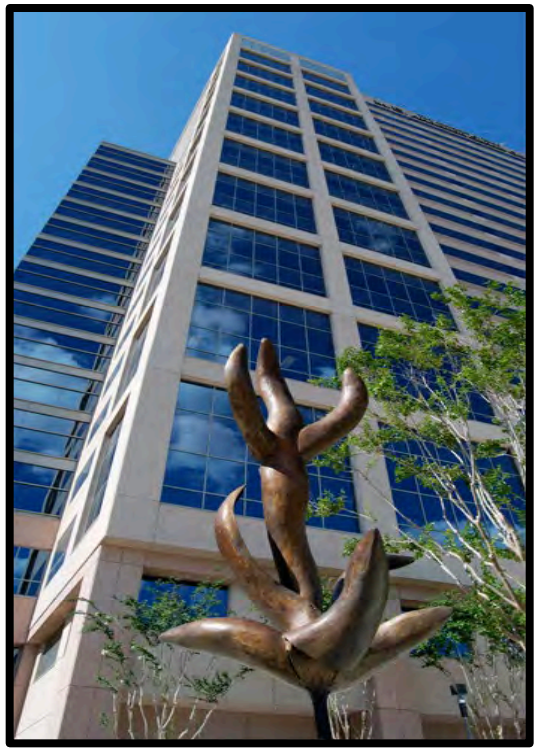

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MD Anderson Cancer Center
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Nutrition and the Microbiome

How does diet impact gut health and cancer from prevention to therapy and beyond?

Carrie Daniel-MacDougall, PhD, MPH

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Director, Bionutrition Research Core & Metabolic Research Kitchen
Resource Leader, Center for Energy Balance in Cancer Prevention and Survivorship
Nutrition and Epidemiology Lead, Platform for Innovative Microbiome and Translational Research
No COI/disclosures

Carrie Daniel / Carrie MacDougall

THE UNIVERSITY OF TEXAS
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13 years this May!

Work: With the tools of epidemiology, metabolic kitchen and biological markers (microbiome), I want to help answer: *What/how should I eat to improve my chances of responding to my cancer treatment and living a long, healthy life?*

Life: Tucson → Atlanta → DC → Houston → burbs. Raising two kids and a puppy. (Also, parents)

The in between: Kickboxing with my husband. Trying "different" New Zealand sauvignon blancs. Rage cleaning. Power naps. Planning trips and outdoor adventures (camping, hiking, skiing).

Dietary considerations for all cancer patients

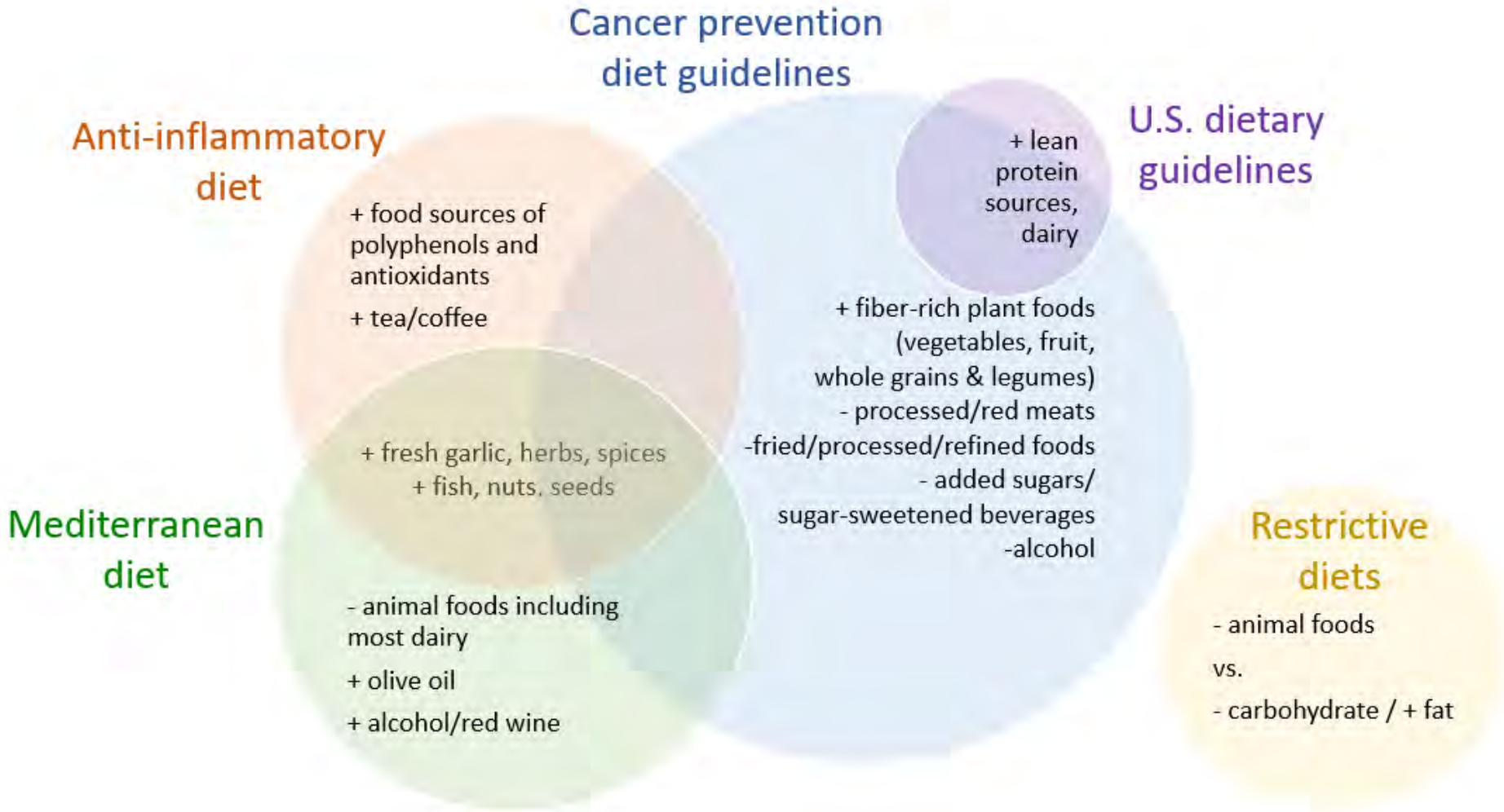
- Adequate calorie and protein intake with foods that support gut health (microbiome and the intestinal barrier)
- Food safety!
  - Thoroughly wash, cook and/or peel raw vegetables and fruits.
  - Frozen fruits and vegetables are also a great option.
  - Some “salads” may not be worth it.
  - Avoid raw/undercooked seafood or meats.
- Foods vs. supplements (unless identified need/prescribed)
- Fatigue and concurrent loss of appetite?
  - Eat more often and earlier in the day/any time energy is higher.
  - Smaller/low volume, nutrient-packed meals and snacks
- **Inpatient and outpatient dietitian support from Clinical Nutrition**

Now let’s talk research!


LIMIT CONSUMPTION OF RED AND PROCESSED MEAT
LIMIT CONSUMPTION OF SUGAR SWEETENED DRINKS
LIMIT CONSUMPTION OF 'FAST FOODS' AND OTHER PROCESSED FOODS HIGH IN FAT, STARCHES OR SUGARS
LIMIT ALCOHOL CONSUMPTION
World Cancer Research Fund
American Institute for Cancer Research
EAT A DIET RICH IN WHOLEGRAINS, VEGETABLES, FRUIT AND BEANS
DO NOT USE SUPPLEMENTS FOR CANCER PREVENTION
OUR CANCER PREVENTION RECOMMENDATIONS
Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk. Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.
BE PHYSICALLY ACTIVE
FOR MOTHERS: BREASTFEED YOUR BABY, IF YOU CAN
BE A HEALTHY WEIGHT
AFTER A CANCER DIAGNOSIS: FOLLOW OUR RECOMMENDATIONS, IF YOU CAN

www.aicr.org

Dietary patterns linked to cancer survival in follow-up studies



Central blue pattern represents what is common to all. Exterior connected circles show unique emphasis (+) or exclusions (-) of each diet. **Restrictive diets** (e.g., vegan vs. ketogenic) restrict or exclude certain types of foods or sources of nutrients but are otherwise flexible regarding food choices to meet those goals.

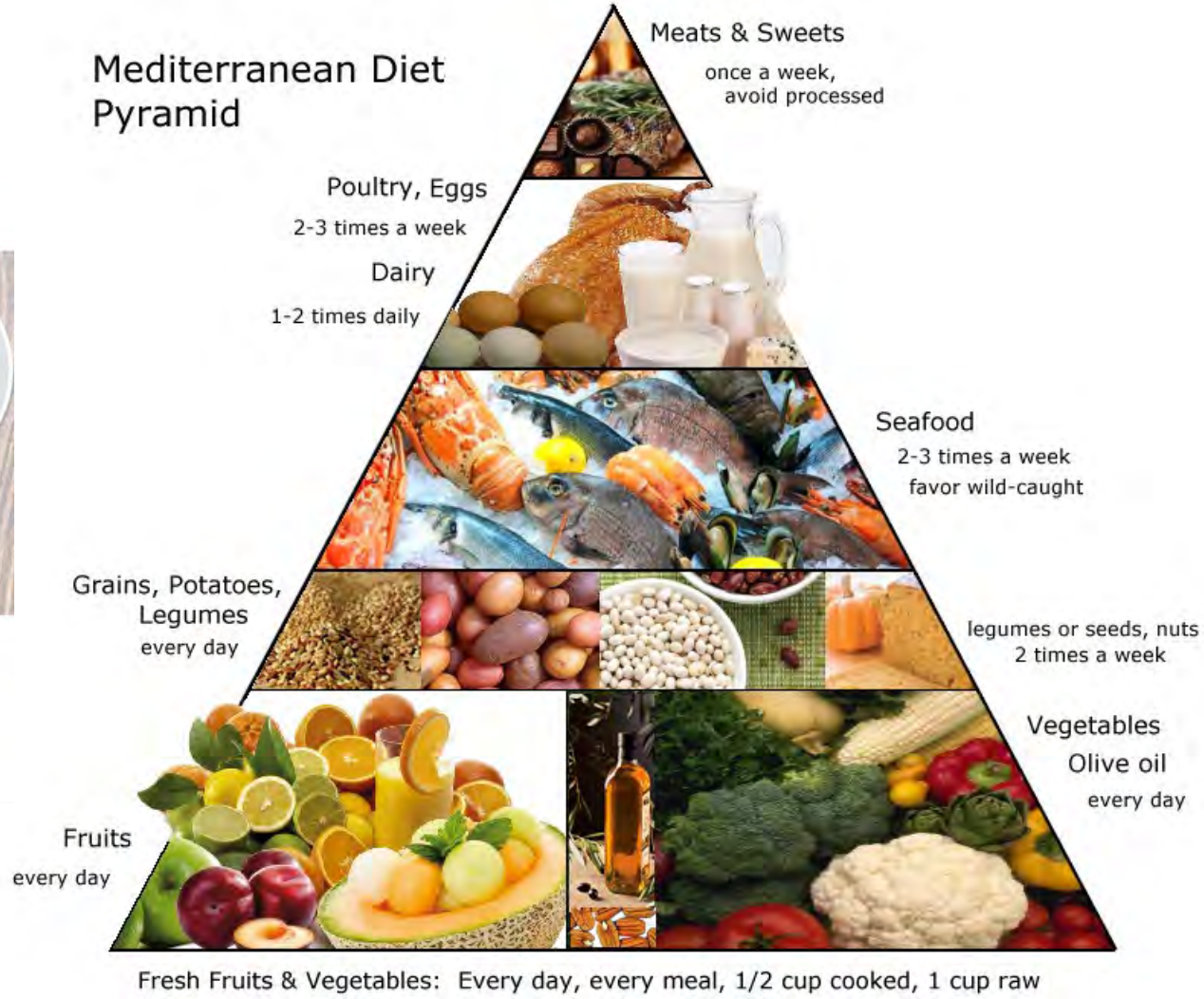
Prepared by CR Daniel for invited review in progress

Whole diet vs. its component parts

American Institute for Cancer Research

CHALLENGE 1

At least 5 of my meals this week will use the 2/3 – 1/3 plate principle.



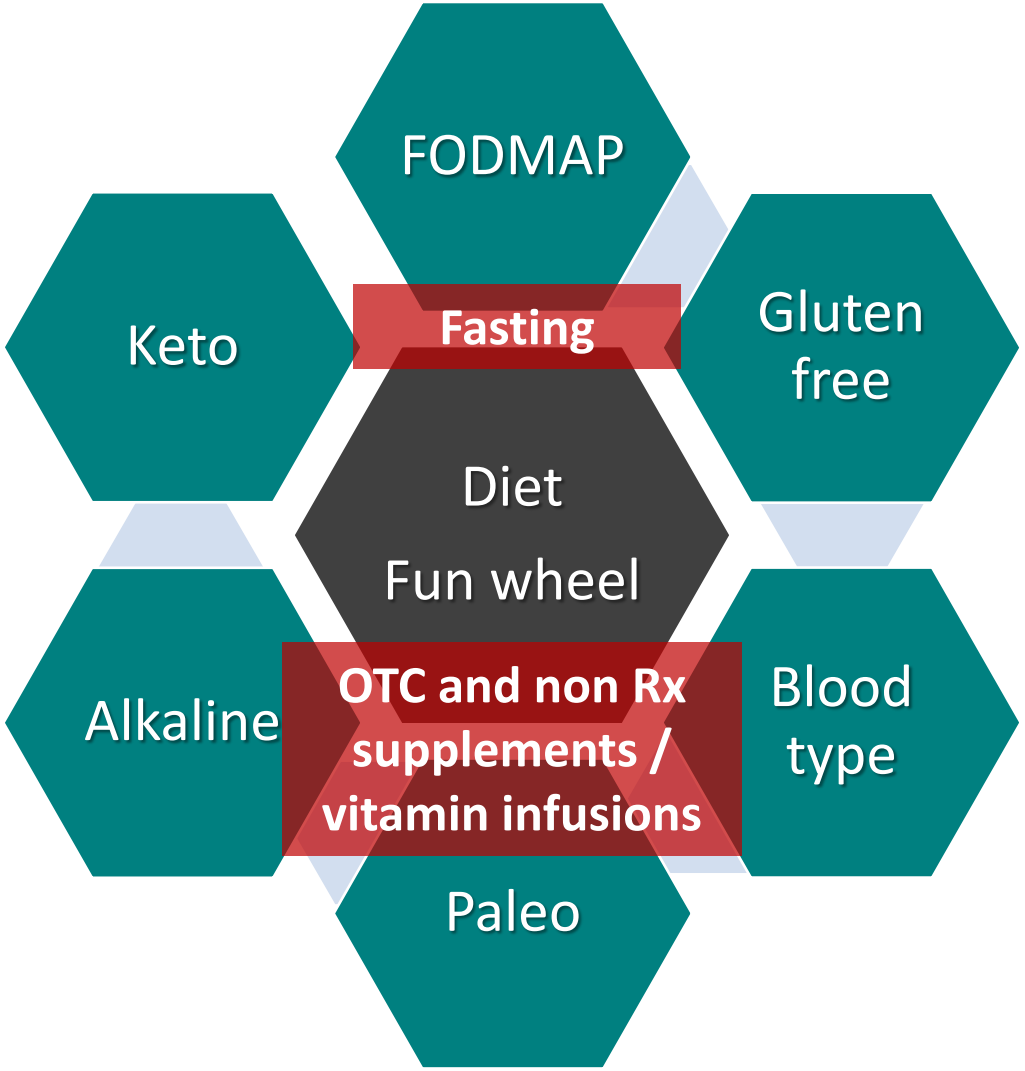
“Modifiable host factors” extend beyond cancer prevention

- Poor diet is a well-established cancer risk factor and increasingly recognized in cancer progression and outcomes
- The link between the gut microbiome and therapeutic response (or resistance) is shaping new research priorities for patients with cancer
- Patient attributes/habits may synergize with or inhibit treatment tolerance and efficacy
- Goal for cancer patient → survivor with ↑QOL, minimizing late effects of treatment, chronic toxicity and fear of cancer returning

Building the evidence to improve cancer care

- Collaborative efforts across research and clinical teams → develop strategies to target the microbiome in cancer with the overall goal to improve treatment response rates, reduce toxicity and extend survival
    - Patient and survivor cohorts (tumor vs. therapy-driven)
    - Parallel “humanized” preclinical studies
    - Clinical trials

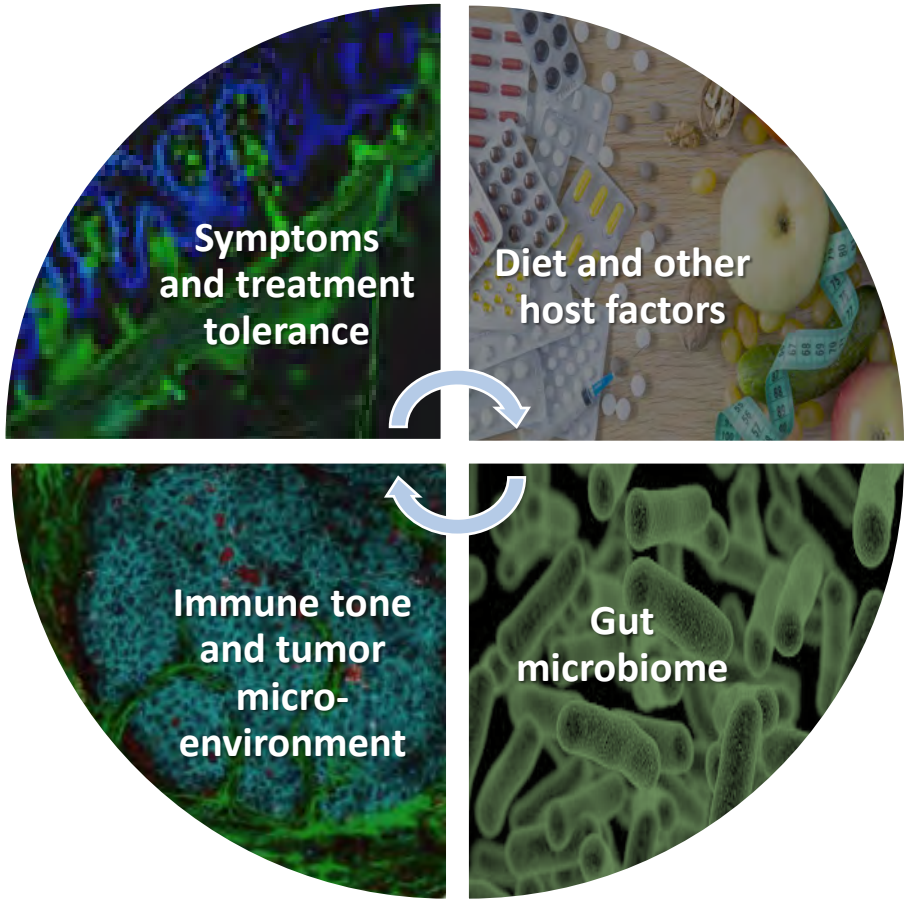
Patients *are* independently exploring different dietary strategies



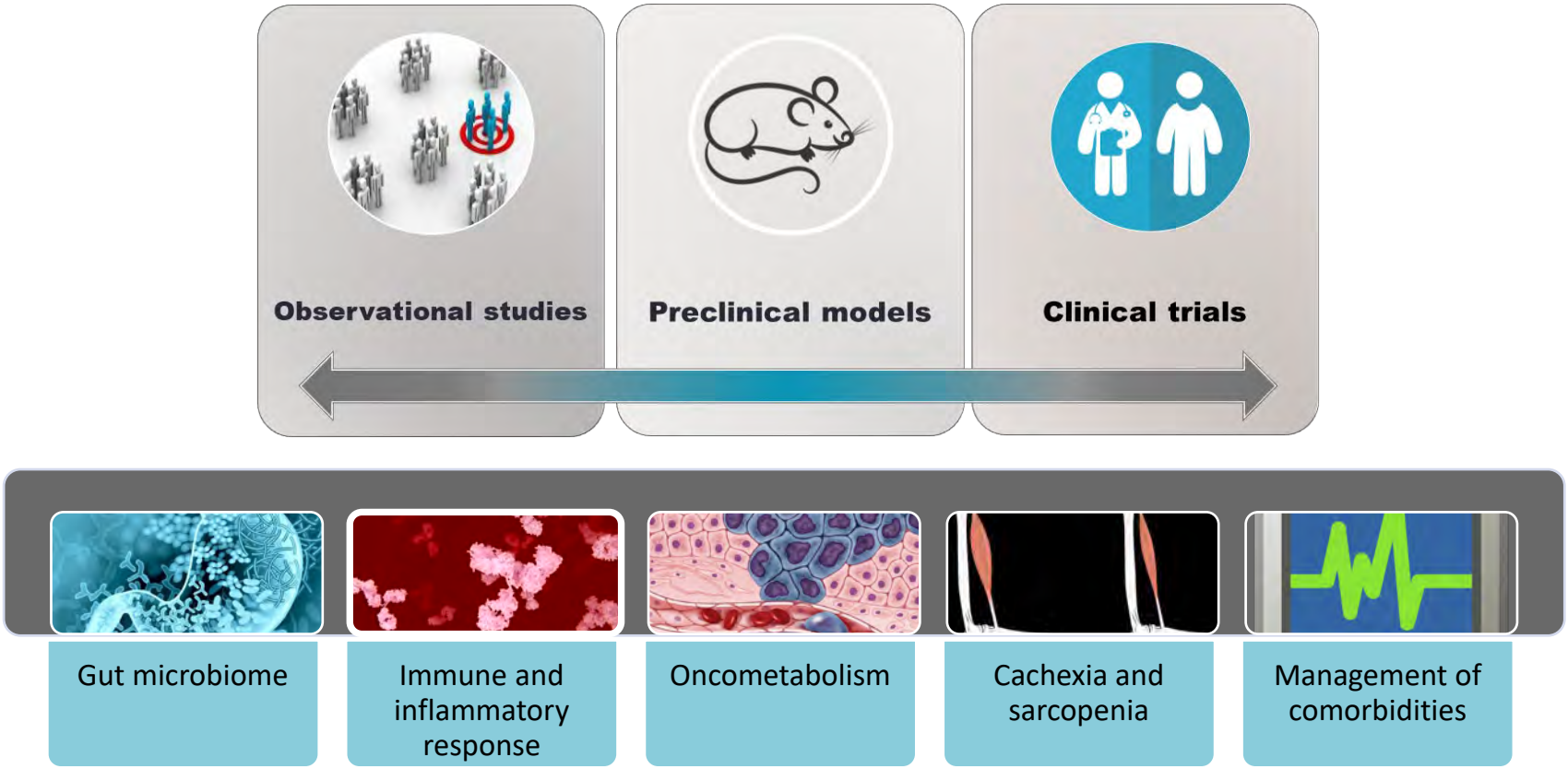
- No secret formula or evidence-based dietary guidelines for cancer patients.
- Lack of dietary data collection in trials and clinical cohorts
- Lack of prospective / interventional dietary studies demonstrating change in treatment response
- The best we can do is extrapolate from evidence-based cancer *prevention* guidelines

*Personal communication MD Anderson Clinical Nutrition

Whole patient = our focus



Clinic to lab and back



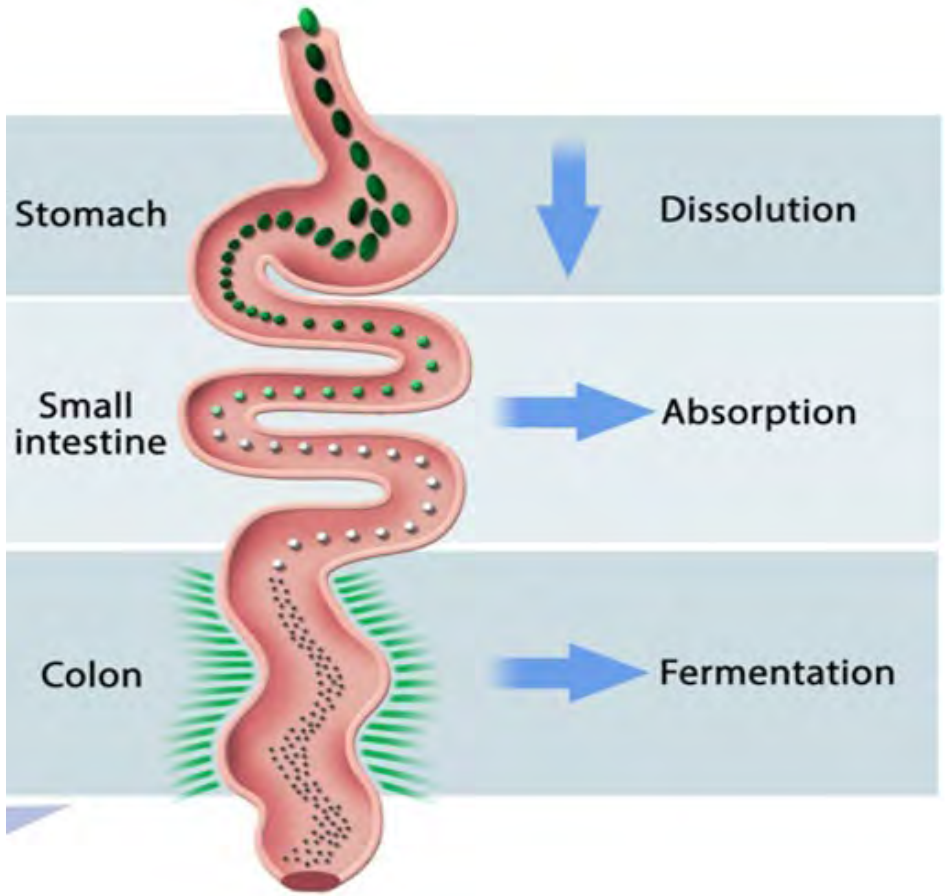
Research framework for moving from studies where we "observe" and follow patients for outcomes to specific preclinical and clinical studies to understand and target diet's biologic effects on cancer survival.

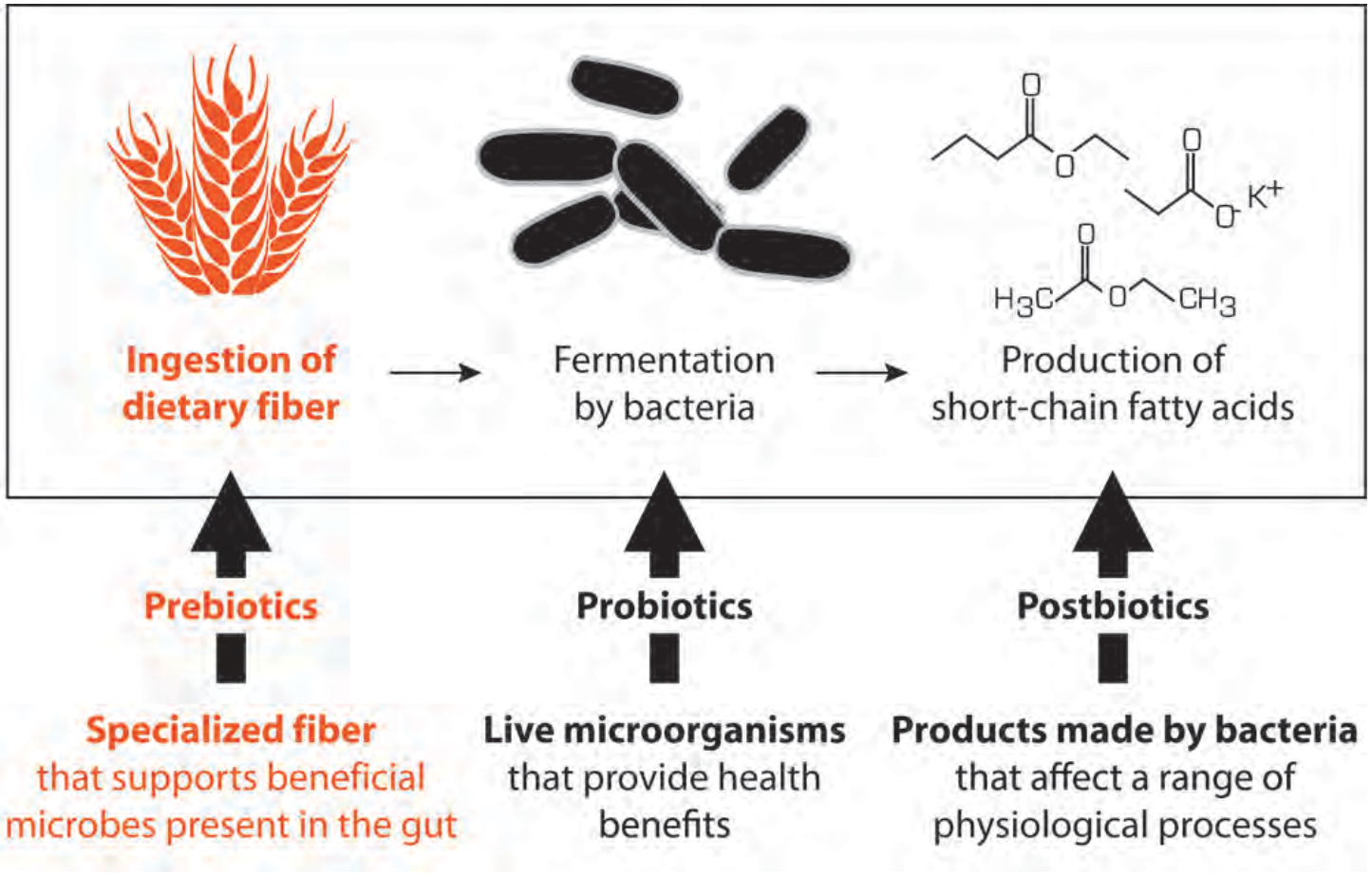
Prepared by CR Daniel

Human microbiome

multifaceted effects of dietary habits on human health

It begins with food and ends with… 💩





A range of factors are known to modulate the microbiome

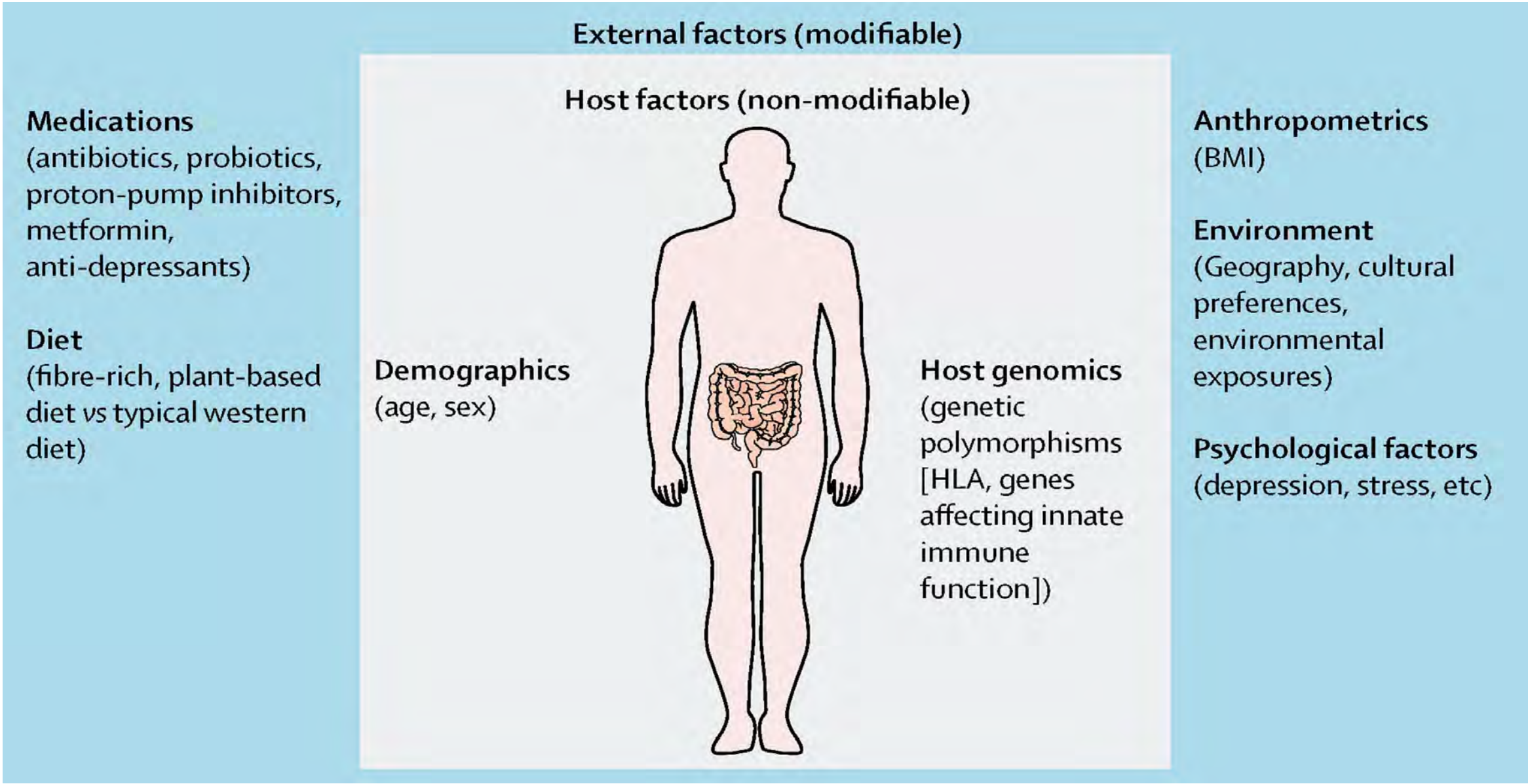
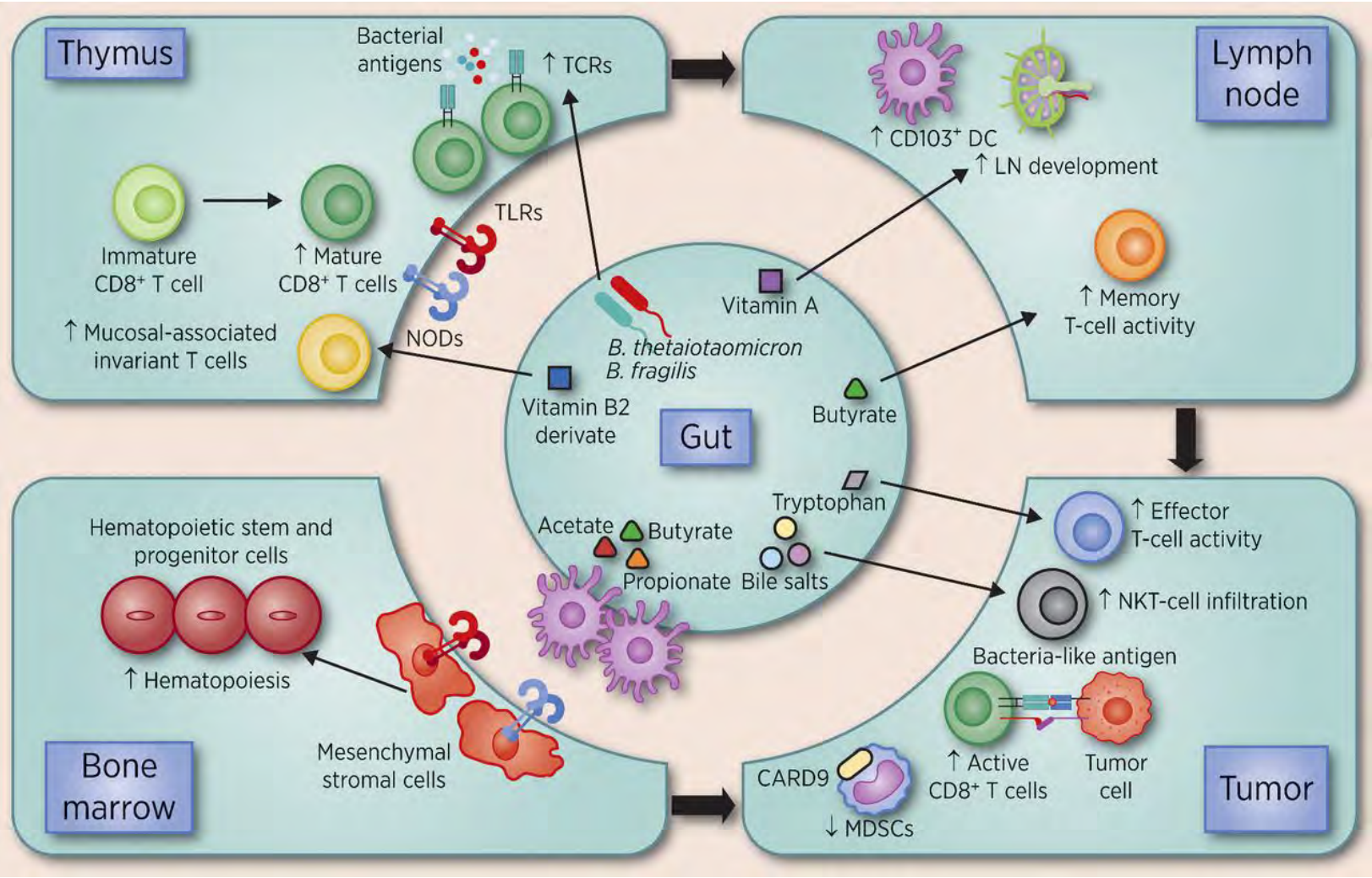


Figure in "Modulating the microbiome to improve therapeutic response in cancer," *Lancet Onc* 2019

The gut microbiome's effect on the immune system



The gut microbiota plays key roles in antitumor immunity via:

- metabolic modulation using vitamins, short-chain fatty acids, bile salts, or amino acids that promote favorable intracellular processes among host cells
- activation of pathogen recognition receptors
- molecular mimicry initiating immune responses against cancer antigens that are similar to bacterial ones

Figure in "Gut Microbiota and Antitumor Immunity: Potential Mechanisms for Clinical Effect", *Cancer Immunol Res* 2021

BE GONE Dietary Trial

Beans to Enrich the Gut microbiome vs. Obesity's Negative Effects

The goal of the trial is to test whether adding cooked dry beans to the usual diet of colorectal cancer survivors can improve healthy bacteria in the digestive system to improve overall health and reduce cancer risk.

Who is Eligible?

Overweight/obese, age 30 or older, history of colorectal cancer.

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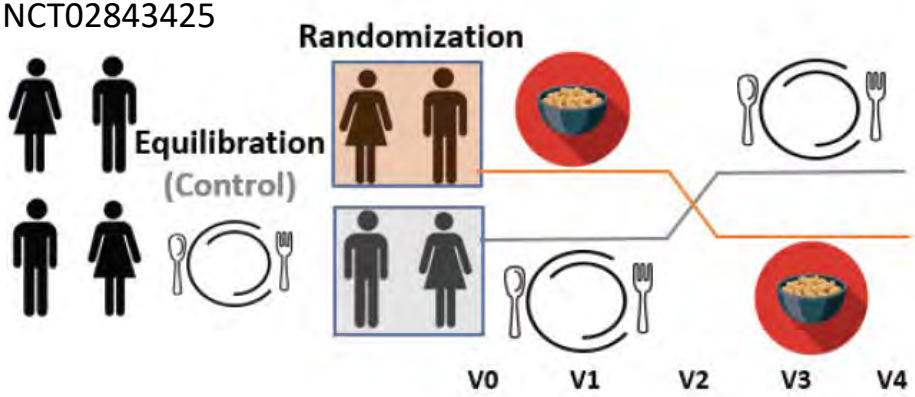
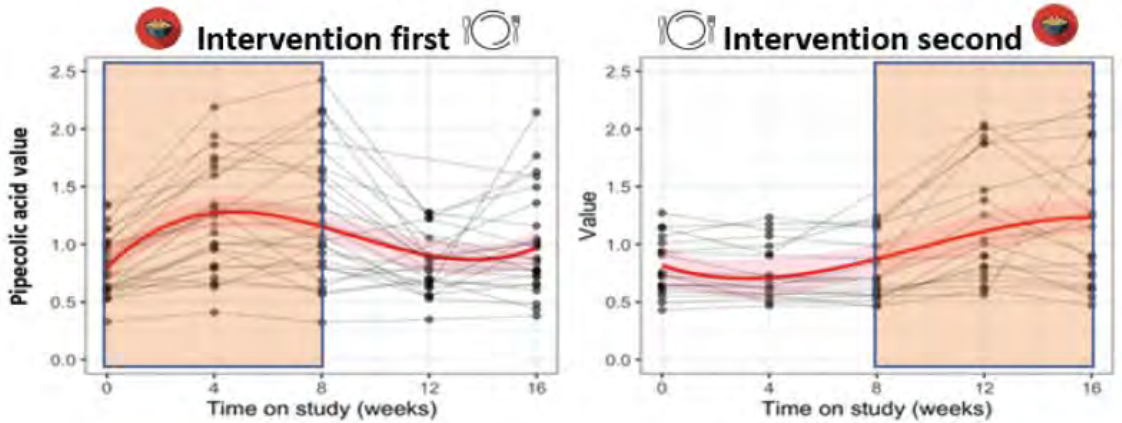
NCT02843425
closed/complete

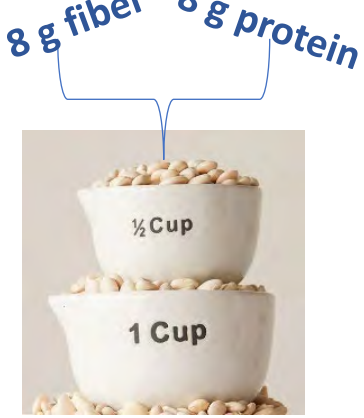
BE GONE Trial: Modulating the microbiome through a single prebiotic food source (beans) in colorectal cancer survivors

NCT02843425





- Surveillance colonoscopy and GI Med Onc follow-up patients with issues jointly managing gut and metabolic health (obese)
- Half on meds (statins and/or metformin)
- Adequate bowel length and “normalized” bowel habits



Dietary fiber, U.S. guidelines
14 g per 1000 kcal

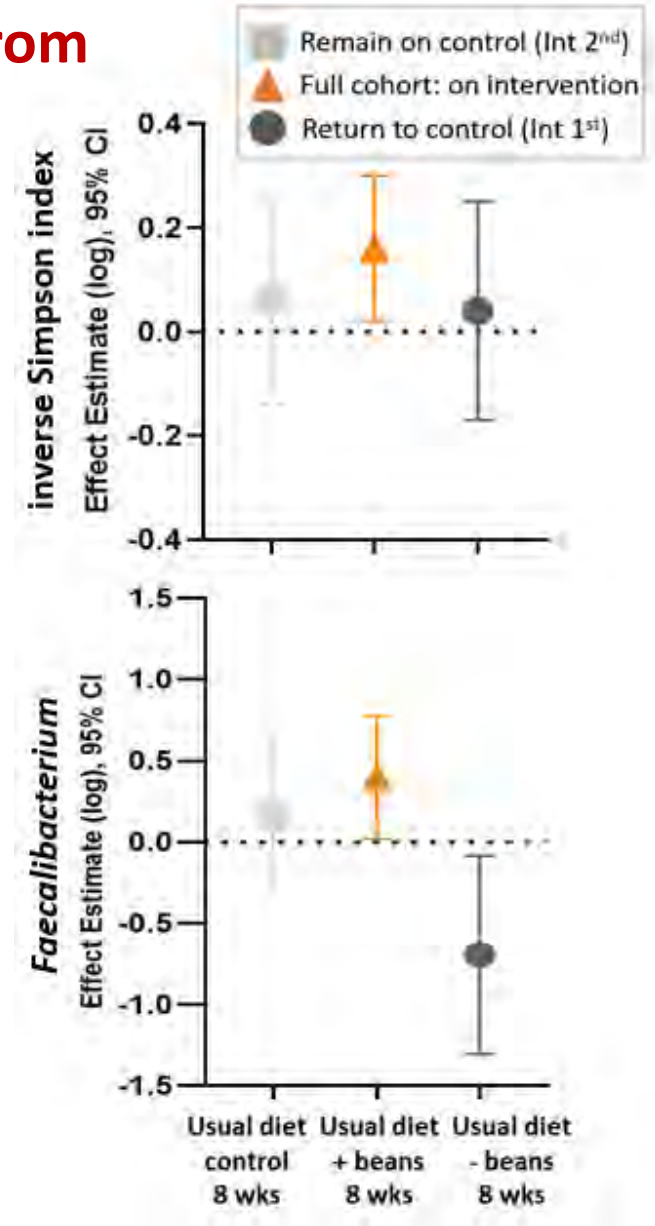
Zhang, Irajizad, Hoffman et al. 2023

eBioMedicine
Part of THE LANCET Discovery Science

Modulating a prebiotic food source (beans) influences inflammation and immune-regulating gut microbes and metabolites: insights from the BE GONE trial

Findings:

- 87% of 55 randomized participants completed the 16-week trial
- Carefully monitored and managed GI side effects
- 2 daily servings of beans↑ multiple bacteria indicative of prebiotic efficacy, including ↑ *Faecalibacterium, Eubacterium* and *Bifidobacterium* and overall diversity
- Circulating metabolome showed parallel shifts in nutrient and microbiome-derived metabolites that regressed upon returning to the usual diet
- Shifts in proteomic biomarkers of intestinal and systemic inflammatory response



NCT02843425

eBioMedicine
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BE GONE Trial: research in context

Evidence before this study

- The gut microbiome is increasingly implicated in patient outcomes from the management of obesity-related cardiometabolic conditions to cancer.
- Prebiotic foods offer a safe and accessible strategy to shape the composition and activity of the gastrointestinal microbiota and to confer benefits to the host's health via inherent dietary nutrients selectively fermented by the large intestine.

Added value of this study

- We conducted the trial in obese surveillance patients with a history of colorectal cancer and/or polyps—a group that may benefit from an intervention that targets both gut health and metabolic health but may have unique challenges when it comes to making and tolerating changes to diet.
- This highly accessible and adaptable prebiotic food intervention required patients to consume up to 1 cup per day of pressure-cooked, canned navy beans within the context of their usual diet (control); and was sufficient to enhance the diversity and composition the gut microbiome within 8 weeks with parallel shifts in host metabolites, immune and inflammatory biomarkers.
- Notably, the effect of returning to the usual diet without beans was quite striking with reversals in favorable changes.

Implications of all the available evidence

- Broad diet–microbiome interactions in clinical cohorts enforce a need for improved understanding of the effects of specific diet changes and predictable strategies to target and modulate the microbiome to ultimately improve outcomes and prolong survival.
- Insights from BE GONE, reflecting practical real-world dietary changes, offer a robust foundation for the development of microbiome-targeted dietary strategies, leveraging measurable host biomarkers toward enhanced patient outcomes.

NCT02843425

eBioMedicine
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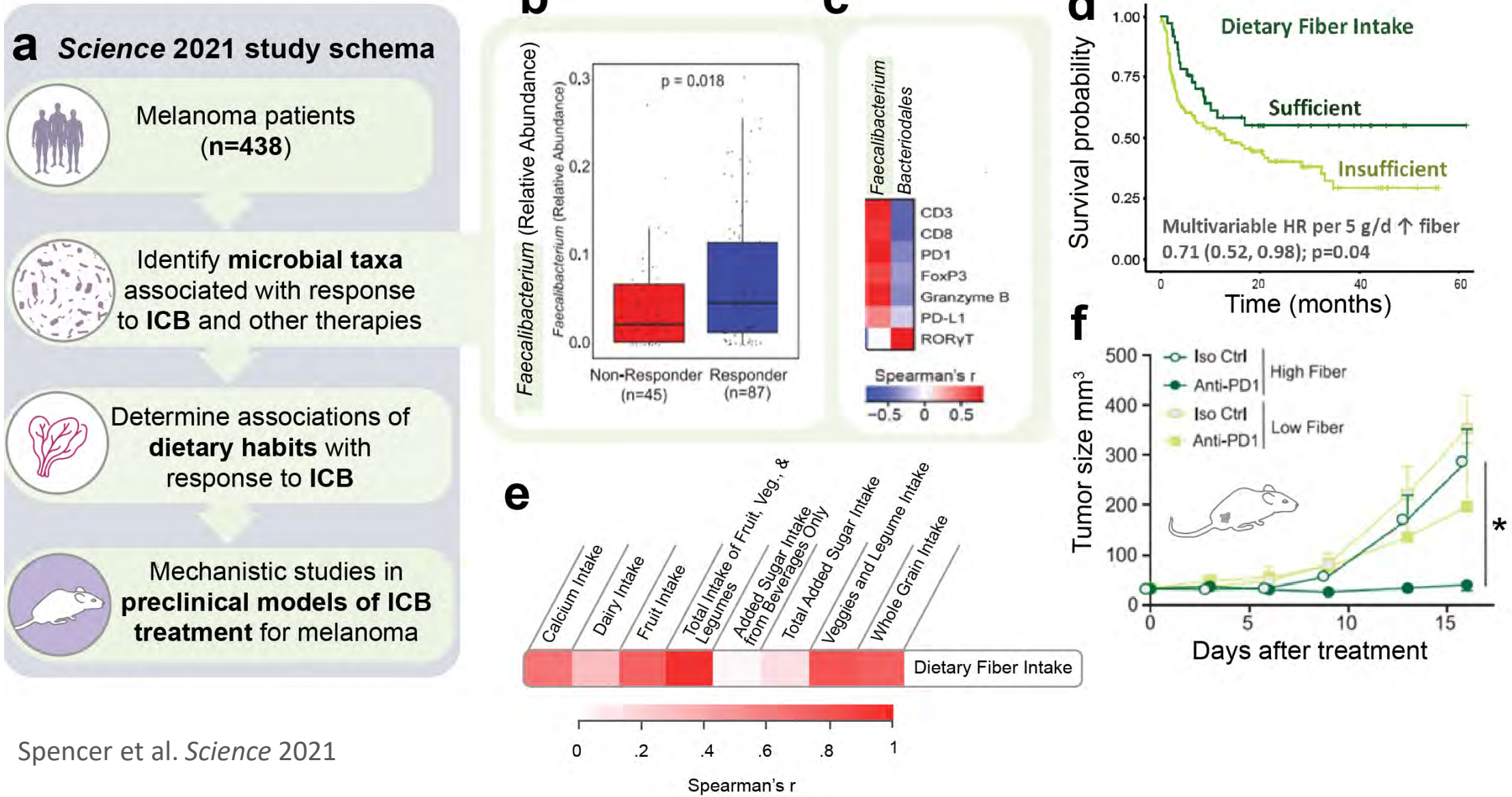
Faecalibacterium and dietary fiber linked to improved response and PFS in melanoma patients treated with immunotherapy



Spencer et al. *Science* 2021

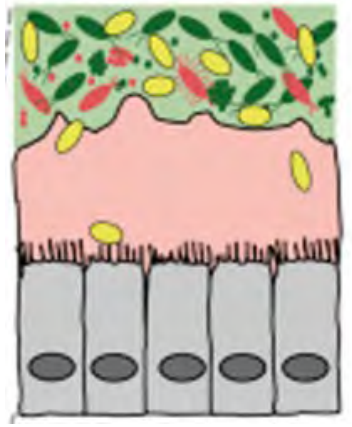
Considerations and challenges ahead to modulate a patient's microbiome

	Advantages	Disadvantages	Considerations
Faecal microbiota transplant	Transplantation of entire ecosystem; direct	Scalability (difficult to access and expensive); procedural risks; potential to transfer other diseases	Donor selection (complete responder to faecal microbiota transplant *vs* healthy donor); delivery mechanism; need for conditioning regimen; how to sustain; banking for potential future autologous transplant
Probiotics and bacterial consortia	Easy to use; affordable; accessible	Variable engraftment in setting of competing commensals; potential for lowering overall microbiome diversity; varying bioavailability; insufficient regulations on quality control	Use of spores *vs* live bacteria; which bacteria to include; personalisation; need for conditioning regimen
Prebiotics (eg, fibre supplements)	Easy to use; affordable; accessible	Whole food might be more important than isolated nutrient supplements (regulated as food rather than drugs)	Single fibre *vs* mixture; predictability of response given resident bacterial community
Diet	Holistic change that might have other health benefits	Low compliance; difficult to sustain; varied effects	Whether to target specific nutrients *vs* overall pattern; dose needed for target modulation; duration needed; predictability of modulation given host variation in microbiome and metabolism

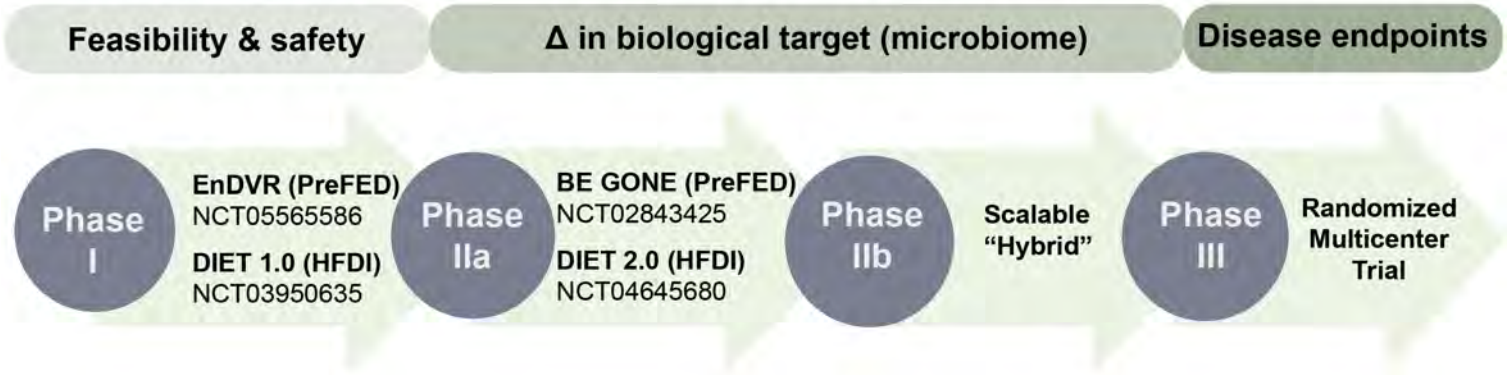
McQuade, Daniel, Helmink, Wargo *Lancet Onc* 2019

Diet to support the patient and the gut microbiome (the need for food is always there)

- Prebiotic foods provide multiple microbiota-accessible nutrients within a single “bite.”
- Support cross-feeding/symbiotic relationships between keystone bacteria (e.g., *Faecalibacterium* and *Bifidobacterium)* that maintain the overall gut ecosystem and modulate metabolites that selectively stimulate the growth of other beneficial bacteria.
- This could address the natural variability in microbiome communities between patients and over time.
- Multiple components of diet/whole foods = multipronged approach to mitigate “stress” within microbiota community
  - For example, common consequence of cytoxic cancer treatments (chemotherapy, radiation) and immune-related adverse events is the expansion of mucus-degraders in the gut—possibly due to poor nutrition/malnutrition—thins the intestinal mucus layer, allowing bacteria to enter the bloodstream and exposing the host to infection and inflammation



A phased approach to dietary intervention studies



End-Goal:

Diet interventions and/or rationally designed pre/pro/syn-biotics to improve disease outcomes

DIET 1.0: Fully controlled high-fiber feeding study in melanoma survivors

- Demonstrated feasibility
- Tolerable
- High compliance
- Shift in microbiome and circulating metabolites

BE GONE trial in overweight/obese colon cancer survivors

- Targeted food provision + counseling approach
- Tolerable
- Increases candidate taxa and diversity with reversion upon return to usual diet (control)
- Shifts in microbiome-derived metabolites, anti-inflammatory and immune markers

DIET 2.0: Controlled high-fiber feeding study melanoma (+RCC) patients starting SOC immunotherapy

- Completed
- Safe but challenging
- Correlative studies are on going

EnDVR (PreFED) trial in MD Anderson employees

- Prebiotic Food Enriched Diet (PreFED) optimized
- Randomized to PreFED snacks + nutritional counseling vs all high fiber meals
- >90% PreFED snack compliance and exceeded the target of +4 prebiotic food servings

Microbiome-targeted dietary intervention trials in relevant treatment settings

- Prebiotic food-enriched diet (PreFED) to enhance the microbiome and immunotherapy response in ***melanoma***:
  - PD1 refractory PreFED NCT06250335
  - Unresectable PreFED NCT06466434
  - Neoadjuvant PreFED NCT06548789

- To progress to a large, multisite trial, we need an effective, scalable strategy that can be delivered as part of the usual care and management plan, similar to prescriptive dietary regimens in other clinical settings that can be personalized and adapted to manage the underlying inflammatory process and symptom burden in parallel with drug therapies

Jennifer McQuade

Jennifer Wargo

Nadim Ajami

Nancy You

Jihye Yun

Scott Kopetz

Nutrition + microbome + YORC clinical and research dream teams

Some ideas

- Foods that provide fiber with protein and/or healthy fats: legumes (e.g., beans, nuts and peas), whole grains (e.g., oats, farro)
- Probiotic foods? Yogurt and cottage cheese also provide protein (skip sweet and overly processed versions)
- Easy snack examples providing fiber + protein + fatty acids:
  - Apple/banana with nut butter
  - Rye toast with smashed beans, avocado
  - Oatmeal with fruit, nuts, dark chocolate (or savory)
  - Cooked leafy greens and leeks in scrambled eggs
  - Blending whole (frozen) fruits and vegetables in smoothies with plain yogurt vs. juicing
- You do not have to “give up” all the foods that make you happy/are comforting or eat different/annoying meals outside of what works for your family
  - Resistant starch secret - chilled potatoes and rice
- Need a plan or label on your gut health-cancer therapy diet? Mediterranean diet with extra focus on protein (can include Mexican, Asian and even Southern cuisine)

Evidence-based resources

- MD Anderson Clinical Nutrition website → Nutrition Basics for Patients and Caregivers
- MD Anderson At the Table → searchable website of recipes coded by symptoms, texture, nutrient restrictions/needs and other criteria
  - https://atthetable.mdanderson.org/
- American Institute for Cancer Research → Cancer Survival tab (before, during and after treatment) and Resources tab
  - https://www.aicr.org/
- American Cancer Society → Nutrition and Physical Activity During and After Cancer Treatment: Answers to Common Questions
- Cleveland Clinic website provides a detailed “Mediterranean Diet: Food List & Meal Plan”

Research-driven / emerging concluding thoughts

- Scientific evidence supporting nutrition for gut health, metabolic health and immune health during cancer and cancer therapy is built on a backbone of adequate total energy (calories) and protein intake with an emphasis on foods rich in immune and inflammation-modulating nutrients and bioactive compounds.
- You may miss them if you are not eating enough plants or fiber-rich carbohydrates and aiming for a healthy balance of anti-inflammatory fat sources (e.g., fish, nuts, seeds, olive oil, avocados). Whole foods and lean proteins in cancer prevention dietary guidelines also provide vitamin D, calcium, B vitamins and other nutrients that are also important.
- Prebiotic (and some probiotic) foods provide multiple microbiota-accessible nutrients within a single “bite”. Support cross-feeding/symbiotic relationships between beneficial bacteria that maintain the overall gut ecosystem. This also helps to address the natural variability in microbiome communities between patients and over time. (Closest thing I’ve got to a one size fits all approach, but don’t forget food safety!)
- Ultra-processed foods typically lack these essential nutrients and contain various additives (emulsifiers, flavor enhancers) and other “hidden” ingredients that further challenge gut and immune health

Thank you to our patients who give their precious time and energy to research and to the families that support them!

cdaniel@mdanderson.org

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Melanoma Research Alliance

Andrew Sabin Family Fellowship

Moon Shot

Patient Mosaic

Additional *peer-reviewed foundation & philanthropic support for DIET* studies:

- Mark Foundation for Cancer Research
- Rising Tide
- Seerave Foundation
- Elkins Foundation