

# Role of nutrition in improving cancer treatment outcomes: *evidence, challenges, and future directions*



Milken Institute School  
of Public Health

THE GEORGE WASHINGTON UNIVERSITY

**GW** Cancer Center



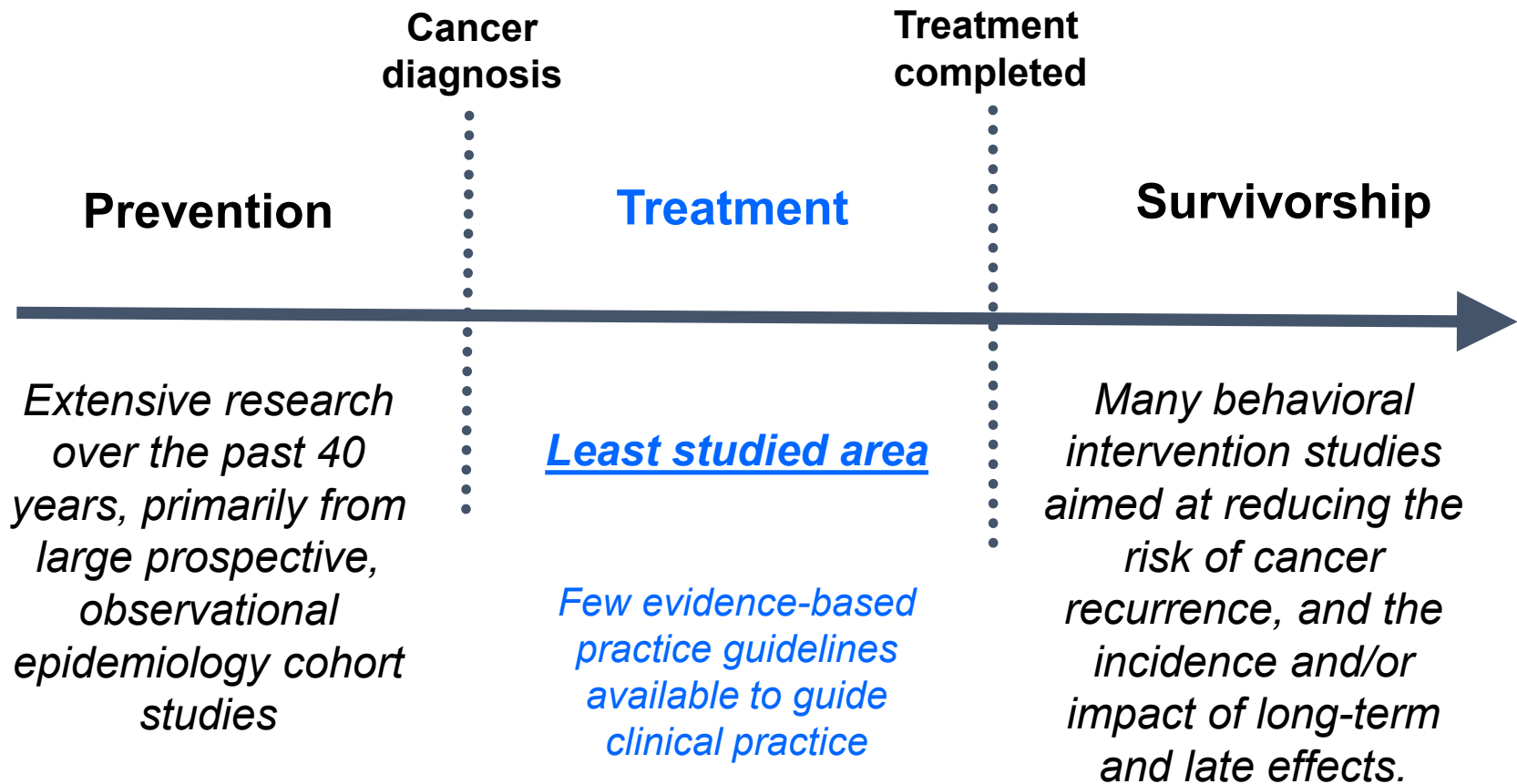
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MPI, ENICTO Coordinating Center

# Research on nutrition interventions across the cancer continuum



# Guidance for cancer survivors

World Cancer Research Fund



American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

## Diet, Nutrition, Physical Activity and Cancer: a Global Perspective

A summary of the Third Expert Report



World Cancer Research Fund International

World Cancer Research Fund UK

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund  
世界癌症研究基金會

Third Expert Report, 2018

<https://www.wcrf.org/diet-activity-and-cancer/global-cancer-update-programme/cancer-survivors>

*“The current evidence on breast cancer survivors, as reviewed by the CUP, has a number of limitations, including a lack of evidence from randomized controlled trials. In addition, the quality of most published studies is limited because they do not account for relevant factors such as cancer subtypes, type and intensity of treatment, and other illnesses. These limitations are also likely to apply to the evidence for survivors of other cancers.”*



# Guidance for cancer survivors

**CA:**  
**A Cancer Journal for Clinicians**



CA CANCER J CLIN 2022;72:230-262

## American Cancer Society nutrition and physical activity guideline for cancer survivors

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*“Nutrition and physical activity recommendations established recently by the ACS for the primary prevention of cancer are broadly relevant to survivors undergoing and immediately after cancer treatment”.*

# Guidance to clinicians: Evidence-based practice guidelines

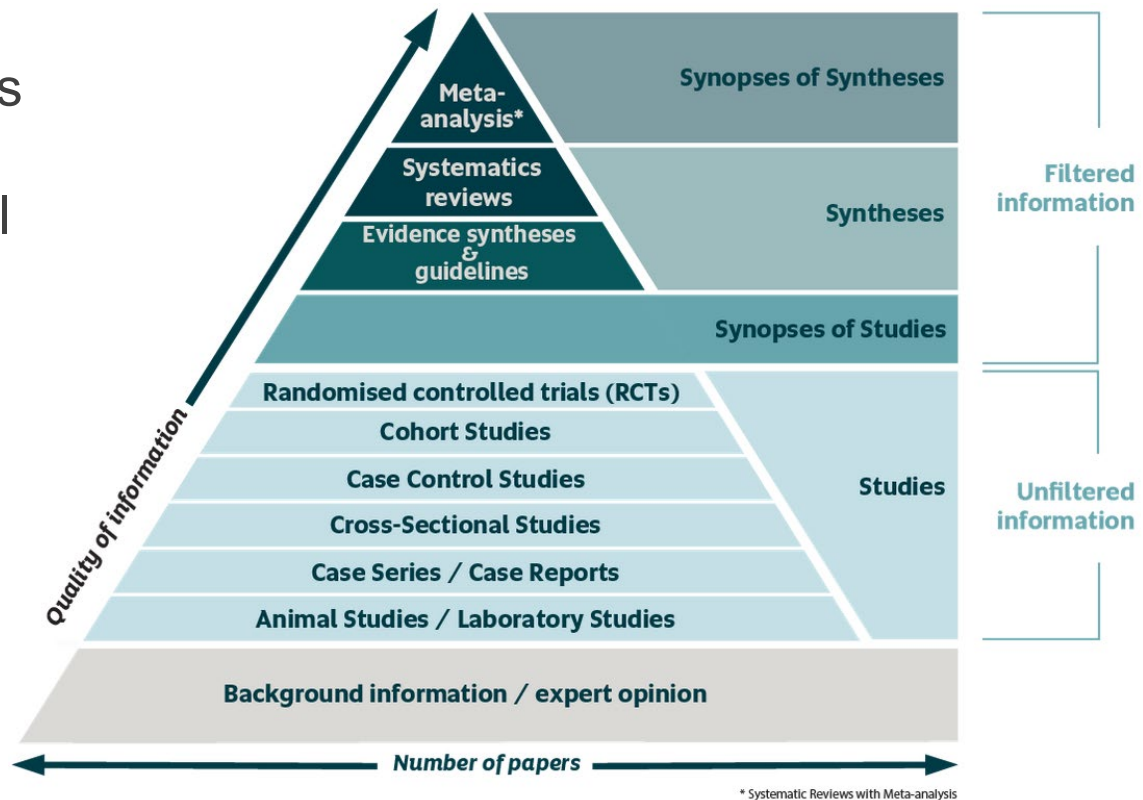


- Summarize best available evidence in the field
- If applied consistently, can standardize quality of care and improve outcomes

# Levels of evidence

Randomized controlled trials (RCTs) are generally considered the highest level of evidence for individual studies.

RCTs are designed to minimize the possibility of selection and information bias, confounding, and chance findings.



'Hierarchy of Evidence Pyramid' adapted from EBP & the Medical Librarian training manual, Duke University 2019, and [Online EBM Page Generator](#), Dartmouth College and Yale University 2019, under the license [CC-BY-NC](#).

Graphic courtesy of: <https://guides.library.unisa.edu.au/SystematicReviews/Protocols>

# Considerations with RCTs



- Randomization is not a “cure” for poor study design or small sample size
- Study population usually very specifically defined to minimize confounding, thus results may not be generalizable beyond the population that was studied.
- RCTs are conducted in very controlled settings that may not reflect the true patient experience
- For some questions, RCTs may not be possible or even the best study design.
- RCTs are often expensive to conduct, and may take 5 or more years to accrue sufficient numbers of participants

# Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline

Jennifer A. Ligibel, MD<sup>1</sup>; Kari Bohlke, ScD<sup>2</sup>; Anne M. May, PhD<sup>3</sup>; Steven K. Clinton, MD, PhD<sup>4</sup>; Wendy Demark-Wahnefried, PhD, RD<sup>5</sup>; Susan C. Gilchrist, MD, MS<sup>6</sup>; Melinda L. Irwin, PhD, MPH<sup>7</sup>; Michele Late<sup>8</sup>; Sami Mansfield, BA<sup>9</sup>; Timothy F. Marshall, PhD, MS<sup>10</sup>; Jeffrey A. Meyerhardt, MD, MPH<sup>1</sup>; Cynthia A. Thomson, PhD, RD<sup>11</sup>; William A. Wood, MD, MPH<sup>12</sup>; and Catherine M. Alfano, PhD<sup>13</sup>

Additional information is available at [www.asco.org/supportive-care-guidelines](http://www.asco.org/supportive-care-guidelines).

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*“Evidence for . . . dietary and weight loss interventions during cancer treatment was very limited”.*



# Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline

Diet-specific question: Does consuming a particular dietary pattern or food(s) during cancer treatment safely improve outcomes related to quality of life, treatment toxicity, or cancer control?

## Methods:

- Only data from individual RCTs or systematic reviews of RCTs were considered.
- Patients with head and neck cancer were excluded from the diet systematic review “because of their unique nutritional challenges”.
- The guideline does not address dietary supplements, cancer cachexia, malnutrition, enteral or parenteral nutrition.
- Interventions considered included: dietary counseling, specific diets (e.g. ketogenic), fasting, functional foods/other changes to dietary composition, weight loss/avoidance of weight gain
- Literature search included studies published between January 1, 2000 – May 17, 2021.

# Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline

Results: Only eight nutrition RCTs (11 publications) met the inclusion criteria.

*“Overall, the quality of evidence was higher for exercise interventions than for dietary interventions in this population.”*

*“There is currently insufficient evidence to recommend for or against dietary interventions such as ketogenic or low-carbohydrate diets, low-fat diets, functional foods, or fasting to improve outcomes related to quality of life, treatment toxicity, or cancer control.”*

*“The heterogeneity of the RCTs that have been conducted and the limited number of rigorously designed studies with robust sample sizes make it difficult to develop recommendations.”*

# Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline

## Discussion:

*“The lack of guidance in these areas should not be interpreted as a statement that dietary change and weight management have no value in patients during or after cancer treatment.”*

*“Our goal was to . . . . underscore the need for more research in areas where evidence is currently insufficient to provide concrete recommendations, in hopes that future guidelines will provide a more comprehensive blueprint to improve short-term and long-term outcomes in patients undergoing cancer treatment.”*

# Pathways to Prevention (P2P) Program



## Nutrition as Prevention for Improved Cancer Health Outcomes

July 2022



<https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/nutrition-prevention-improved-cancer-health-outcomes>

# Pathways to Prevention (P2P) Program



## Nutrition as Prevention for Improved Cancer Health Outcomes

July 2022

### Key questions (KQ) for the systematic literature review:

- In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutrition interventions before (KQ1) or during (KQ2) cancer treatment in preventing negative treatment outcomes such as effects on dose tolerance, hospital use, adverse events, and survival?
- What is the effect of nutrition interventions before or during cancer treatment on associated symptoms such as fatigue, nausea, vomiting, appetite, physical and functional status and quality of life (KQ3)?

# Pathways to Prevention (P2P) Program



## Nutrition as Prevention for Improved Cancer Health Outcomes

July 2022

### Key questions (KQ) for the systematic literature review - continued:

- In adults diagnosed with cancer who are overweight or obese, what is the effect of nutrition interventions intended for weight loss before or during cancer treatment in preventing negative treatment outcomes such as effects on dose, hospital use, adverse events, and survival (KQ4)

# Pathways to Prevention (P2P) Program



## Nutrition as Prevention for Improved Cancer Health Outcomes

July 2022

### Methods for the systematic literature review:

- Literature search limited to:
  - Randomized controlled trials (RCTs)
  - Published in English
  - Randomly assigned at least 50 participants
- Literature search included studies published between January 1, 2000 – July 2022.

# Pathways to Prevention (P2P) Program



## Nutrition as Prevention for Improved Cancer Health Outcomes

July 2022

### Results of the systematic literature review:

- 206 RCTs described in 219 publications met the eligibility criteria
- Studies were predominantly conducted in populations with gastrointestinal and head and neck cancers
- Almost all studies were conducted outside of the US
- The reviewers were struck by the lack of adherence to basic reporting standards (e.g. Consolidated Standards of Reporting Trials (CONSORT) statement) of the included studies
- Nutrition interventions varied significantly, and outcome often poorly defined
- Literature broadly lacked a clear conceptual framework describing how each intervention would be expected to improve outcomes.



# Pathways to Prevention (P2P) Program



## Nutrition as Prevention for Improved Cancer Health Outcomes

July 2022

### Results of the systematic literature review:

*“Two decades of randomized trial evidence on nutrition interventions for adults prior and/or during cancer treatment provide only limited high-quality evidence to improve cancer treatment outcomes.”*

### Recommendations:

1. Standardizing definitions and taxonomies for populations, interventions, and outcomes
2. Improving rigor in the primary intent, design and reporting of studies
3. Coordinating efforts to develop detailed conceptual frameworks for mechanisms of nutrition interventions across patient nutrition risk categories, cancers and treatments.



Contents lists available at [ScienceDirect](#)

## Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>



ESPEN Guideline

2021, PMID: 33946039

### ESPEN practical guideline: Clinical Nutrition in cancer

43 recommendations on all aspects of oncology nutrition care (screening, assessment, interventions - not limited to parenteral/enteral nutrition support):

- Most with low/very low (31, 72%) or moderate (7, 16%) level of evidence
- 5 recommendations with high level of evidence:
  - Maintain or increase physical activity to support muscle mass, physical function, metabolism
  - Consider use of corticosteroids and progestins for appetite stimulation
  - Use of enhanced recovery after surgery (ERAS) protocols for patients scheduled for curative or palliative surgery
  - Use of oral/enteral immunonutrition (e.g. arginine, n-3 fatty acids) nutritional supplements for patients with upper GI cancers undergoing surgical resection

# Site specific oncology nutrition practice guidelines – head and neck cancer

## **UK National Multidisciplinary Guidelines: Nutritional management of head and neck cancer** (PMID: 27841109)

- R (evidence-based recommendation): 18 recommendations (64%)
- G (good practice point/clinical experience): 10 recommendations (36%)

**American Society for Parenteral and Enteral Nutrition (ASPEN) Nutrition Guidelines for Adult Head and Neck Cancer** are currently under development (<https://www.nutritioncare.org/clinicalguidelines/>)

# Older oncology nutrition guidelines

- **Academy of Nutrition and Dietetics (AND)** - Oncology Nutrition Guidelines (2011-2013)
- **American Society for Parenteral and Enteral Nutrition (ASPEN)**: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation (2009, PMID: 19713551)
- **Clinical Oncology Society of Australia (COSA)** - Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer (2011)

# Why the lack of evidence on the role of nutrition during cancer treatment?



Historical concerns with nutrition intervention studies:

- Patients being overwhelmed with their cancer diagnosis
- Competition with other oncology treatment trials
- Concern that nutrients may feed cancer growth and progression

More recently: solitary focus on RCTs

# Challenges in oncology nutrition research

- More than 100 different types of cancer, each with different treatment regimens and different nutrition-related issues to be addressed
- Current dietary assessment tools can be burdensome to participants, and measurement errors are concerns
- Lack of common terminology (e.g. “malnutrition”)
- Lack of common data collection and reporting
- Limited research funding



# Building a stronger base to support future oncology nutrition RCTs



## Need:

- More basic science research to better understand mechanisms by which nutritional status/dietary factors alter treatment outcomes
- More clinical observational data to guide RCT development
  - Documenting the prevalence of nutrition issues
  - Hypothesis generation
  - Prioritization of issues
  - Clues for dose finding

# Include clinical observational research in evidence-based practice guidelines

- Well designed clinical observational studies with rigorous data collection and reporting is better than poor quality RCTs and “expert consensus”
- May better represent “real world” patient experience than data from a tightly controlled RCT?

WCRF/AICR, American Cancer Society and Academy of Nutrition and Dietetics evidence analysis processes already include large, high-quality observational studies





# Real World Data (RWD)

## Real World Evidence (RWE)

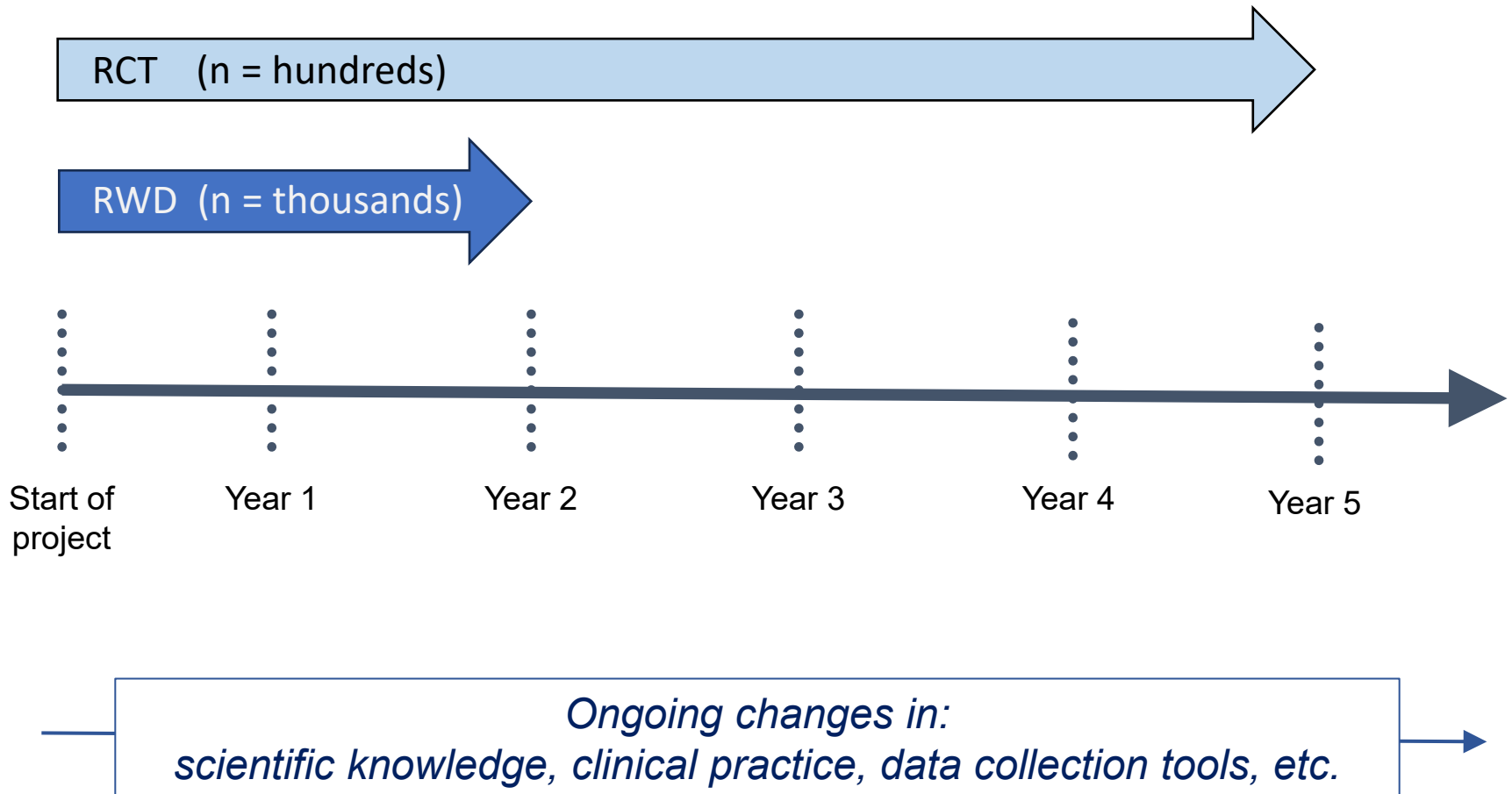
- Big data sets from a variety of sources, including electronic health records, medical claims data, registries, patient-reported data, wearables
- Can be used to conduct pragmatic studies, “target trial emulation” studies
- Accelerating the pace of oncology research exponentially

Need large data sets to be able to stratify on key demographics and clinical factors (e.g. cancer subtypes, treatment regimens)

**BUT:** Dietary intake and body composition are not currently captured in these data sets



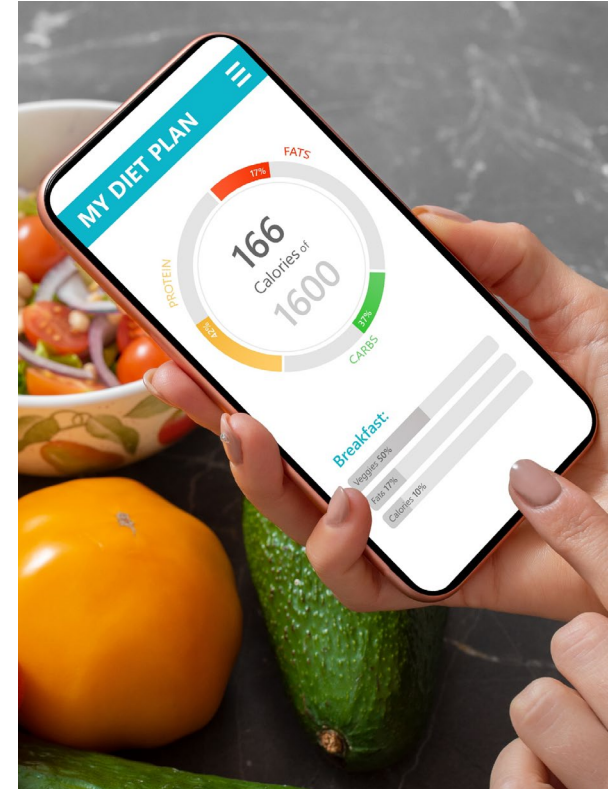
# RCTs vs. RWD studies



# Overcoming the challenges: Collecting nutrition-related data

Improving accuracy and ease of dietary intake reporting:

- Electronic tools for dietary assessment  
e.g. NCI's ASA24 and DHQ, VioScreen, DietID
- Include these dietary assessment tools with patient intake surveys?



# Overcoming the challenges: Collecting nutrition-related data

Routinely collect and report other nutrition-related variables, such as:

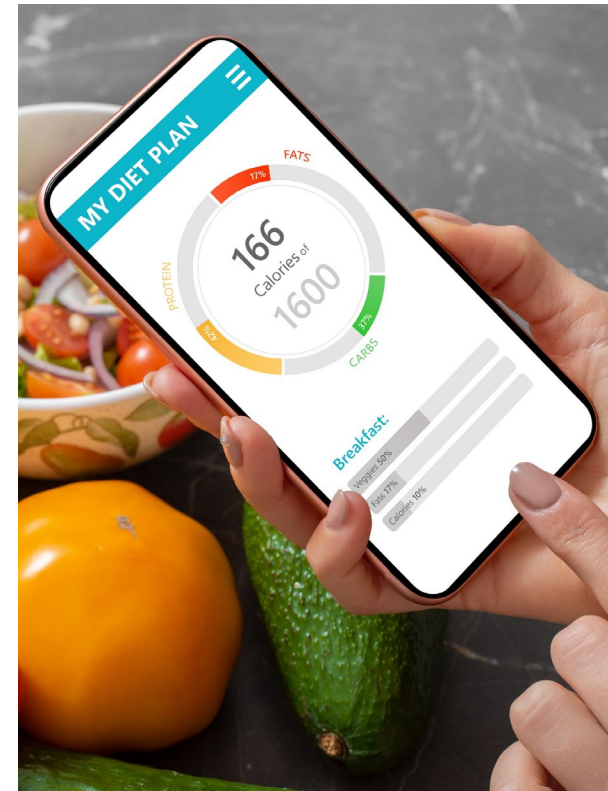
## Malnutrition:

- Global Malnutrition Composite Score (GMCS) electronic Clinical Quality Measure (eCQM)
- Small Business Innovative Research (SBIR 2023 – Topic 459): Automated Software for Point-of-Care Testing to Identify Cancer-Associated Malnutrition

## Nutrition impact symptoms:

Patient Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Food security status: Hunger Vital Sign



# Need for routine oncology nutrition data collection and reporting

## Example of the problem:

Current knowledge on the prevalence of malnutrition or food insecurity among people being treated for cancer comes from cobbling together data from individual studies or from large administrative datasets

In 2017, AACR, ACS, ASCO and NCI called for routine collection of data on the social determinants of health, including food security status, followed by *“meaningful action and continued monitoring to ensure that the action was successful”*.



# Need for routine oncology nutrition data collection and reporting



Need further discussion on which data elements should be routinely collected and reported

Work with electronic health record companies to develop structured data fields for nutrition-related data collection

What data collection/reporting can/should be:

- Patient-reported
- Automated (e.g. malnutrition scores, body composition estimates from routine imaging)
- Documented by the dietitian?

# Rigor

Guidance on rigorous conduct and reporting of clinical observational research:

Observational study reporting should follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (PMID: 18313558)

FDA guidance on the Use of Electronic Health Record Data in Clinical Investigation

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry>

Ramsey SD, Onar-Thomas A, Wheeler SB. Real-World Database Studies in Oncology: A Call for Standards. *J Clin Oncol* February 2024 (PMID: 38320235)

# ENICTO Consortium



The **Exercise and Nutrition Interventions to Improve Cancer Treatment-related Outcomes (ENICTO)** Consortium is a collaborative research program funded by the National Cancer Institute

Primary research question:  
Does exercise during chemotherapy improve the patient's ability to receive all scheduled chemotherapy?



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Web: [enicto.org](http://enicto.org)  
Twitter: [@ENICTO\\_Study](https://twitter.com/ENICTO_Study)  
Instagram: [enicto\\_consortium](https://www.instagram.com/enicto_consortium)  
Facebook: [Enicto Study](https://www.facebook.com/EnictoStudy)





# ENICTO project teams



study	cancer	intervention	delivery site	end point	N	U01 MPIs	recruitment sites
TNT	<b>rectal</b> <i>(locally advanced)</i>	aerobic exercise	home with real-time monitoring	RDI	225	*Scott, Jessica Cercek, Andrea	Memorial Sloan Kettering
 TEAL <small>Trial of Exercise And Lifestyle in Women with Ovarian Cancer</small>	<b>ovarian</b>	aerobic exercise strength training nutrition	clinic and home-based	RDI	200	Irwin, Melinda Crane, Tracy	Yale, University of Miami
 ACTION	<b>colon</b>	aerobic exercise	home with virtual monitoring	RDI	219	*Brown, Justin Meyerhardt, Jeff Caan, Bette	LSU, Dana Farber, Kaiser Permanente of Northern California
 thrive <small>sixty-five</small>	<b>breast</b> <i>(age ≥ 65yrs)</i>	aerobic exercise strength training nutrition	clinic-to-home with tele-health monitoring	RDI	270	Schmitz, Katie Ligibel, Jennifer Berger, Nathan	Pittsburgh, Dana Farber, Case Western

\*Recent New Investigators. Abbreviations: RDI = relative dose intensity

GW serving as the ENICTO Coordinating Center (MPIs: Scott Evans, Kim Robien)

# Dietary interventions



The ovarian cancer project (TEAL study) is the only ENICTO group to include a full dietary intervention component

- 18 weekly (30 minute) sessions with an RD
- $\geq 5$  servings of fruit and vegetables/day
- $\geq 25$  g fiber/day
- 1.2 g protein/kg/day
- $\leq 30$  g added sugar/day
- $< 18$  oz red meat/week
- $\geq 64$  fl oz water/day
- Avoid alcohol

The breast cancer project (THRIVE 65) is encouraging adequate dietary protein intake (1.2 g/kg body weight) to maintain muscle.

# Dietary data collection



ENICTO teams will collect the following data:

- 24-hour dietary recall data from participants at baseline and at the end of treatment/intervention
- Dietary supplement use
- Nutrition-impact symptoms at each chemotherapy cycle (PRO-CTCAE)
- Malnutrition (PG-SGA)
- Food security status



At the end of the funding period (~July 2027), a de-identified dataset will be made available to the broader research community through one of the controlled-access data repositories maintained by the NIH, such as dbGAP

# Planned cross-consortium nutrition questions

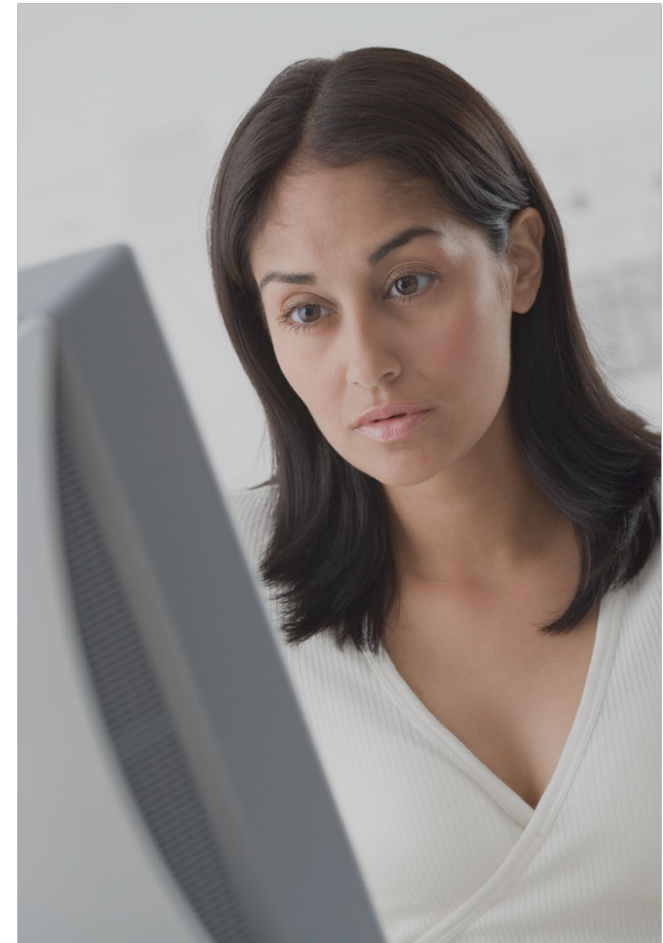


Planned nutrition-related research questions:

- Documenting the clinical course of nutrition impact symptoms during cancer treatment
- Association between baseline diet quality and RDI
- Evaluating how diet quality changes from pre- to post-treatment
- Additional questions to be determined

Pilot projects underway:

- Feasibility of continuous glucose monitoring
- End of intervention participant survey on preferred sources of diet and physical activity information



# What do evidence-based practice guidelines look like in the era of precision nutrition?



“Providing the right treatment at the right time to the right person taking into account patients’ health history, genes, environments, and lifestyles” - *Precision Medicine Initiative*

<https://obamawhitehouse.archives.gov/the-press-office/2016/02/25/fact-sheet-obama-administration-announces-key-actions-accelerate>

In the future, we will tailor nutrition interventions to the patient’s cancer type and planned treatment regimen AND their: comorbidities, social determinants of health, readiness for behavior change, chronobiology, genetics, metabolomics, microbiome . . . .

Large datasets will be needed!

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*especially the members of the  
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<http://enicto.org>



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