Medical Nutrition Therapy in Cancer Patients
Basic to Frontier in Onconutrition

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Outlines

- Cancer Cachexia and Metabolic Alteration
- Medical Nutrition Therapy (MNT)
- Immunonutrients
- Cancer Prevention

  Data from World Cancer Research Fund (WCRF)
- Frontier Onconutrition

Weight Loss and Malnutrition among Cancer Treatment

Diagnose
Loss of weight and muscle

50%

of cancer patients have some Nutrition deficit prior to diagnosis

Treatment
Continued loss of weight and muscle

85%

of patients experience malnutrition and weight loss at some point during cancer treatment

Cachexia
Distinct Metabolic Change

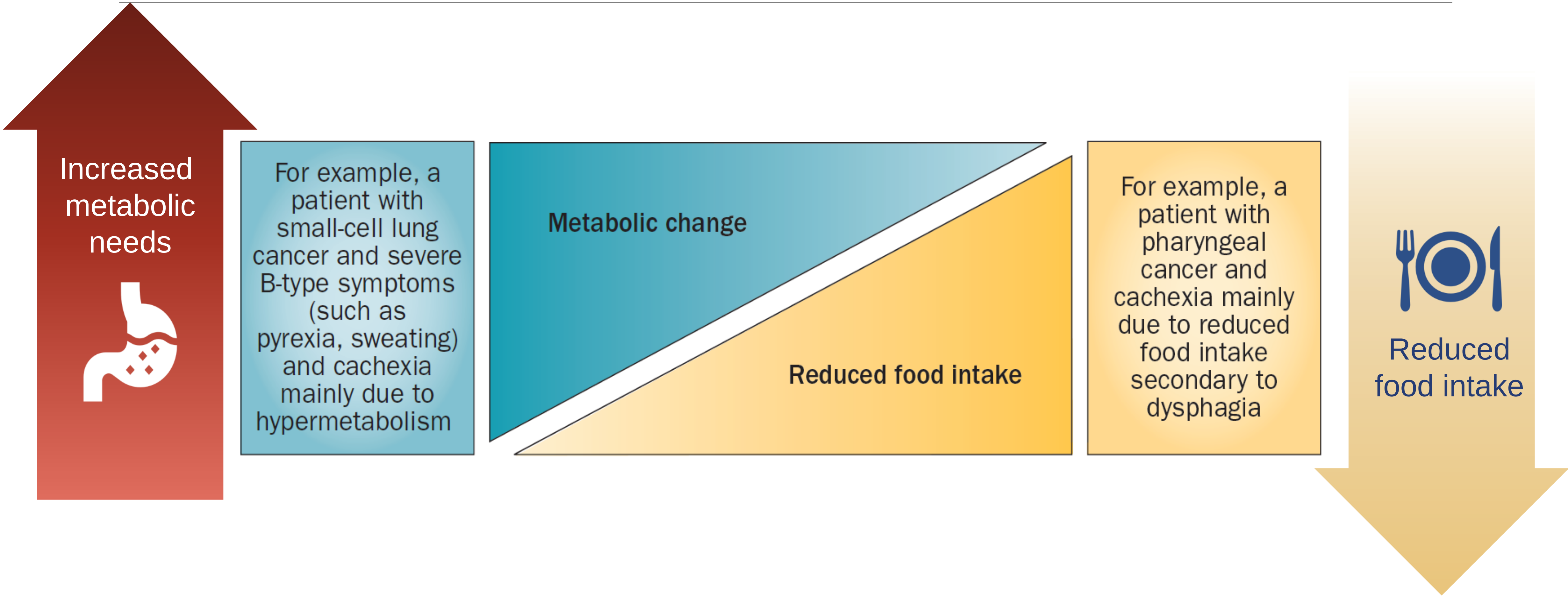
50%

of all patients with cancer eventually develop a syndrome of cachexia

1. Halpern-Silveria D, et al. *Support Care Cancer.* 2010;18:617-625 2. Dewys WD, et al. *AM J Med.*1980;(4):491-497
2. 3. Laviano A, et al. *Nutrition*. 1996;12;358-371 4. Aoyagi T, et al. *World journal of gastrointestinal oncology*. 2015 Apr 15;7(4):17.

Metabolic Alteration during Cancer Cachexia

Metabolic Change during Cancer Cachexia

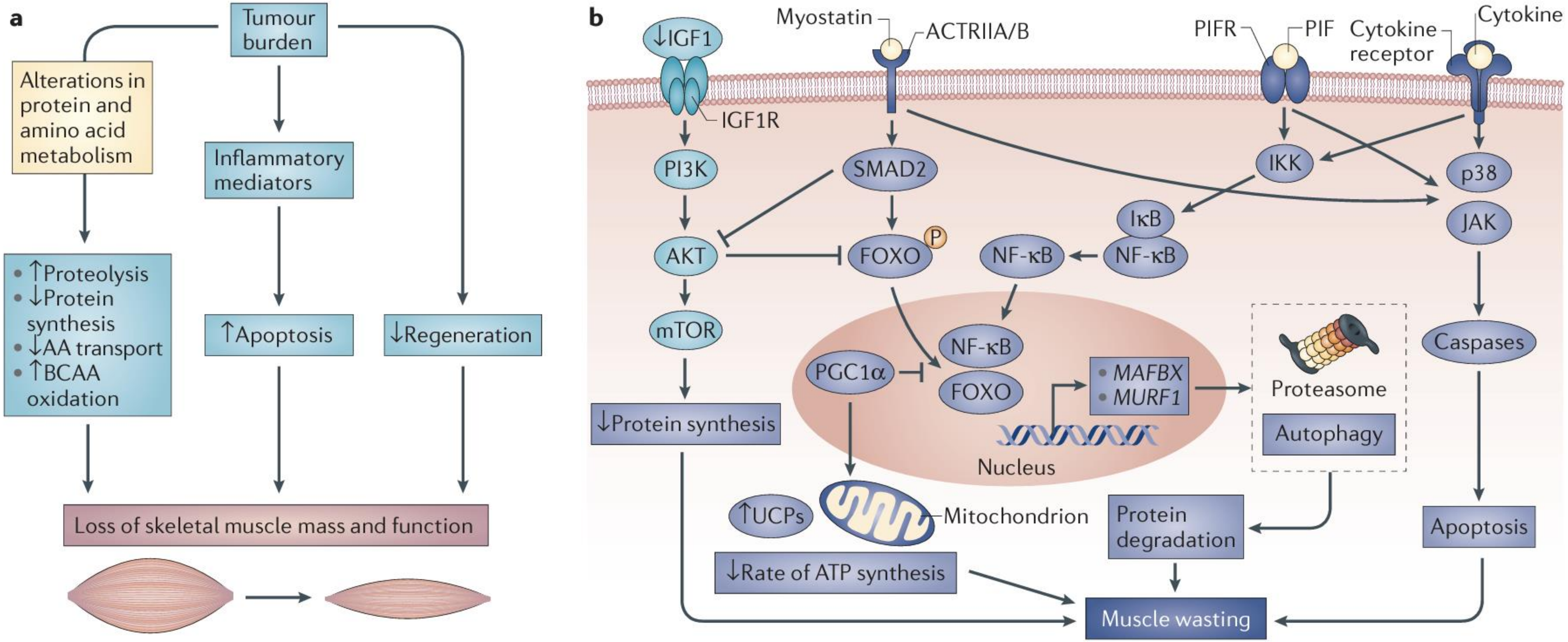


Fearon, K. et al .Understanding the mechanisms and treatment options in cancer cachexia. Nat. Rev. Clin. Oncol. 10, 90–99 (2013)

Metabolic change during Starvation and Cancer Cachexia

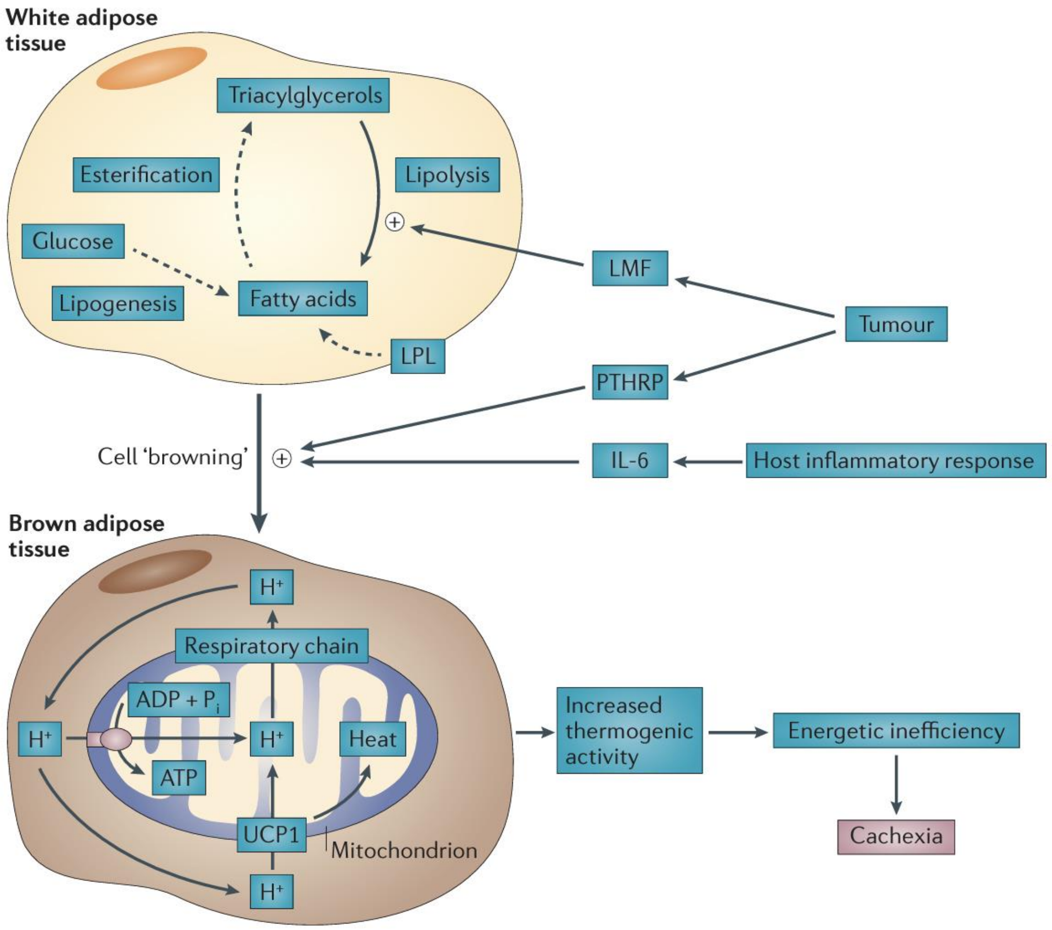
Physiologic characteristic	Starvation-related, none inflammation, Hypometabolic	Stress-related, with inflammation, Hypermetabolic
Metabolic rate	↓	↑
Cytokines, Catecholamine, Glucagon, Cortisol	↓	↑
Gluconeogenesis	↓	↑
Proteolysis	↓	↑↑
Protein turn over	↓	↑
Fat catabolism	↑	↑↑
Albumin	Normal	Decrease, Edematous
Adaptation to starvation	Normal	Abnormal

Alterations in Metabolic Pathways and Intracellular Signals of Muscle Wasting



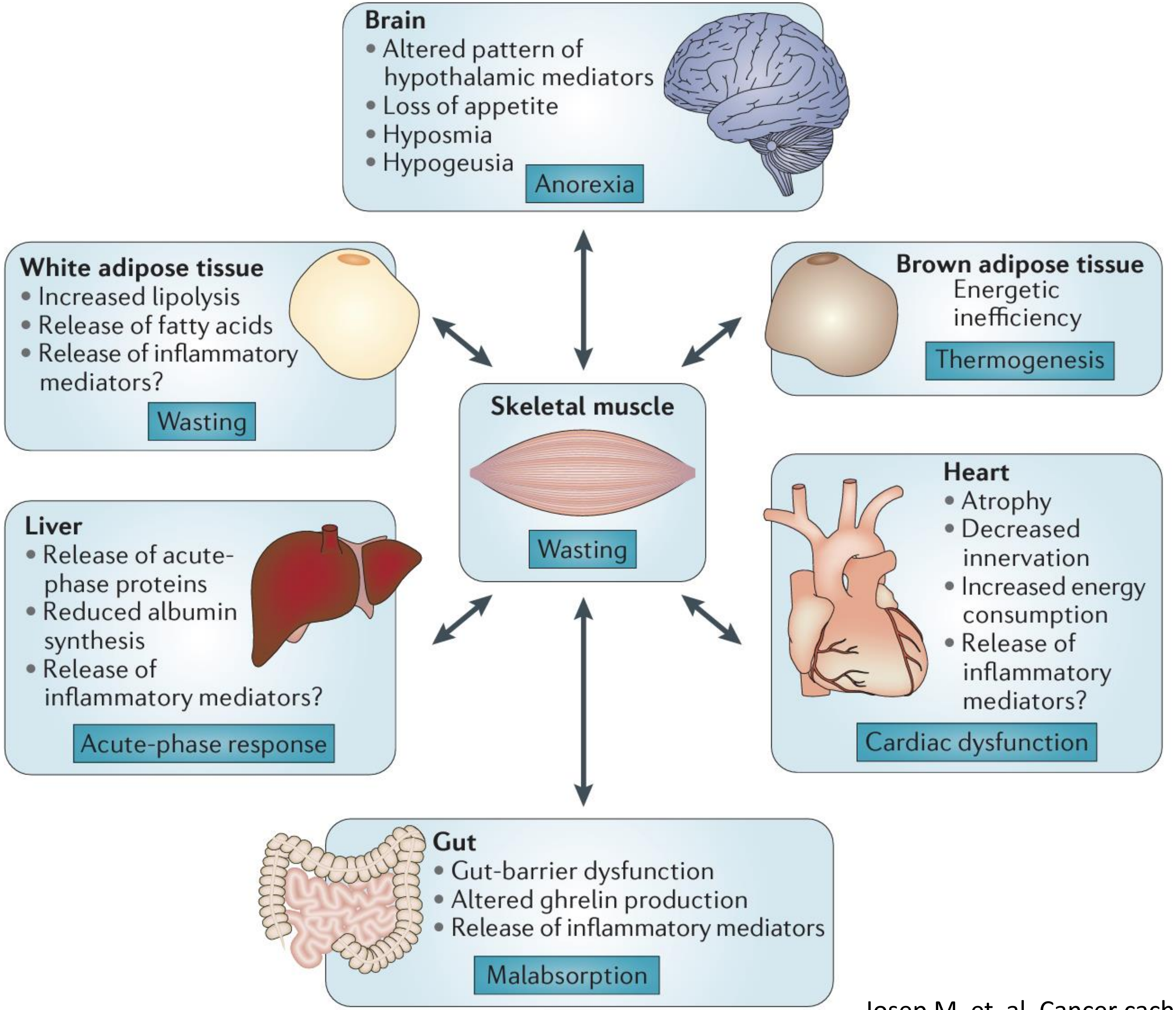
Josep M. et al. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer. 2014

Alterations in Metabolic Pathways in Adipocyte and Browning Adipose Effect



- Lipid Mobilizing Factor (LMF)
  - Adipose tissue wasting
  - Increase lipolysis
  - Decrease LPL activity
- Inflammatory Response
  - Browning adipose tissue
  - Promote UCP1
  - Heat production
  - Energetic inefficiency

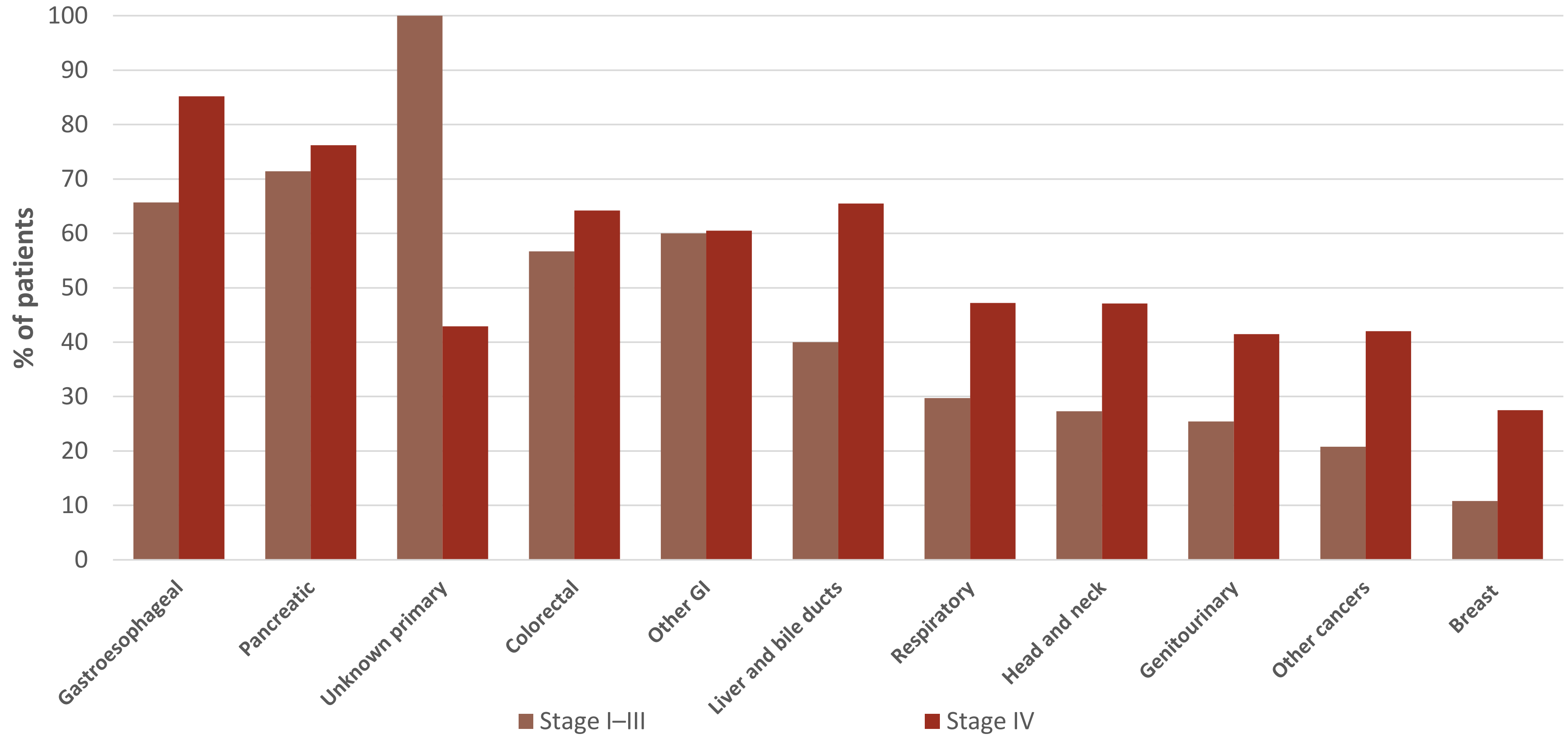
Josep M. et al. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer. 2014



Cachexia Syndrome

Josep M. et al. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer. 2014

Prevalence of Cachexia by Cancer Site and Stage



Cancer Cachexia Staging

Precachexia	Cachexia	Refractory Cachexia
Weight Loss < 5% Anorexia Metabolic change	Weight Loss > 5% or BMI < 20 kg/m^2 with wt loss >2% or Sarcopenia with wt loss >2%	Catabolic, no response to treatment, expected survival <3 months

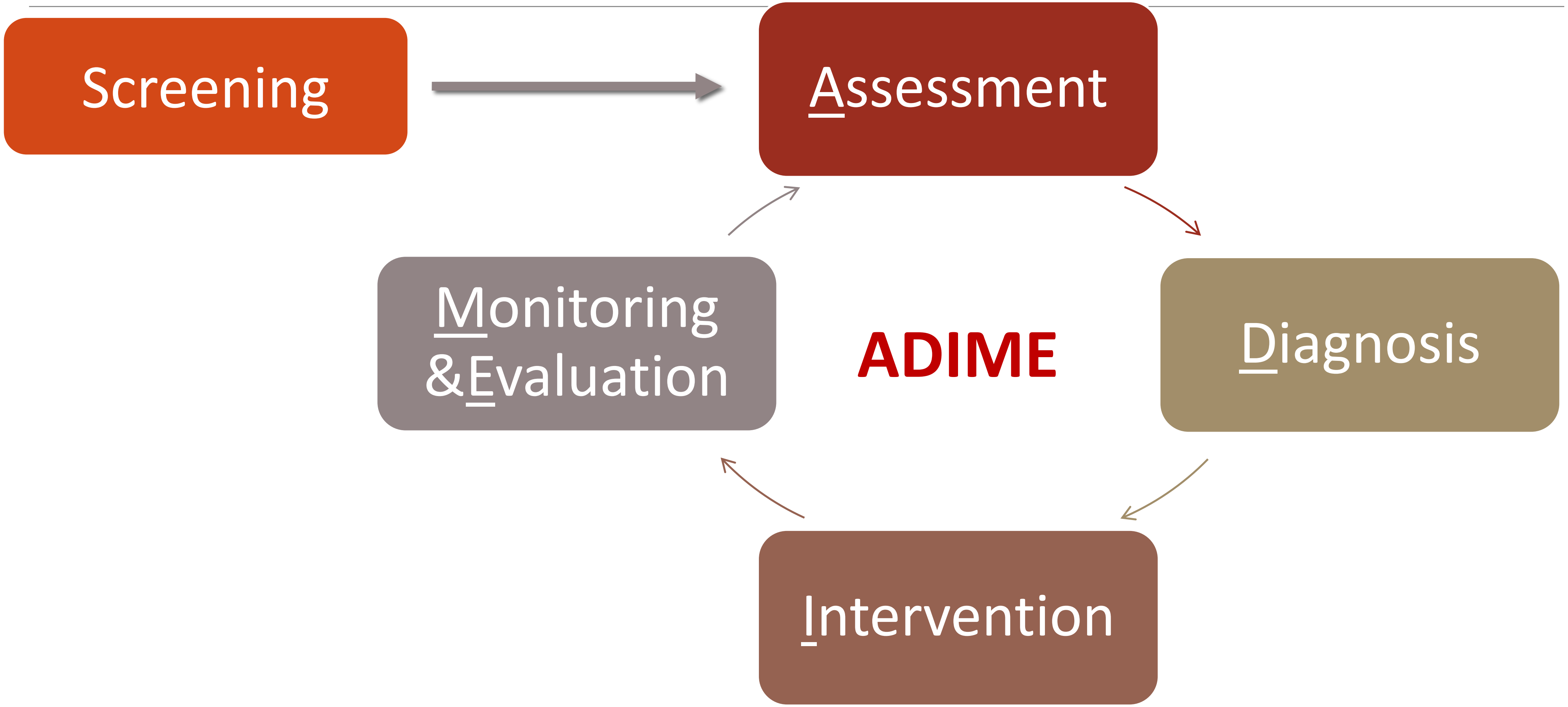
J.Arend. et al. ESPEN expert group recommendations for against cancer-related malnutrition. Clin Nutr.2017

Consequences of Malnutrition and Cancer Cachexia

- Impaired Quality of Life, Decreased Muscle Function and Reduced Performance Status
- Reduces Response to Chemotherapy, Increase CMT Toxicity
- Impaired Immune Competence
- Increase Risks of Post-operative Complication
- Longer Hospital Stay, and Increased Health Care Costs
- Decrease Free Survival

Medical Nutrition Therapy for Cancer Patients

Nutrition Care Process



Nutrition Screening

แบบคัดกรองภาวะโภชนาการ
สมาคมผู้ให้อาหารทางหลอดเลือดดำและทางเดินอาหารแห่งประเทศไทย
(SPENT Nutrition Screening Tool)

หัวข้อการคัดกรอง	ครั้งที่ 1 วันที่................		ครั้งที่ 2 วันที่................		ครั้งที่ 3 วันที่...............	
	ใช่	ไม่ใช่	ใช่	ไม่ใช่	ใช่	ไม่ใช่
1. ผู้ป่วยมีน้ำหนักตัวลดลง โดยไม่ได้ตั้งใจในช่วง 6 เดือนที่ผ่านมาหรือไม่						
2. ผู้ป่วยได้รับอาหารน้อยกว่าที่เคยได้ (> 7 วัน)						
3. BMI < 18.5 หรือ ≥ 25.0 กก./ตร.ม. หรือไม่						
4. ผู้ป่วยมีภาวะโรควิกฤต หรือกึ่งวิกฤตร่วมด้วยหรือไม่						
ผู้คัดกรอง						

ผลการคัดกรอง

- ❑ ถ้าตอบ ใช่ ≥ 2 ข้อ ทำการประเมินภาวะโภชนาการต่อ หรือปรึกษานักกำหนดอาหาร/ทีมโภชนบำบัด
- ❑ ถ้าตอบ ใช่ ≤ 1 ข้อ ให้คัดกรอง <u>ซ้ำสัปดาห์ละ 1 ครั้ง</u> ในช่วงที่อยู่โรงพยาบาล

Nutrition Assessment

- A: Anthropometry
  B: Biochemistry
  C: Clinical Signs
  D: Dietary Assessment

- Nutrition Assessment Tools
  - Nutrition Triage (NT)
  - Nutrition Alert Form (NAF)
  - Patient-generated Subjective Global Assessment (PG-SGA)

Patient-generated Subjective Global Assessment (PG-SGA)

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

กรอบที่ 1-4 สำหรับผู้ป่วยเป็นผู้กรอกข้อมูล

[กรอบที่ 1-4 เป็น PG-SGA ฉบับย่อ]

ข้อมูลผู้ป่วย

1. น้ำหนักตัว *(ดูแผ่นงานที่ 1)*

สรุปน้ำหนักตัวปัจจุบัน และน้ำหนักตัวล่าสุดของฉัน:
ปัจจุบันฉันมีน้ำหนักตัวประมาณ______ กิโลกรัม
ฉันสูงประมาณ ______ เซนติเมตร

1 เดือนก่อนฉันมีน้ำหนักประมาณ______ กิโลกรัม
6 เดือนก่อนฉันมีน้ำหนักประมาณ______ กิโลกรัม

ระหว่าง 2 สัปดาห์ที่ผ่านมา น้ำหนักของฉัน :

☐ ลดลง (1) ☐ ไม่เปลี่ยนแปลง (0) ☐ เพิ่มขึ้น (0)

คะแนนรวมของกรอบที่ 1 ☐

2. การรับประทานอาหาร: เมื่อเปรียบเทียบกับการรับประทานอาหารตามปกติของฉัน ฉันคิดว่าในช่วง 1 เดือนที่ผ่านมา การรับประทานอาหารของฉัน

- ☐ ไม่เปลี่ยนแปลง (0)
- ☐ เพิ่มขึ้นกว่าปกติ (0)
- ☐ น้อยกว่าปกติ (1)

ปัจจุบันฉันรับประทาน

- ☐ อาหารตามปกติ แต่ปริมาณน้อยกว่าเดิม (1)
- ☐ อาหารตามปกติ แต่ปริมาณน้อยกว่าเดิมมาก (2)
- ☐ เฉพาะอาหารเหลวเท่านั้น (3)
- ☐ เฉพาะอาหารเสริมทางการแพทย์เท่านั้น (3)
- ☐ แทบไม่รับประทานอะไรเลย (4)
- ☐ ได้รับอาหารทางสายให้อาหาร หรือได้รับอาหารทางหลอดเลือดดำ (0)

คะแนนรวมของกรอบที่ 2 ☐

3. อาการ: ระหว่าง 2 สัปดาห์ที่ผ่านมา ฉันรับประทานอาหารได้ไม่เพียงพอ เนื่องจากฉันมีปัญหาดังต่อไปนี้ (เลือกได้มากกว่า 1 ข้อ)

- ☐ ไม่มีปัญหาในการรับประทานอาหาร (0)
- ☐ เบื่ออาหาร,ไม่อยากรับประทานอาหาร (3)
- ☐ คลื่นไส้ (1)
- ☐ ท้องผูก (1)
- ☐ เจ็บแสบในช่องปาก (2)
- ☐ การรับรสเปลี่ยนหรือไม่รู้รส (1)
- ☐ มีปัญหาการกลืน (2)
- ☐ ปวด; บริเวณ ? (3) ________________
- ☐ อื่นๆ(1)** ________________
- ☐ อาเจียน (3)
- ☐ ท้องเสีย (3)
- ☐ ปากแห้ง (1)
- ☐ เหม็นกลิ่นอาหาร (1)
- ☐ อิ่มเร็ว (1)
- ☐ อ่อนเพลีย (1)

**ตัวอย่างเช่น ซึมเศร้า, ปัญหาทางการเงิน, หรือปัญหาสุขภาพฟัน

คะแนนรวมของกรอบที่ 3 ☐

4. กิจกรรมต่างๆ และการทำงานของร่างกาย:

ในช่วง 1 เดือนที่ผ่านมา ฉันทำกิจกรรมต่างๆได้ในระดับ

- ☐ ปกติ ไม่มีข้อจำกัด (0)
- ☐ ไม่เป็นปกติ แต่ยังสามารถทำกิจกรรมได้ใกล้เคียงกับปกติ (1)
- ☐ ไม่รู้สึกอยากทำอะไร อยู่บนเตียงหรือนั่งเก้าอี้ในช่วงเวลาน้อยกว่าครึ่งวัน (2)
- ☐ ทำกิจกรรมได้เพียงเล็กน้อย และใช้เวลาส่วนใหญ่ของวันอยู่บนเตียงหรือเก้าอี้ (3)
- ☐ ส่วนใหญ่จะนอนติดเตียง อยู่บนเตียงเกือบทั้งวัน (3)

คะแนนรวมของกรอบที่ 4 ☐

ส่วนที่เหลือของแบบประเมินนี้กรอกโดยแพทย์ พยาบาล นักกำหนดอาหาร หรือบุคลากรทางแพทย์อื่น ขอขอบคุณ

คะแนนรวมของกรอบที่ 1-4 ☐ A

Thailand 16-010 v07.09.17

email: faithotterymdphd@aol.com or info@pt-global.org

Nutrition Diagnosis

- Malnutrition
  - Starvation-related underweight
  - Cachexia/ Disease-related Malnutrition
  - Sarcopenia
  - Frailty

T. Cederholm. et al. ESPEN endorsed recommendation: Diagnostic criteria for malnutrition. Clin Nutr.2015

Route for Nutrition Support

Oral Diet

↓

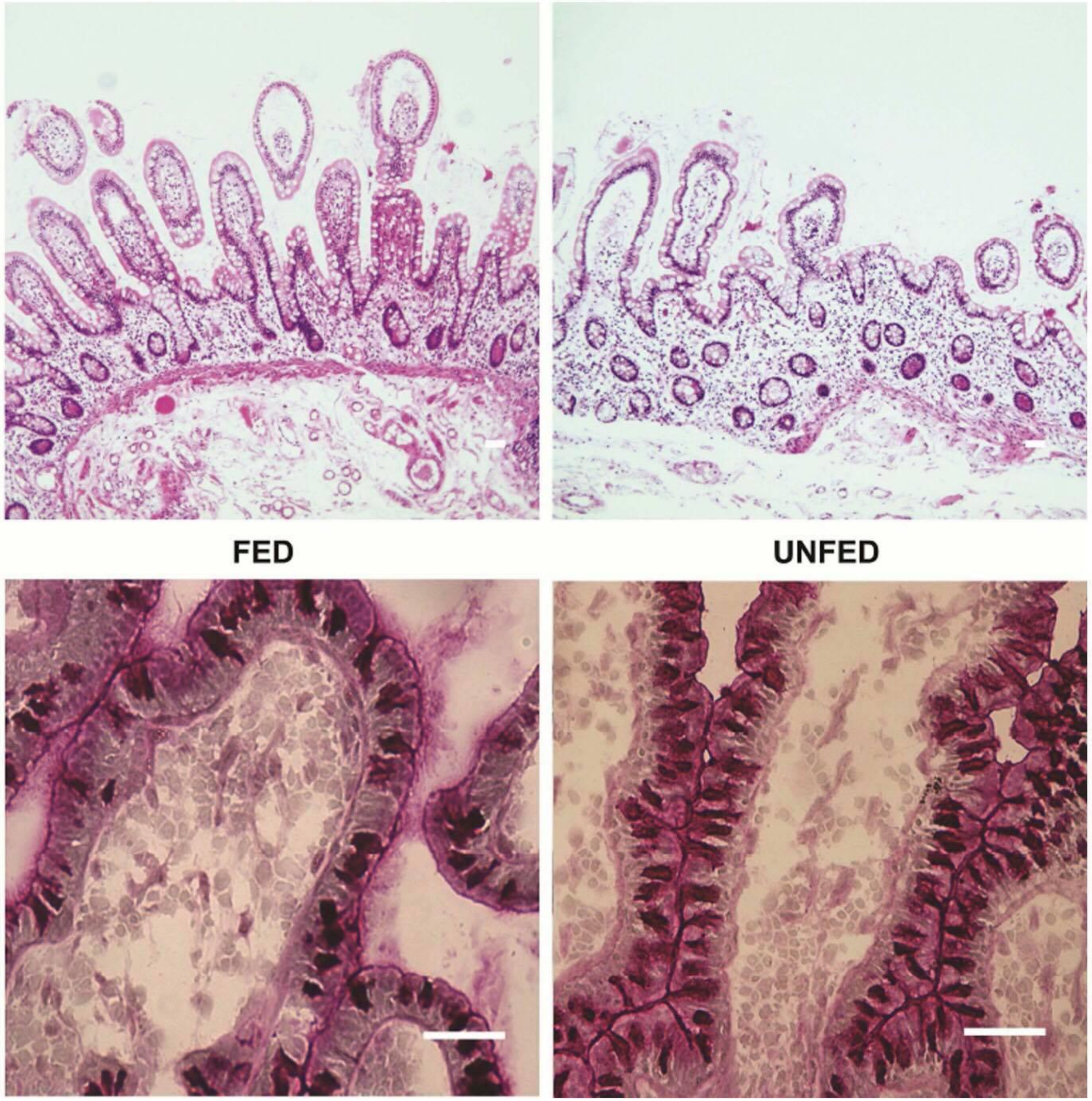
Oral Nutrition Supplement (ONS)

↓

Enteral Nutrition (EN)

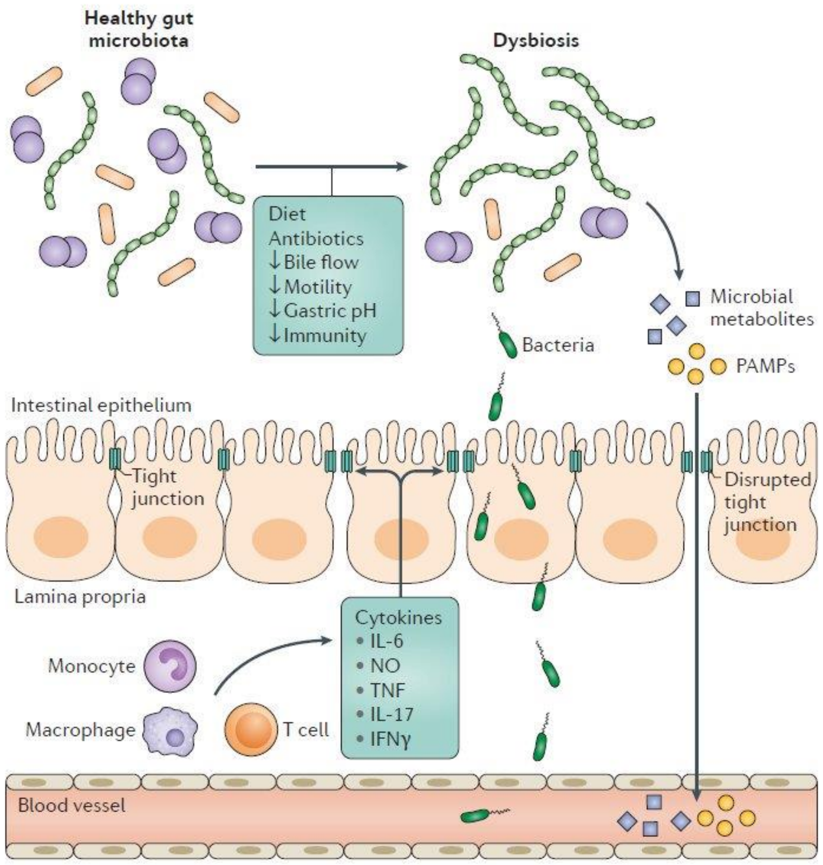
↓ **Supplemental Parenteral Nutrition: SPN**

Parenteral Nutrition (PN)



Matthew Ralls.et al. Enteral nutrition deprivation in patients leads to a loss of intestinal epithelial barrier function. Surgery. 2015

Benefits of Enteral Nutrition



Non-calorie protein Benefits of EN

- Increase GALT & MALT

  Increase Immunity response
- Increase Incretin Hormones

  help better glycemic control
- Increase Villi Proliferation
- Decrease Gut Permeability
- Decrease Bacterial Translocation

GALT : gut-associated lymphoid tissue
MALT: mucosa-associated lymphoid tissue

Indications and Contraindications of Enteral Nutrition

Indications

Indications of EN should meet all these criteria

- Malnutrition patients or risks of malnourished in moderate to severe stage
- Inadequate oral intake or suspected inadequate < 60% of requirement >7 days
- Stable of hemodynamic and vital sign status
- Not in the end of life care

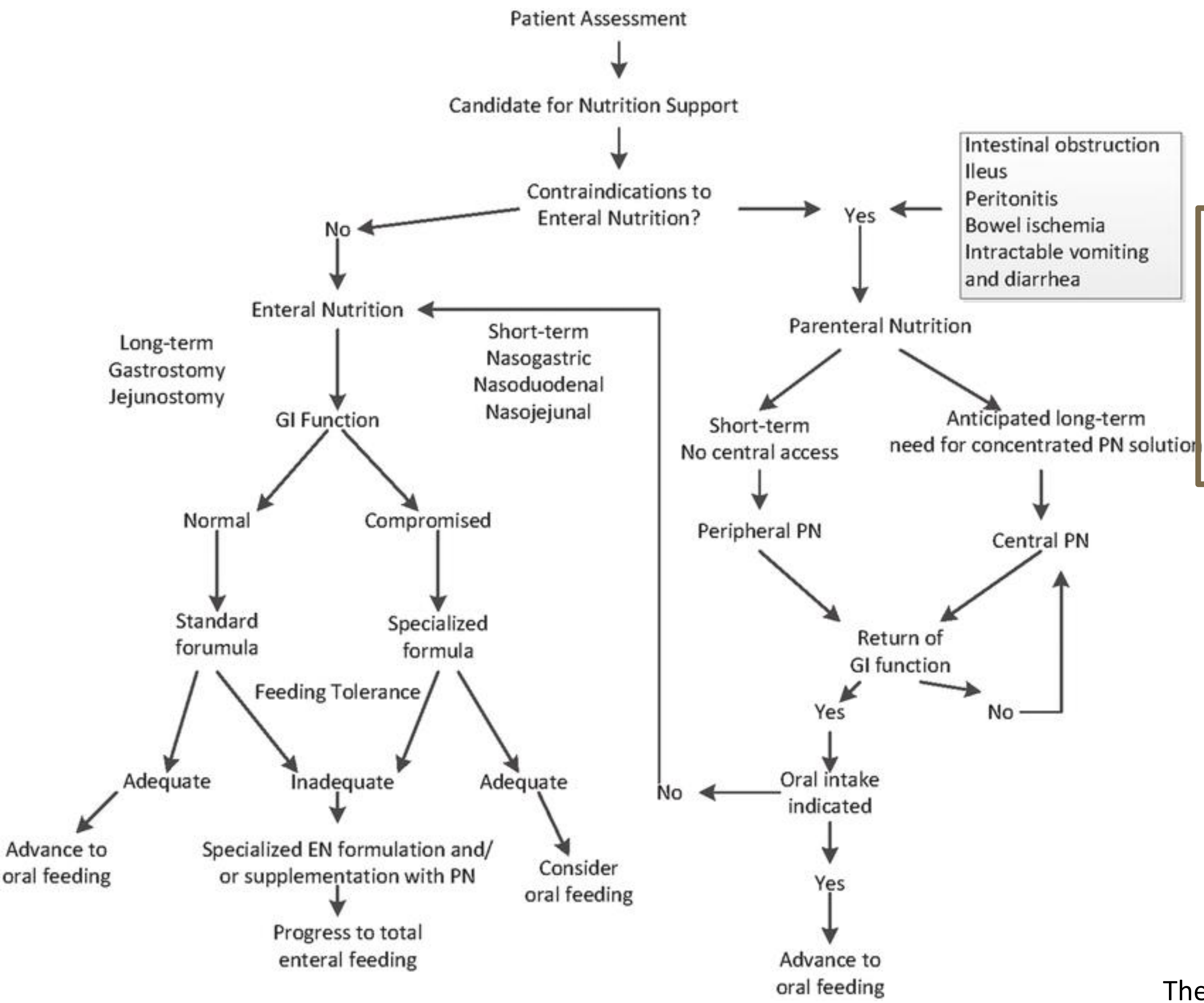
- Enteral Nutrition can be initiate after 24 -48 hours after hemodynamic was stable and without contraindications

Contraindications

- Severe short-bowel syndrome
  (remaining small bowel <100-150 cm without colon
  or remaining small bowel <50-70 cm with presence of colon)
- Other severe malabsorption conditions
- Severe GI bleed
- Distal high-output fistulas
- Paralytic ileus
- Intractable vomiting/diarrhea refractory to medical management
- Inoperative mechanical GI obstruction
- Inability to gain access to GI tract

Overview of Enteral Nutrition. The ASPEN Adult Nutrition Support Core Curriculum, 3 rd Edition

Algorithm of Nutrition Support



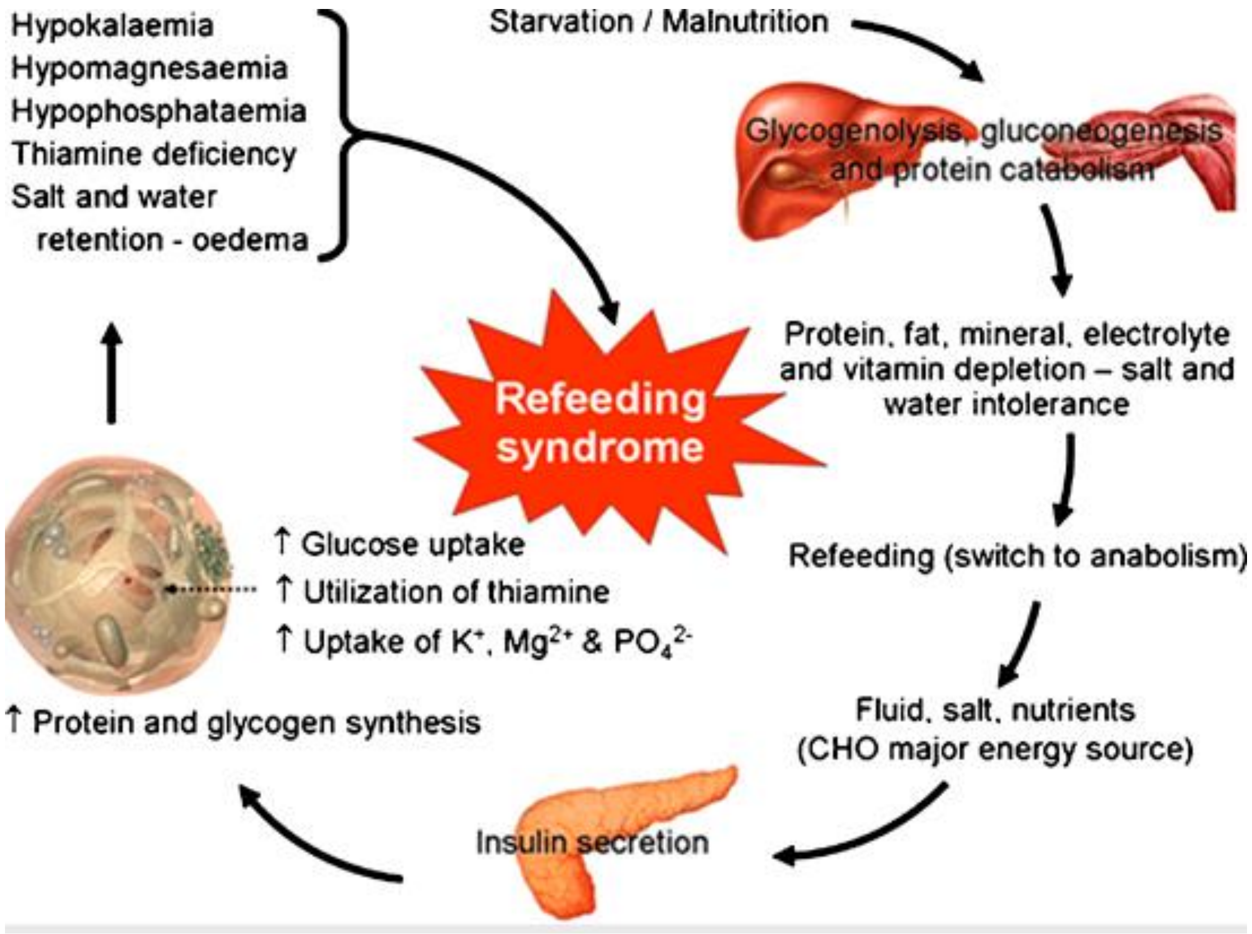
The ASPEN Adult Nutrition Support Core Curriculum

Nutrition Intervention during Cancer Stage

Precachexia	Cachexia	Refractory Cachexia
Nutrition Counseling, fortified Food, ONS (consider anti-inflammatory formula)	ONS, Enteral Feeds with adequate Energy and Protein (consider anti-inflammatory formula)	Palliative Nutrition, as needed to Alleviate Feelings of Hunger and Thirst

J.Arend. et al. ESPEN expert group recommendations for against cancer-related malnutrition. Clin Nutr.2017

Refeeding Syndrome



Criteria for determining risks of Refeeding Syndrome (RFS)

Minor risk factors	Major risk factors	Specific patient populations at high risk
BMI < 18.5 kg/m^2	BMI < 16 kg/m^2	Hunger strike Chronic severe dieting
Unintentional weight loss > 10% in past 3-6 mo	Unintentional weight loss > 15% in past 3-6 mo	History of bariatric surgery Short bowel syndrome
Little or no nutritional intake for >5 d	Little or no nutritional intake for >10 d	Tumor patients Frail elderly patients with chronic debilitating disease
History of alcohol abuse or drugs including insulin, chemotherapy, antacids, or diuretics	Low baseline level of potassium (K), Phosphate (P), or magnesium (Mg) before feeding	

Low Risk of RFS :1 minor risk factor
High Risk of RFS : 1 major or 2 minor risk factors
Very High Risk : BMI < 14 kg/m^2, Weight Loss > 20%, or Starvation > 15d

Natile Friedli. et al. Management and prevention of refeeding syndrome in medical inpatients. Nutrition. 2018

Energy Requirement

Strength of recommendation **STRONG**	**We recommend, that total energy expenditure of cancer patients, if not measured individually, be assumed to be similar to healthy subjects and generally between <u>25 – 30 kcal/kg/day</u>**
Level of Evidence	Low

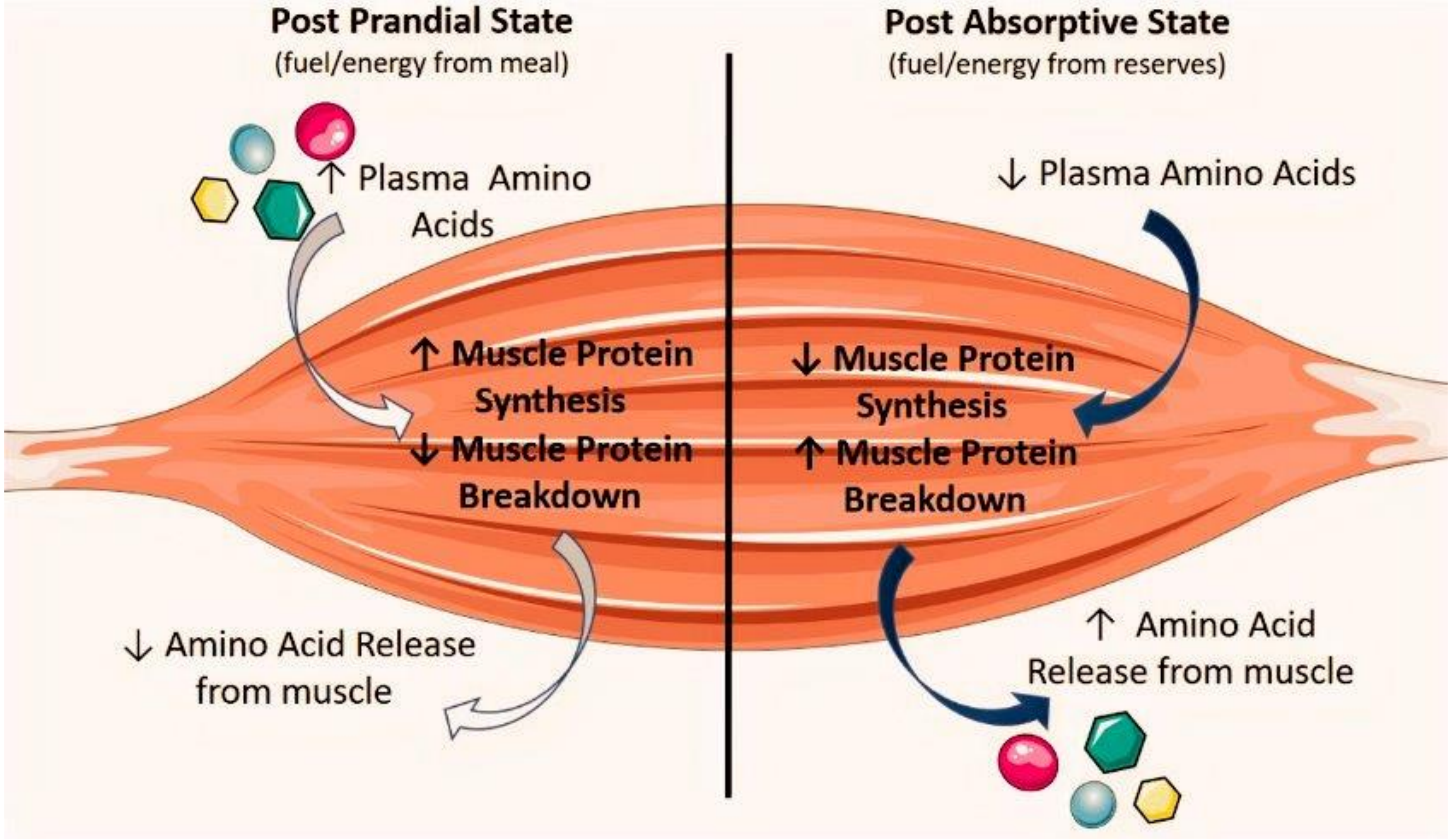
Nutritional Management during Side Effects of Cancer Treatment

Symptoms	Nutritional Management
Dysphagia	Initiate texture-modified diet, obtain a swallow evaluation
Nausea/ Vomiting	Initiate small, frequent low-fat meals, initiate antiemetic drugs
Loos of appetite/ Early satiety	Initiate small, frequent meals, modify menu to preference, initiate appetite stimulant drugs
Taste changes	Modify menu to preference and tolerance, initiate mouth rinse
Mouth sores	Initiate texture modification, modify menu to tolerance, initiate mouth rinse containing anesthetic, pain management
Diarrhea	Initiate a low-fiber and residue diet, antidiarrheal drugs, increase fluids or Oral Rehydration Solution (ORS), considered Zn supplement
Constipation	Initiate fiber-containing diet or fiber containing enteral nutrition formula, laxative, soluble fiber supplement, increase fluids
Fatigue	Provide suffient energy and protein, increased fluids, sleep mangement

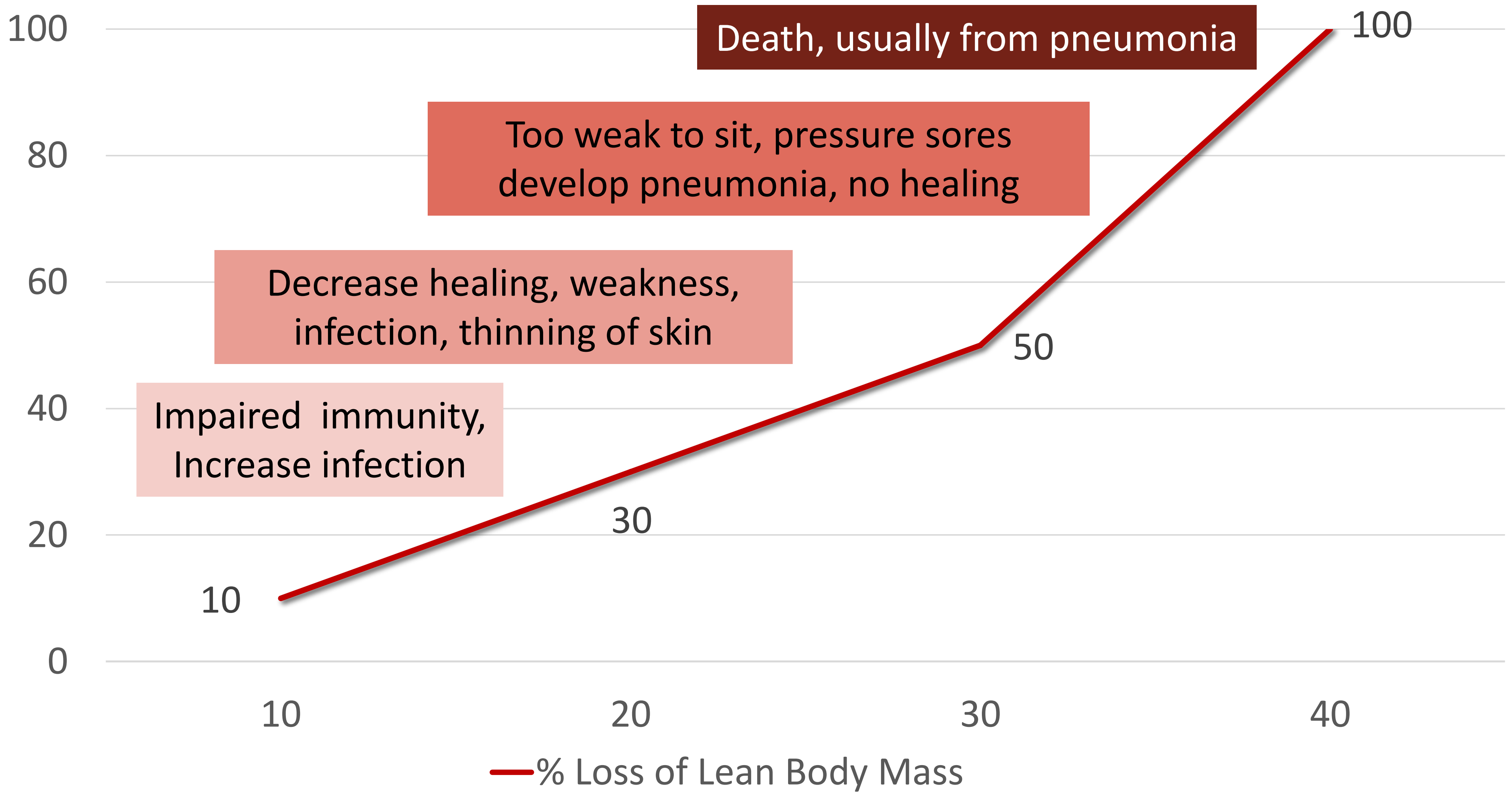
Protein Requirement

Strength of recommendation **STRONG**	**We recommend that protein intake should be <u>above 1 g/kg/d</u>, if possible up to <u>1.5 g/kg/day</u>**
Level of Evidence	Moderate

Muscle Protein Synthesis (MPS)



Loss of Lean Body Mass and Mortality



Demling RH. Nutrition, Anabolism, and the Wound Healing Process: An Overview. Eplasty. 2009

Nutrition Plan for Adequate Protein Intake

- Eggs
    - Add to fried rice, salads, soups, sandwich
    - Make omelet instead of boiled egg
- Meat, Poultry, Fish and Seafoods
    - Add to main dish
    - Deep fried meat
    - Dried meat
- Milk
    - Add in soup, smoothie
    - Make ice cream, dessert, chocolate drink
    - Hard cheese

Immuno-modulating Formula

- High Protein Distribution
- High Concentration, High Caloric Dense
- Immuno-nutrients
    - Omega-3 Fish Oil; EPA
    - Glutamine
    - Arginine
    - Ribonucleotide

Name	NEO-MUNE	Prosure	Oral Impact	Nutricia Forticare
				
Company	Thai Otsuka	Abbott	Nestle	BJC HEALTHCARE
Caloric distribution C:P:F (%)	50:25:25	61:21:18	53:22:25	49:22:29
Kcal/ 1 scoop (g)	35 (8.5 g)	280 kcal/ 220 mL	303 kcal/ sachet (74 g)	204 kcal/ 125 mL
Protein(g)/ 1 serving	15.4 (250 kcal)	14.6 (280 kcal, bottle)	17 (303 kcal, Sachet)	11.0 (204 kcal, bottle)
Protein(g)/ 1,000 kcal	61.5 Casein, **Glutamine 6.16 g , Arginine 12.3 g**	52 Whey, Casein	56 Whey, **L-arginine 12.5 g, R-Nucleotide 1.5 g**	54 Milk protein isolate
Fat source	**Fish oil 5.5 g /1,000 kcal,** MCT oil (12% total calorie),	**Fish oil (EPA 1.0 g, DHA 0.43 g) /bottle,** MCT oil	**Fish oil 3.4 g /sachet,** MCT oil (6% total calorie)	**Fish oil (EPA 0.751 g, DHA 0.373 g)** /bottle
Osmolality mOsm/kg.H2O	400	753	620	730

Omega-3 Fatty acids to Improve Appetite and Body Weight

Strength of recommendation WEAK	In patients with advanced cancer undergoing CMT and at risk of weight loss or malnourished, we suggest to use supplementation with long-chain N-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass and body weight
Level of Evidence	Low

Effective Dose of Fish Oil was 4 – 6 g/d, or Long-chain Omega-3 Fatty Acids (EPA) was 1 – 2 g/d for Decrease Inflammatory Response

Immunonutrients

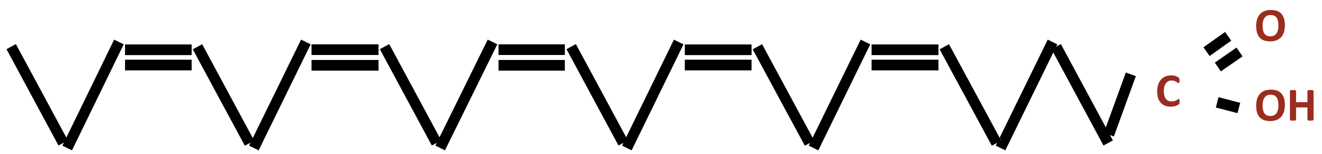
Strength of recommendation STRONG	In upper GI cancer patients undergoing surgical resection in the context of traditional perioperative care We recommended oral/enteral immunonutrition (arginine, n-3 fatty acids, nucleotides)
Level of Evidence	High

Pre- or Perioperative Intake of ONS (3x250 ml) enriched with immune modulating substrates for 5 – 7 days reduces postoperative morbidity and length of stay after major abdominal cancer surgery

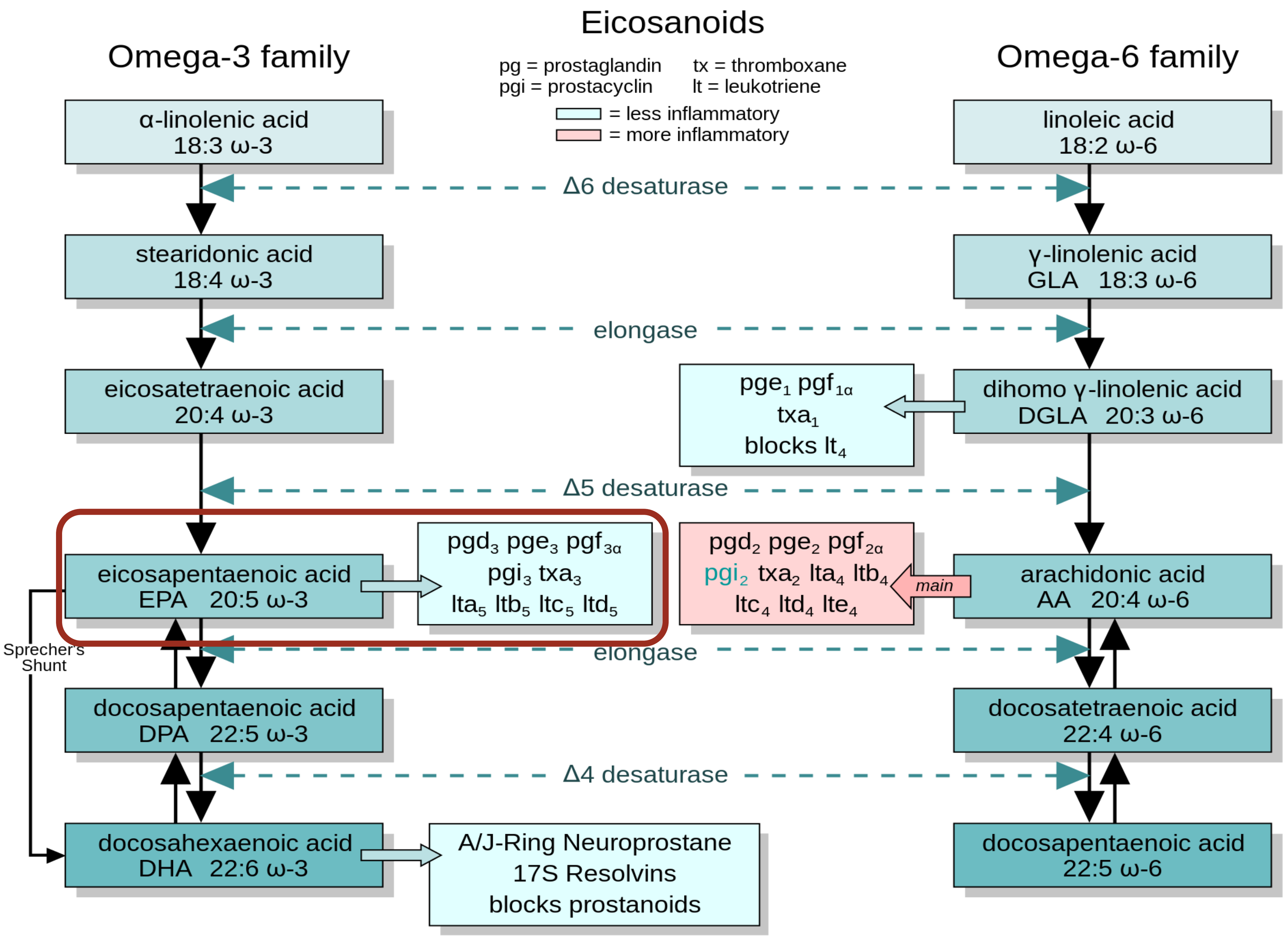
Eicosapentaenoic Acid (EPA), an Anti-inflammatory Nutrition

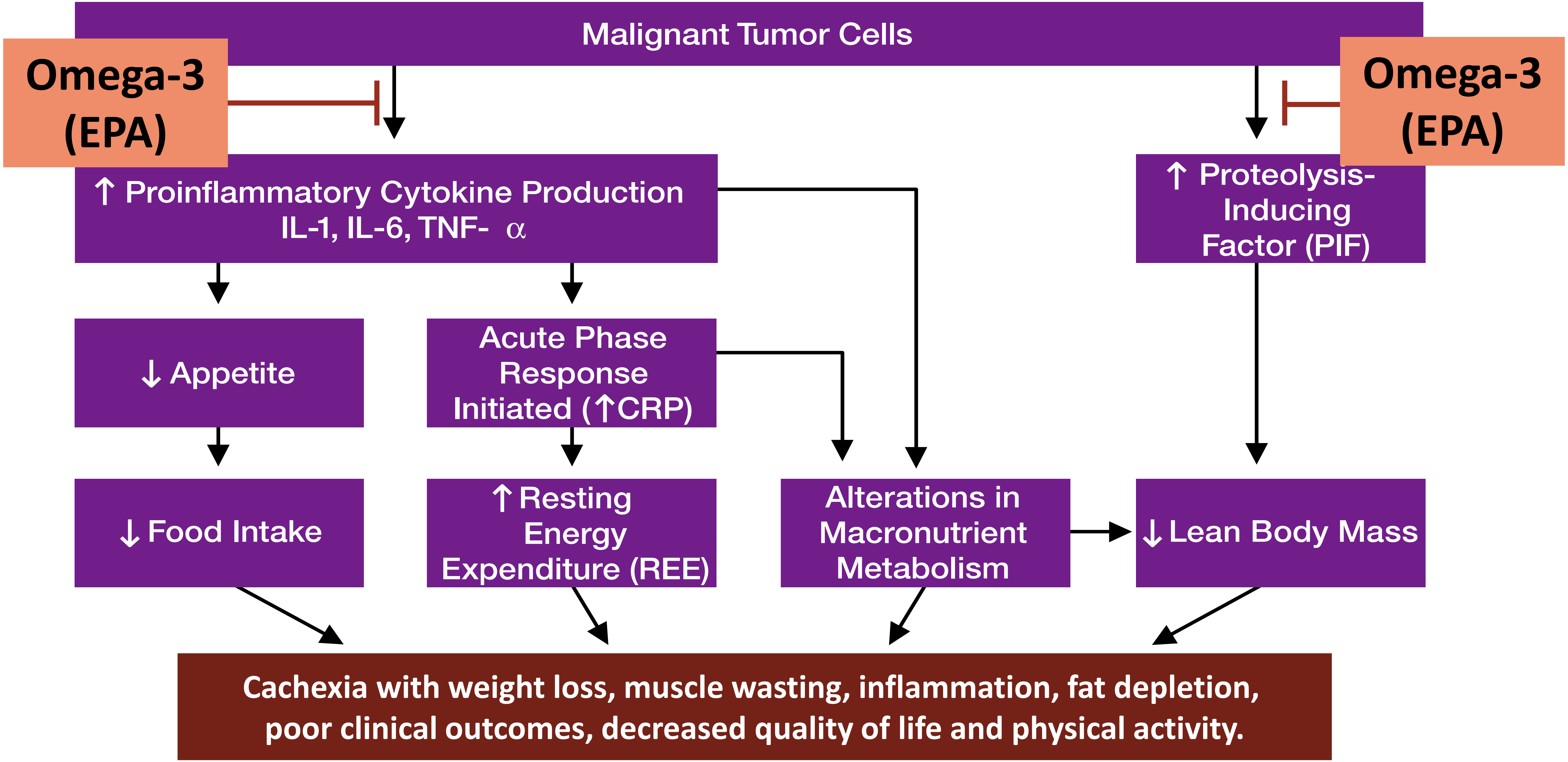
- Long-chain omega-3 fatty acid (20:5n-3) found naturally in deep-sea oily fish
- Component of cell membranes
- Decreases proinflammatory cytokine production
- Down-regulates the inflammatory response
- Down-regulates level/activity of proteolysis-inducing factor (PIF)

Eicosapentaenoic acid (EPA)



1. Wigmore SJ, et al. *Nutrition*. Jan 1996;12(1 Suppl):S27-30. 2. Wigmore SJ, et al. *Clin Sci (Lond).* Feb 1997;92(2):215-221. 3. Barber MD, et al. *Nutr Cancer*. 2001;40:118-124. 4. Endres S, et al. *N Engl J Med*. Feb 2 1989;320(5):265-271. 5. Jho D, et al. *Am Surg*. Jan 2003;69(1):32-36. 6. Lorite MJ, et al. *Br J Cancer*. 1997;76(8):1035-1040.


Eicosanoids
Omega-3 family
Omega-6 family
pg = prostaglandin
pgi = prostacyclin
tx = thromboxane
lt = leukotriene
= less inflammatory
= more inflammatory
α-linolenic acid 18:3 ω-3
linoleic acid 18:2 ω-6
Δ6 desaturase
stearidonic acid 18:4 ω-3
γ-linolenic acid GLA 18:3 ω-6
elongase
eicosatetraenoic acid 20:4 ω-3
pge1 pgf1α txa1 blocks lt4
dihomo γ-linolenic acid DGLA 20:3 ω-6
Δ5 desaturase
eicosapentaenoic acid EPA 20:5 ω-3
pgd3 pge3 pgf3α pgi3 txa3 lta5 ltb5 ltc5 ltd5
pgd2 pge2 pgf2α pgi2 txa2 lta4 ltb4 ltc4 ltd4 lte4
main
arachidonic acid AA 20:4 ω-6
Sprecher's Shunt
elongase
docosapentaenoic acid DPA 22:5 ω-3
docosatetraenoic acid 22:4 ω-6
Δ4 desaturase
docosahexaenoic acid DHA 22:6 ω-3
A/J-Ring Neuroprostane
17S Resolvins
blocks prostanoids
docosapentaenoic acid 22:5 ω-6


Malignant Tumor Cells
Omega-3 (EPA)
Omega-3 (EPA)
↑ Proinflammatory Cytokine Production IL-1, IL-6, TNF- α
↑ Proteolysis-Inducing Factor (PIF)
↓ Appetite
Acute Phase Response Initiated (↑CRP)
↓ Food Intake
↑ Resting Energy Expenditure (REE)
Alterations in Macronutrient Metabolism
↓ Lean Body Mass
Cachexia with weight loss, muscle wasting, inflammation, fat depletion, poor clinical outcomes, decreased quality of life and physical activity.

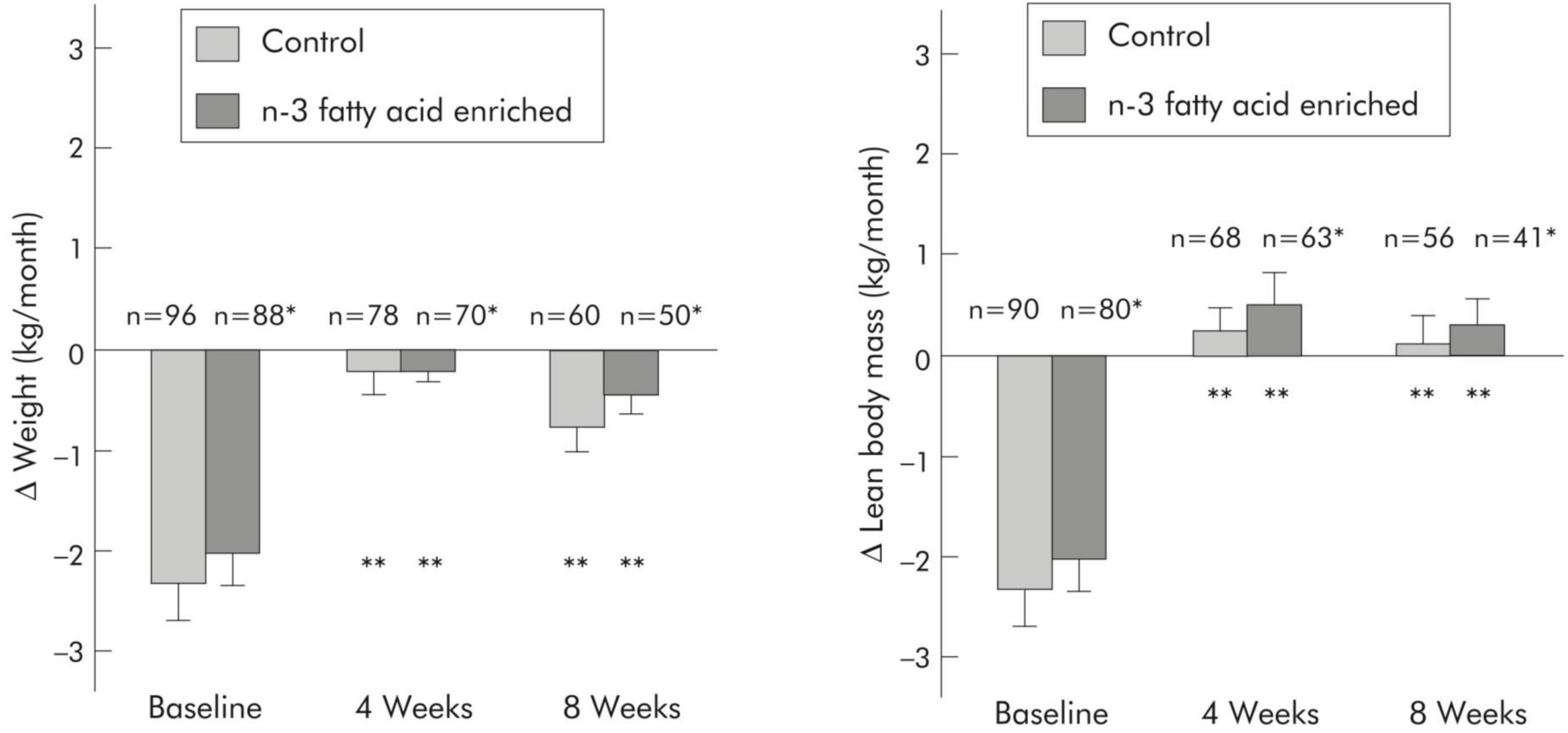
Clinical Evidence
The Benefits of Immune-Modulating Formula

Effect of a Protein and Energy Dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer

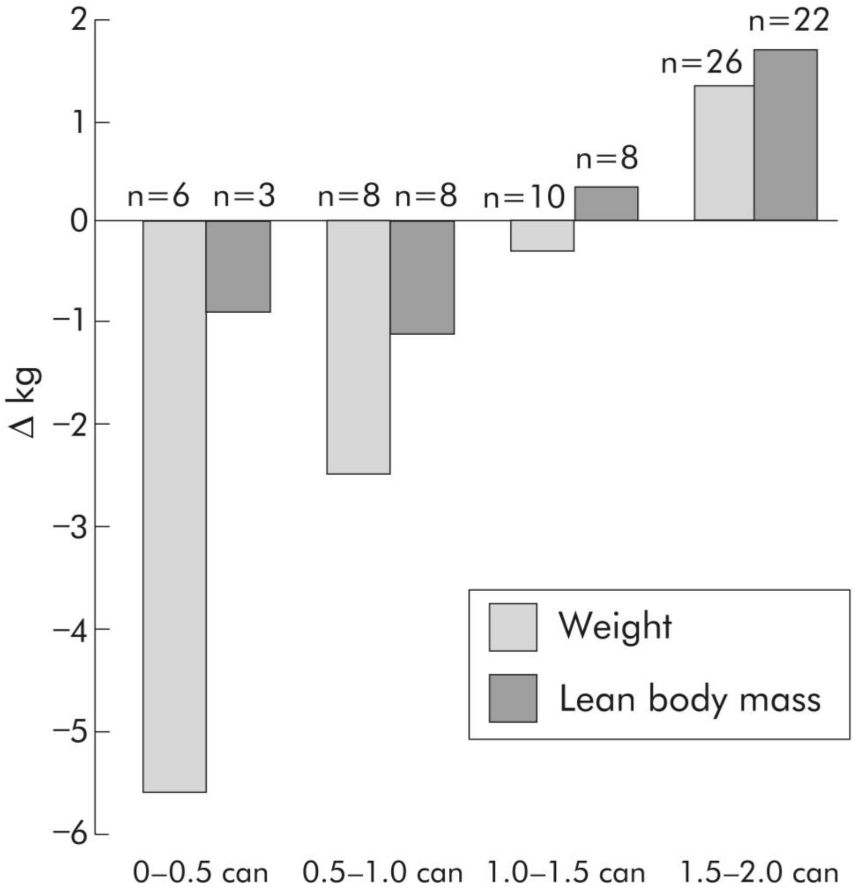
Study design

- Prospective, randomized, controlled, double-blind multicenter trial in 200 patients with advanced unresectable malnourished pancreatic cancer mean weight loss at baseline 3.3kg/month
- 2 servings ProSure® vs control ONS per day for 8 weeks (isocaloric isonitrogenous control)
- After 8 weeks of intervention
  mean weight loss in ProSure® vs. Control = -0.25 kg/mo vs. -0.37 kg/mo
  change in LBM in ProSure® vs. Control = +0.27 kg/mo vs. +0.12 kg/mo

Effect of a Protein and Energy Dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer

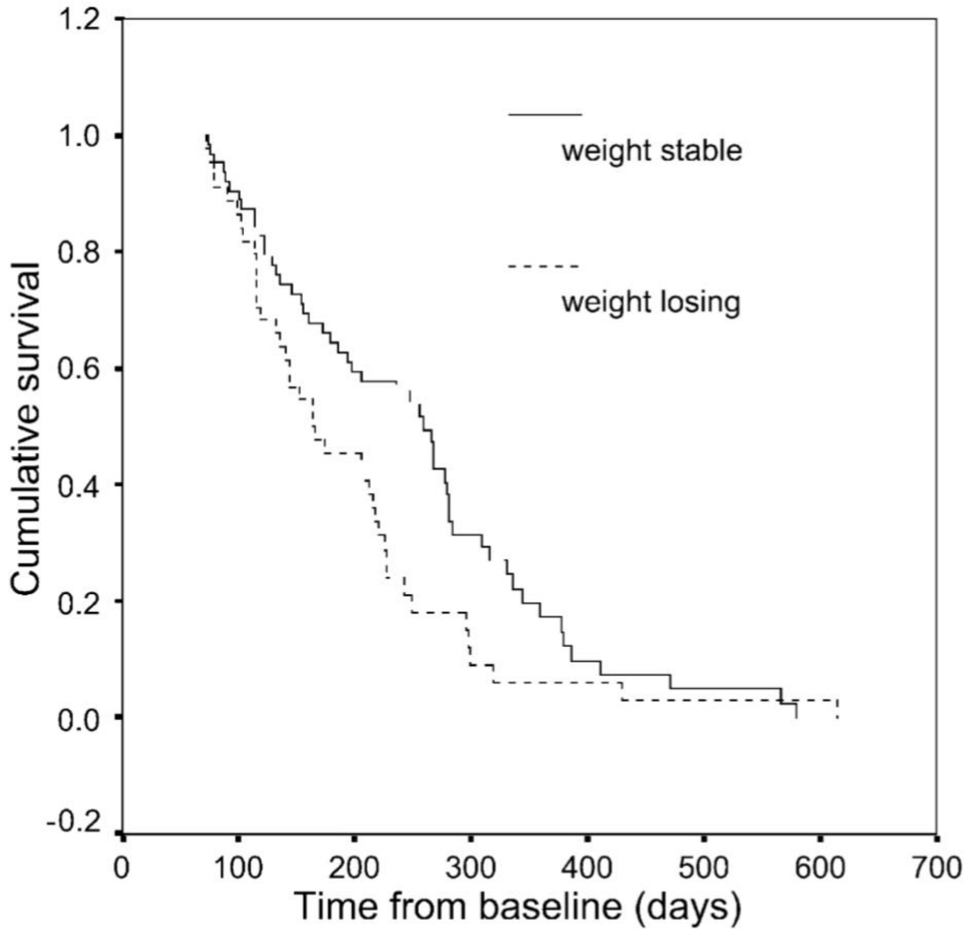


Effect of a Protein and Energy Dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer



Adherence to dietary intervention show more effective on weight gain, lean body mass and clinical outcome

Weight Stabilization is associated with Improved Survival Duration and Quality of Life in Unresectable Pancreatic Cancer



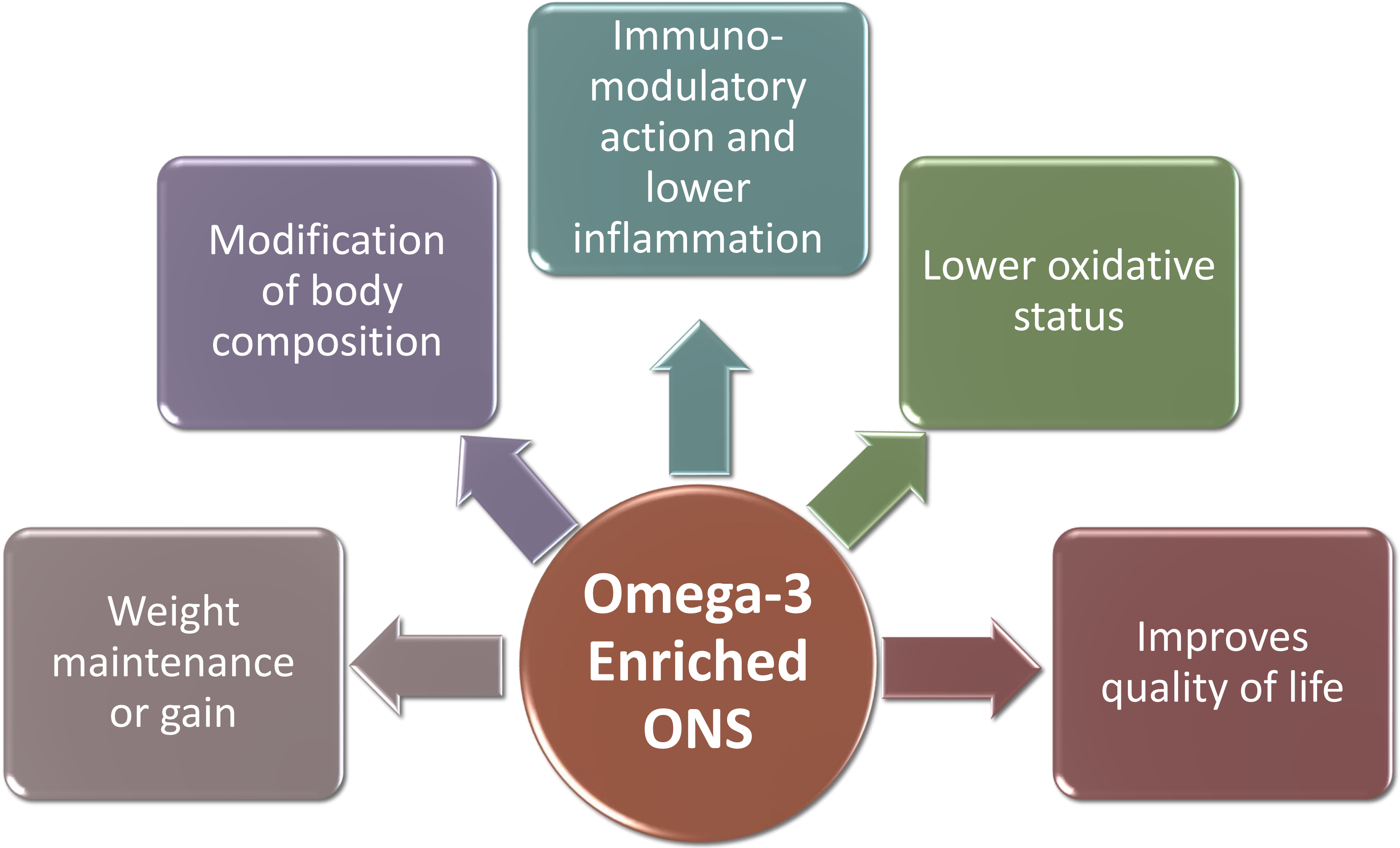
Weight stable patients have longer survival than patients with weight loss among unresectable pancreatic cancer patients

Wendy Davidson. et al. Weight Stabilisation is associated with Improved Survival Duration and Quality of Life in Unresectable Pancreatic Cancer. Clin Nutr. 20004

Omega-3 Supplements for Patients in CMT/RT: A Systematic Review

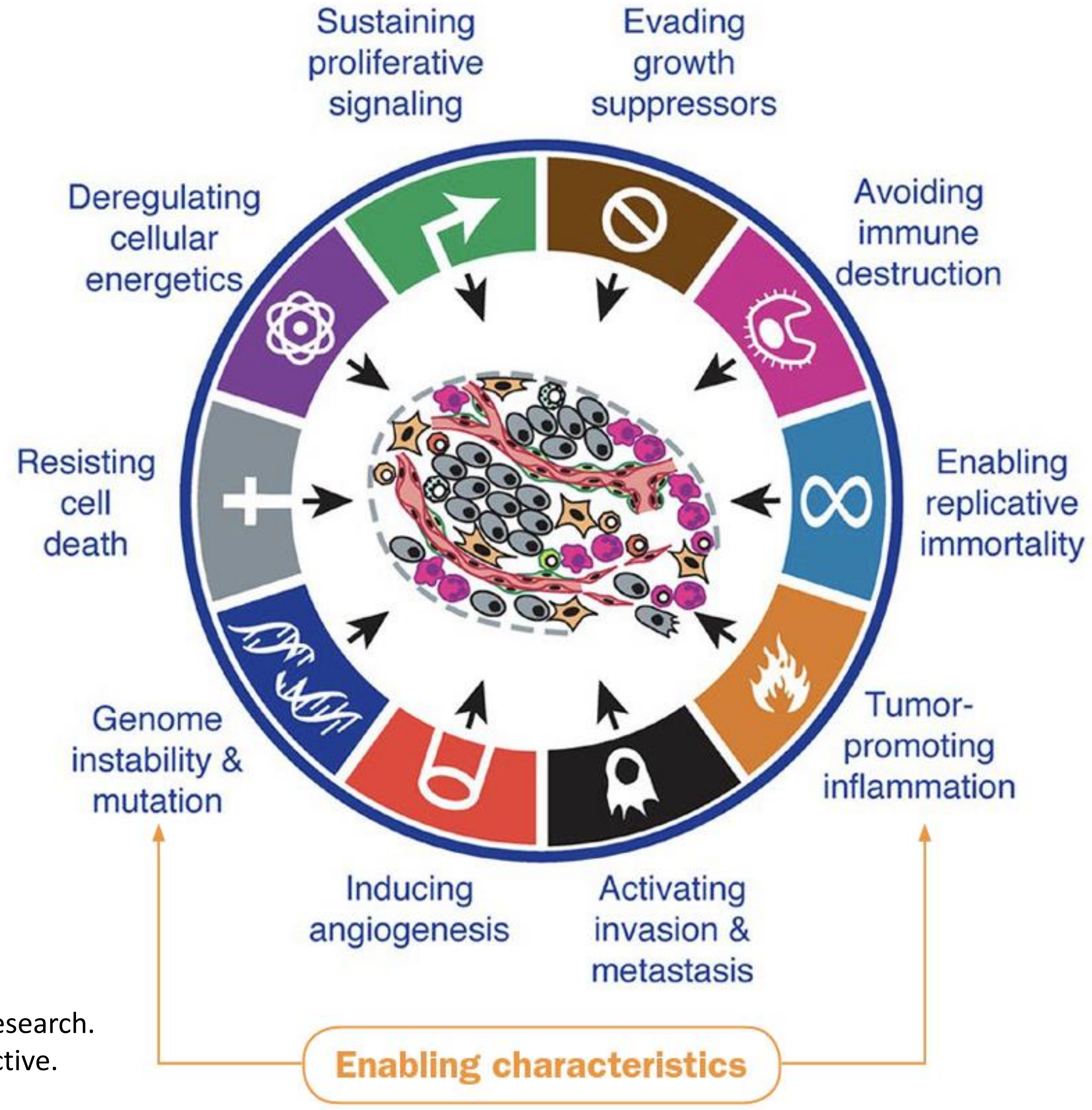
Study design

- 10 RCT studies, (N = 11 – 92 /study), duration 5 – 12 weeks
- Oncologic patients undergoing chemotherapy and/or radiotherapy
- Intervention
  - Oral Nutrition Supplement with N-3 fish oil or Fish oil supplement
- Comparator
  - Did not received supplement
  - Or Isocaloric, isonitrogenous supplement


Immuno-modulatory action and lower inflammation
Modification of body composition
Lower oxidative status
Weight maintenance or gain
Omega-3 Enriched ONS
Improves quality of life

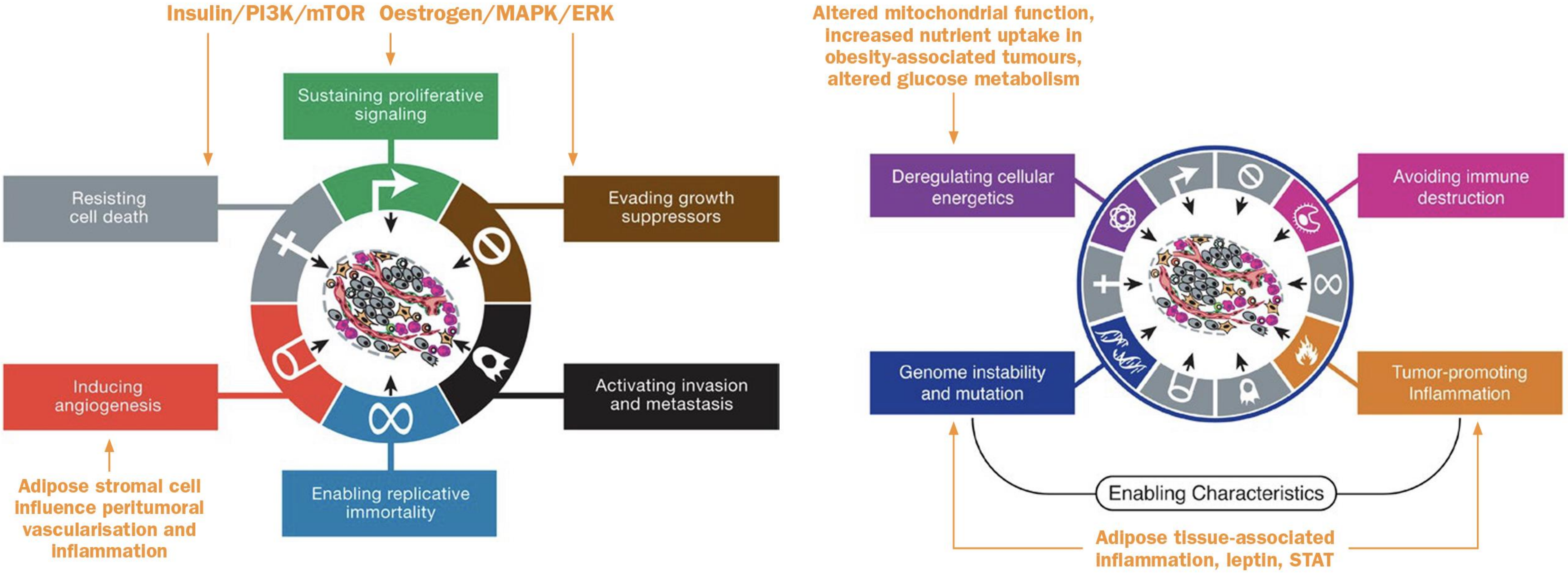
Cancer Prevention

Hallmarks of Cancer



World Cancer Research Fund/American Institute of Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018

Obesity and The Hallmarks of Cancer



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Exposure	Systemic impact	Cell function	Hallmarks possibly affected
Greater body fatness	Hyperinsulinemia	mTOR/PI3K/AKT, MAPK	Reduced apoptosis; increased proliferation, genome instability
	Increased oestradiol	MAPK/ERK/PI3K	Increased proliferation in ER+ tissues; genome instability
	Inflammation	STAT3/NF-κB	Reduced apoptosis, increased cell division, altered macrophage function, etc.; genome instability
		E.g. WNT, P53	E.g. cellular energetics, etc.
Lower fruit and vegetable intake	Folate deficiency	DNA uracil misincorporation	Genome instability
	Low dietary fibre intake	Low butyrate	Reduced apoptosis; increased proliferation
	Low levels of carotenoids, vitamin A, C, E	Oxidative stress, inflammation	Increased inflammation, genomic instability, reduced apoptosis; increased proliferation
Greater intake of red and processed meat	Elevated exposure to nitrites; endogenous N-nitroso compound formation	DNA adduct formation -> mutations in p53, KRAS, etc.	Reduced apoptosis; increased proliferation; genomic instability
		Oxidative stress, inflammation	Increased inflammation, genomic instability

World Cancer Research Fund/American Institute of Cancer Research.
Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018

Exposure	Systemic impact	Cell function	Hallmarks possibly affected
Greater intake of dairy foods	Higher IGF-I	mTOR/PI3K/AKT, MAPK	Reduced apoptosis; increased proliferation
Greater alcohol intake	Elevated acetaldehyde	Oxidative stress, lipid peroxidation	Increased inflammation, genomic instability
	Increased oestradiol	MAPK/ERK/PI3K	Increased proliferation in ER+ tissues
	Inflammation	STAT3/NF-κB	Reduced apoptosis, increased cell division, altered macrophage function, etc.
	Folate deficiency; interference with 1-carbon metabolism	DNA uracil misincorporation	Genome instability
Greater physical activity	Reduction in insulin	mTOR/PI3K/AKT, MAPK	Increased apoptosis; reduced proliferation, less genome instability
	Reduction in oestradiol and testosterone	MAPK/ERK/PI3K	Reduced proliferation in ER+ tissues; reduced genome instability
	Reduced inflammation (long term); improved immune function	STAT3/NF-κB	Increased apoptosis, increased cell division, altered macrophage function etc; reduced genome instability
		E.g. WNT, P53	E.g. cellular energetics, etc.
Greater height	Higher IGF-I	mTOR/PI3K/AKT, MAPK	Reduced apoptosis; increased proliferation

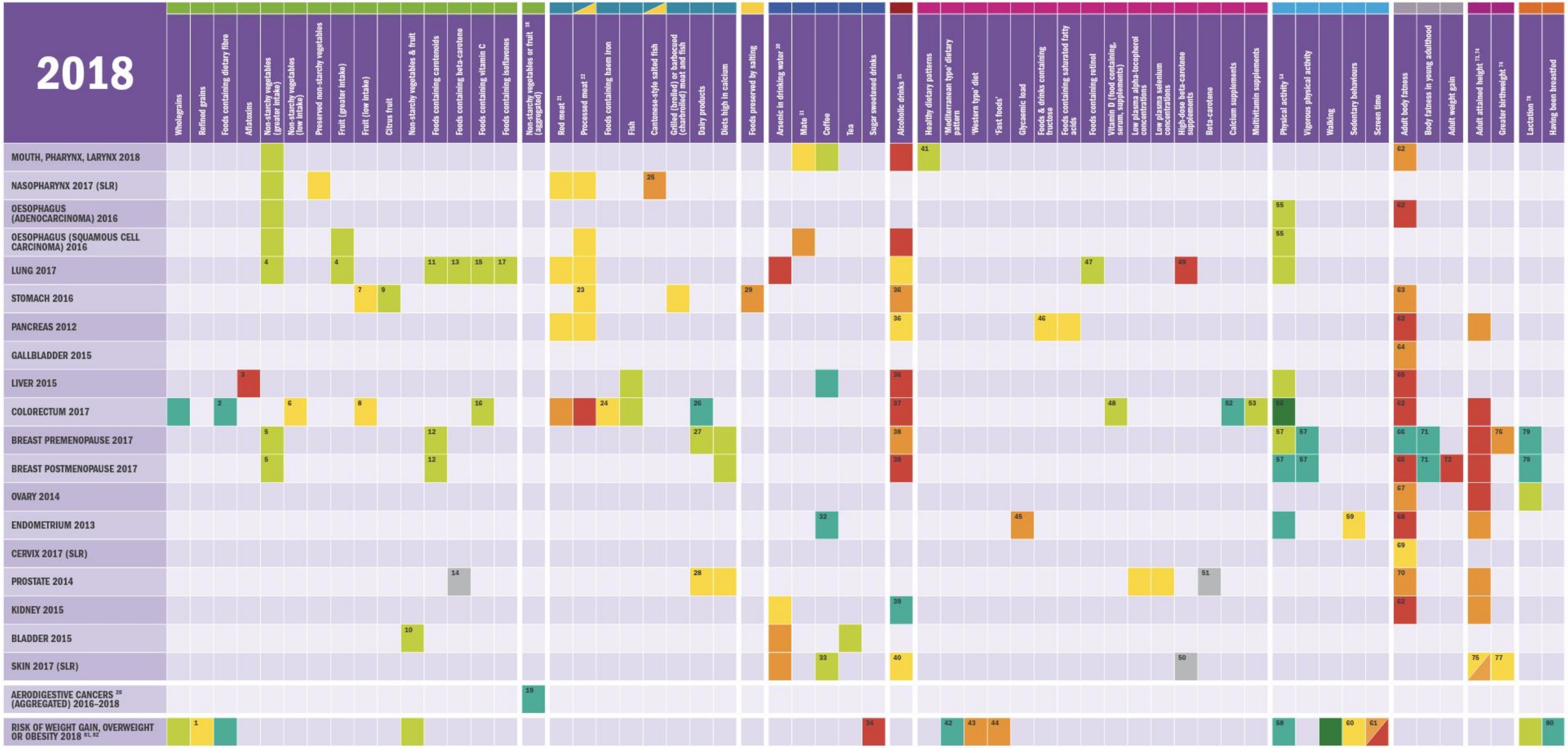
World Cancer Research Fund/American Institute of Cancer Research.
Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018

World Cancer Research Fund | American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Summary of conclusions



Conclusions Key

- Convincing decreases risk
- Probable decreases risk
- Limited – suggestive decreases risk
- Convincing increases risk
- Probable increases risk
- Limited – suggestive increases risk
- Substantial effect on risk unlikely

Exposure Group Key

- Wholegrains, vegetables and fruit
- Meat, fish and dairy products
- Preservation and processing of foods
- Non-alcoholic drinks
- Alcoholic drinks
- Other dietary exposures
- Physical activity
- Body fatness and weight gain
- Height and birthweight
- Lactation/having been breastfed

To reference this matrix please use the following citation:
World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project. Diet, Nutrition, Physical Activity and the Prevention of Cancer. Summary of evidence. Available at: wcrf.org/matrix. Accessed on DD-MM-YYYY

Abbreviation: SLR, systematic literature review.

dietandcancerreport.org

SUMMARY OF STRONG EVIDENCE ON DIET, NUTRITION, PHYSICAL ACTIVITY AND THE PREVENTION OF CANCER

To reference this matrix please use the following citation:

World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project: Diet, Nutrition, Physical Activity and the Prevention of Cancer. Summary of Strong Evidence. Available at: wcrf.org/cupmatrix accessed on DD-MM-YYYY

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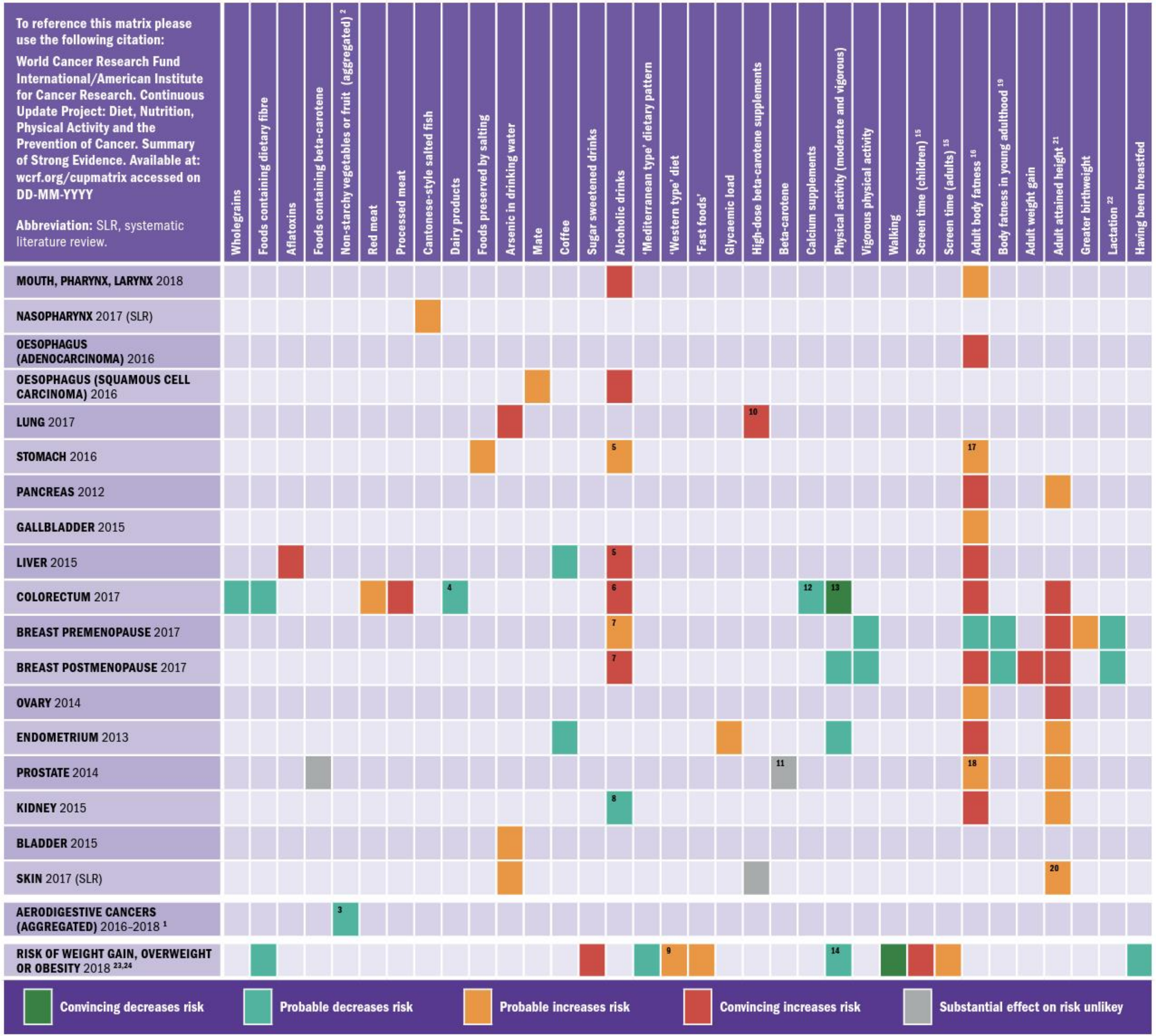
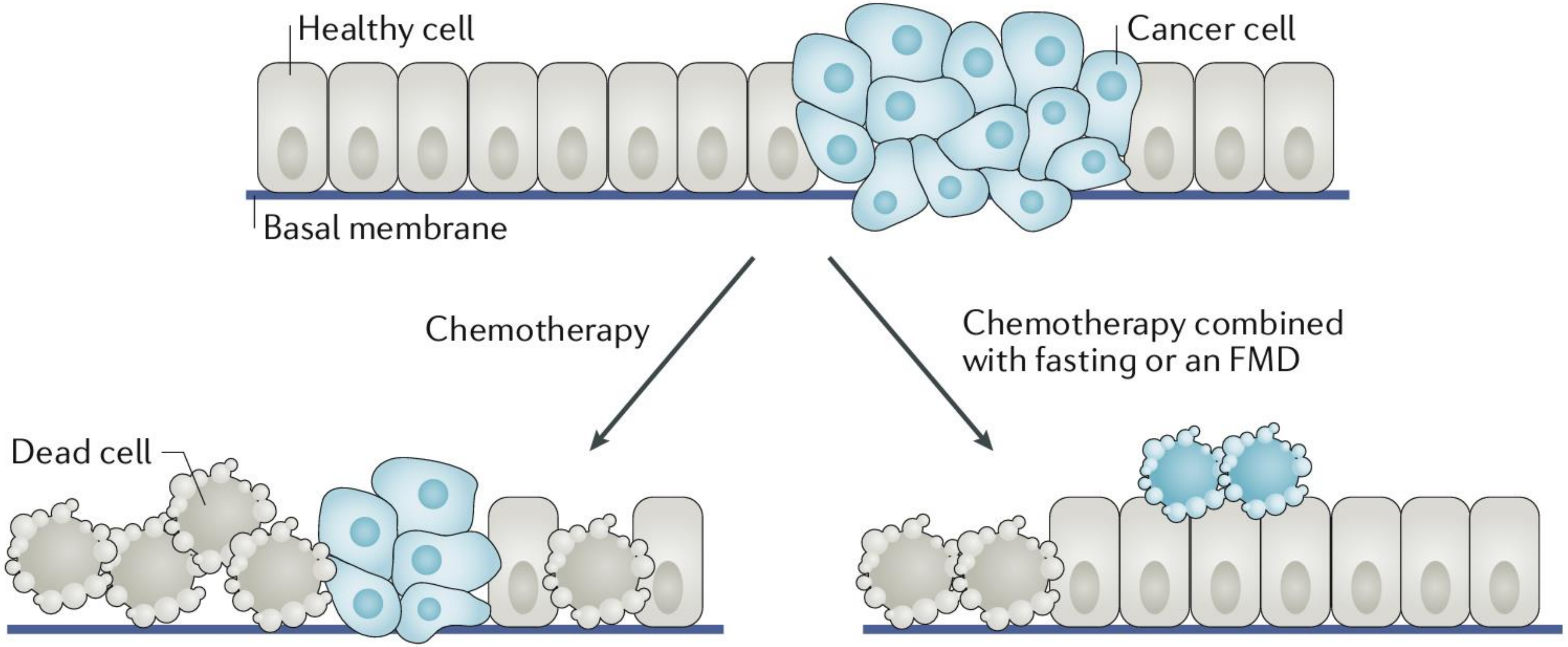


Frontier in Onconutrition

Fasting and Cancer
Molecular Mechanisms and Clinical Application

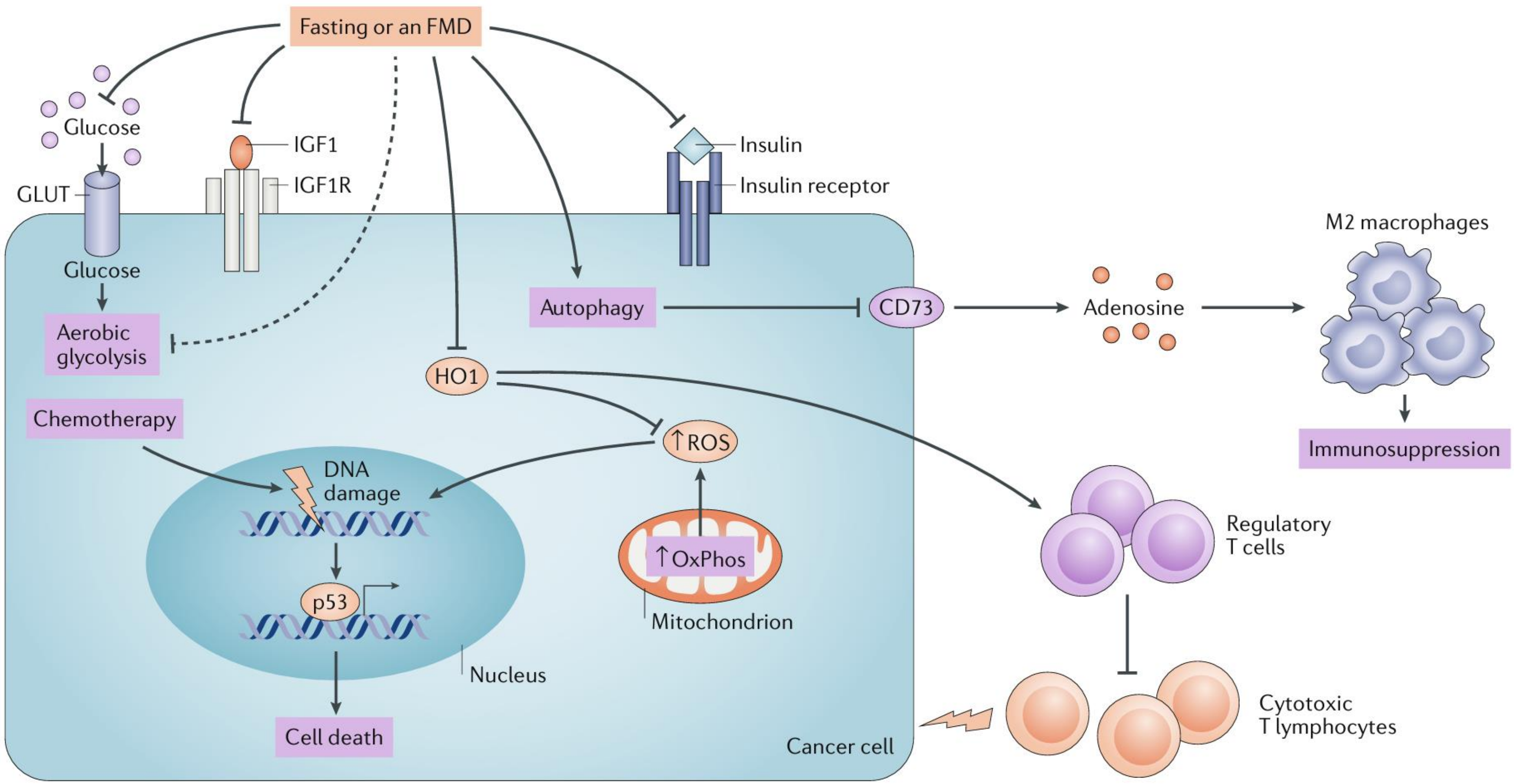


Fasting and Cancer
Molecular Mechanisms and Clinical Application

Type of diet	Restriction in calories	Composition	Schedule	IGF1 reduction (humans)	Glucose reduction (humans)	Ketone bodies increase (humans)	Location of pro-regenerative effects	Protection from chemotherapy toxicity
Fasting or FMD	>50%	Vegan and low-protein and low-sugar, high-plant-based fat composition, with micronutrient supplementation	Typically 2–5 consecutive days per month	Yes	Yes	Yes	Haematopoietic system, central nervous system, skeletal muscle and pancreatic β-cells (mouse data)[22,25,41,153]	Yes (mouse data and DNA damage analyses in patient leukocytes)[12,25,26,29,51–53]
Calorie restriction	20–40%	Reduction in all diet constituents except for vitamins and minerals	Chronic	Only in the presence of protein restriction[117]	No	No	Intestinal niche stem cells (mouse data)[118,119]	Yes (effect lower than that with fasting or FMDs; mouse data)[51]
Ketogenic diet	None (isocaloric)	High-fat, low-carbohydrate composition, with adequate protein content	Chronic	Yes	No	Yes	Peripheral nerves (rat data)[87]	NA

FMD, fasting-mimicking diet; NA, not available.

Fasting and Cancer
Molecular Mechanisms and Clinical Application



Alessio Nencioni. et al. Fasting and cancer: molecular mechanisms and clinical application. Nature Reviews Cancer. 2018

World Cancer Research Fund/American Institute of Cancer Research.
Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018

Together
We Can Help Improve
Outcome of Cancer Patients

THANK YOU

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