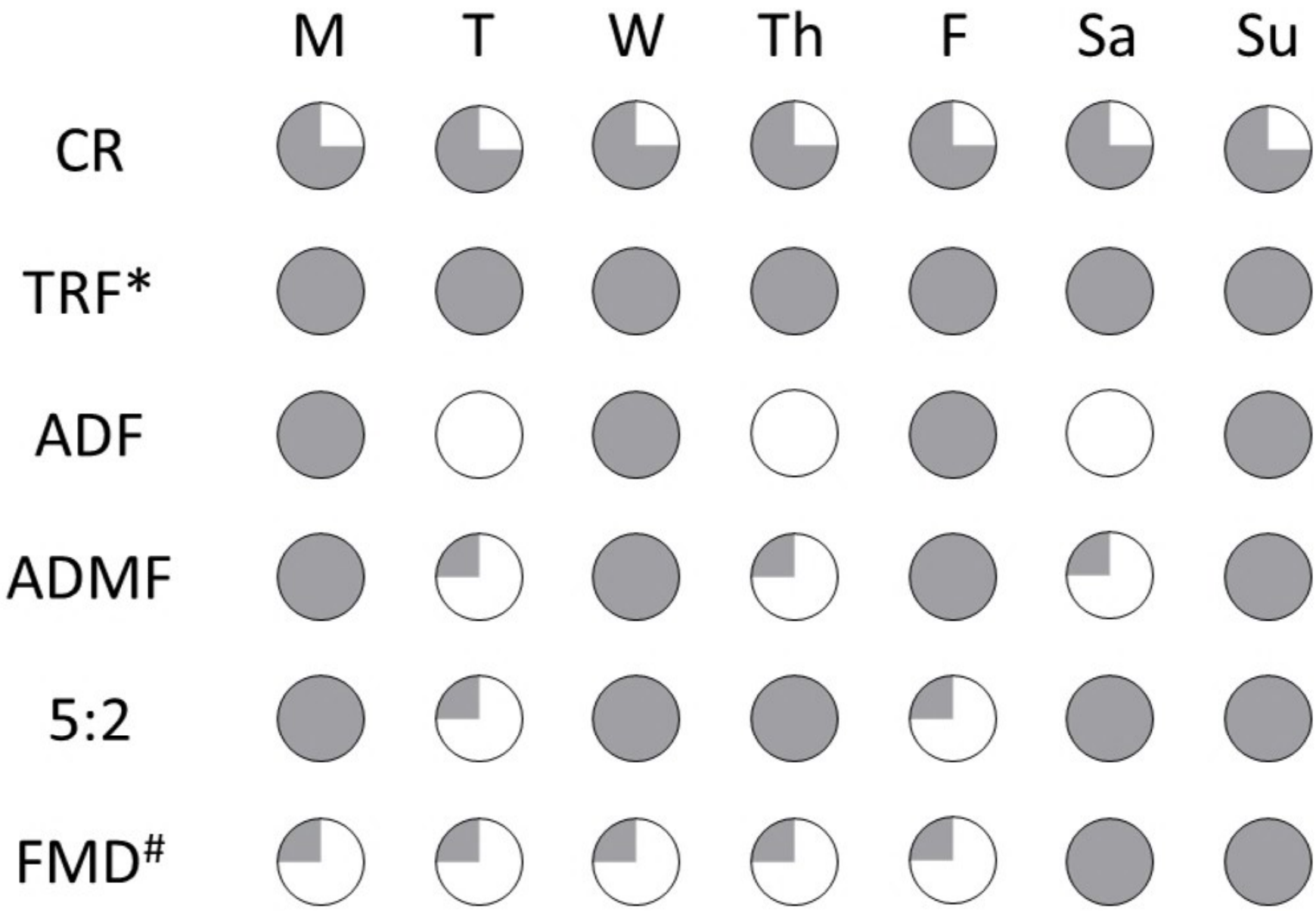
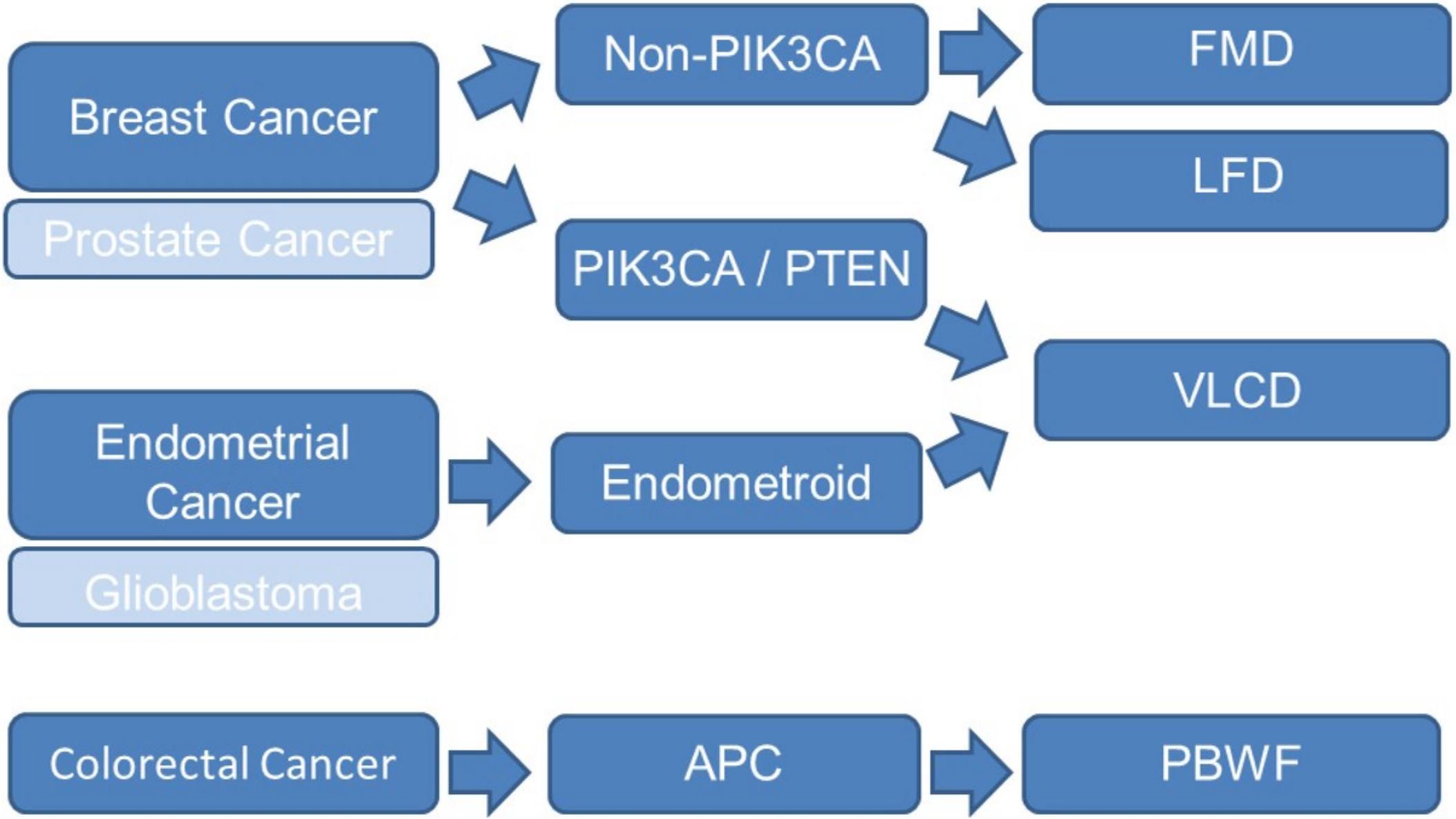
Ref 43: This is a mouse study showcasing an improvement in efficacy when CDK4/6 inhibitors are paired with fuvestrant and a fasting mimicking diet. The authors also present robust clinical feasibility data.


High Protein
(35 %)
Carnivore
Zone
Paleo
Atkins
South Beach
Ornish
DASH
Low Fat
(65 %) Low Carb
PBWF
NHANES
Mediterranean
WFKD
3:1 Keto
Low Protein


M
T
W
Th
F
Sa
Su
CR
TRF*
ADF
ADMF
5:2
FMD#


Breast Cancer
Prostate Cancer
Non-PIK3CA
PIK3CA / PTEN
FMD
LFD
VLCD
Endometrial Cancer
Glioblastoma
Endometroid
Colorectal Cancer
APC
PBWF