NUTRIGENOMICS AND CANCER CACHEXIA

TIRTA PRAWITA SARI

Updated 2023

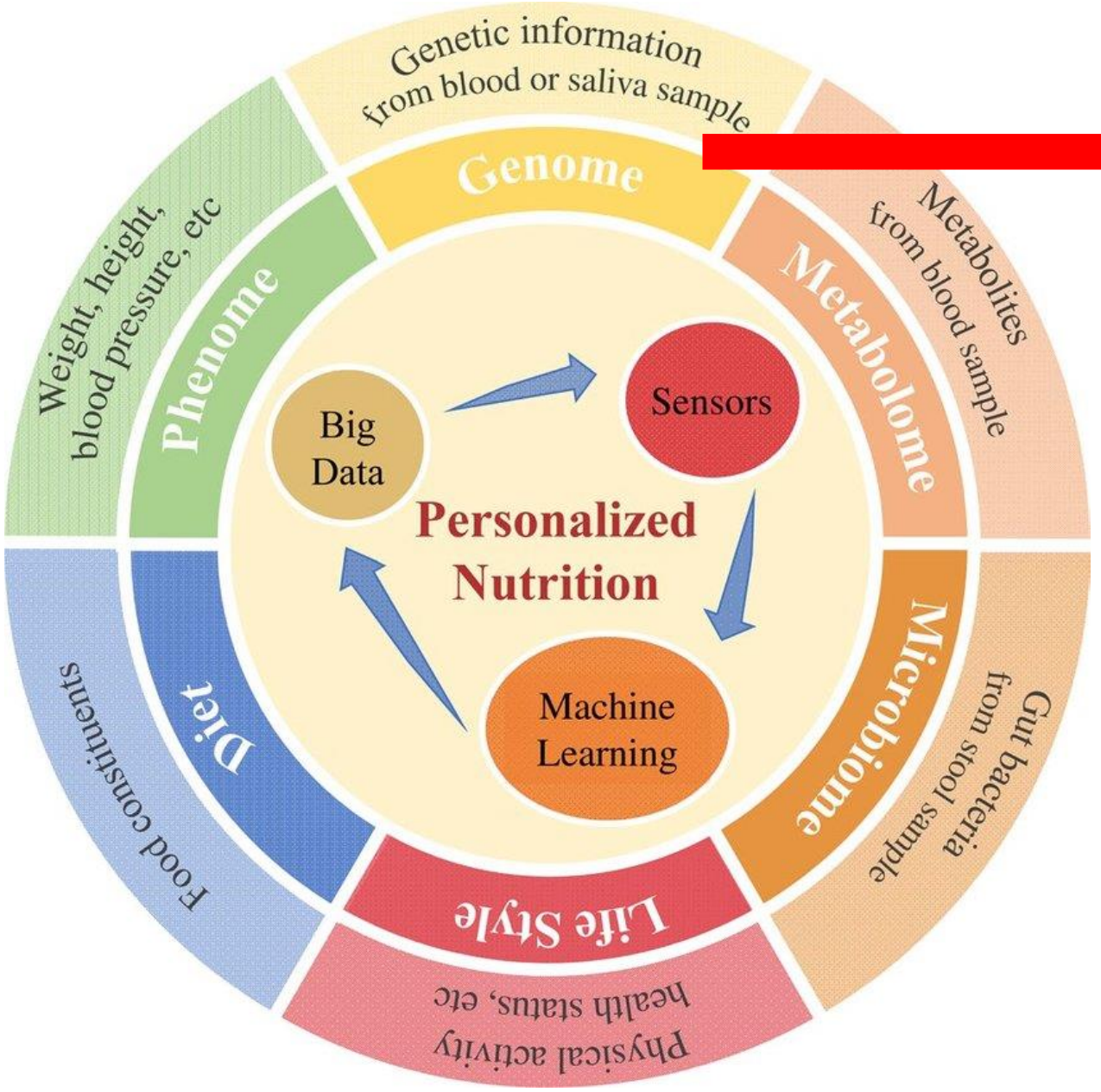
Personalized nutrition

An approach that counts on details of an individual characteristics to evolve a package of nutritional counsel, products, or services. Gibney et al. (2016), explained it as a perspective "assists individuals in achieving a lasting dietary behavior change that is beneficial for health".

Precision nutrition

characterization of gene products influenced by nutrient intake and their resulted metabolic consequences (Ordovas et al., 2018). Zeisel (2020), has recommended and justified the use of term "precision nutrition" rather than "personalized nutrition" because the concept has even greater potential to categorize the whole population in different groups based on biomarkers studies.

Specific healthy eating or nutritional guidance as per need



nutrigenomics

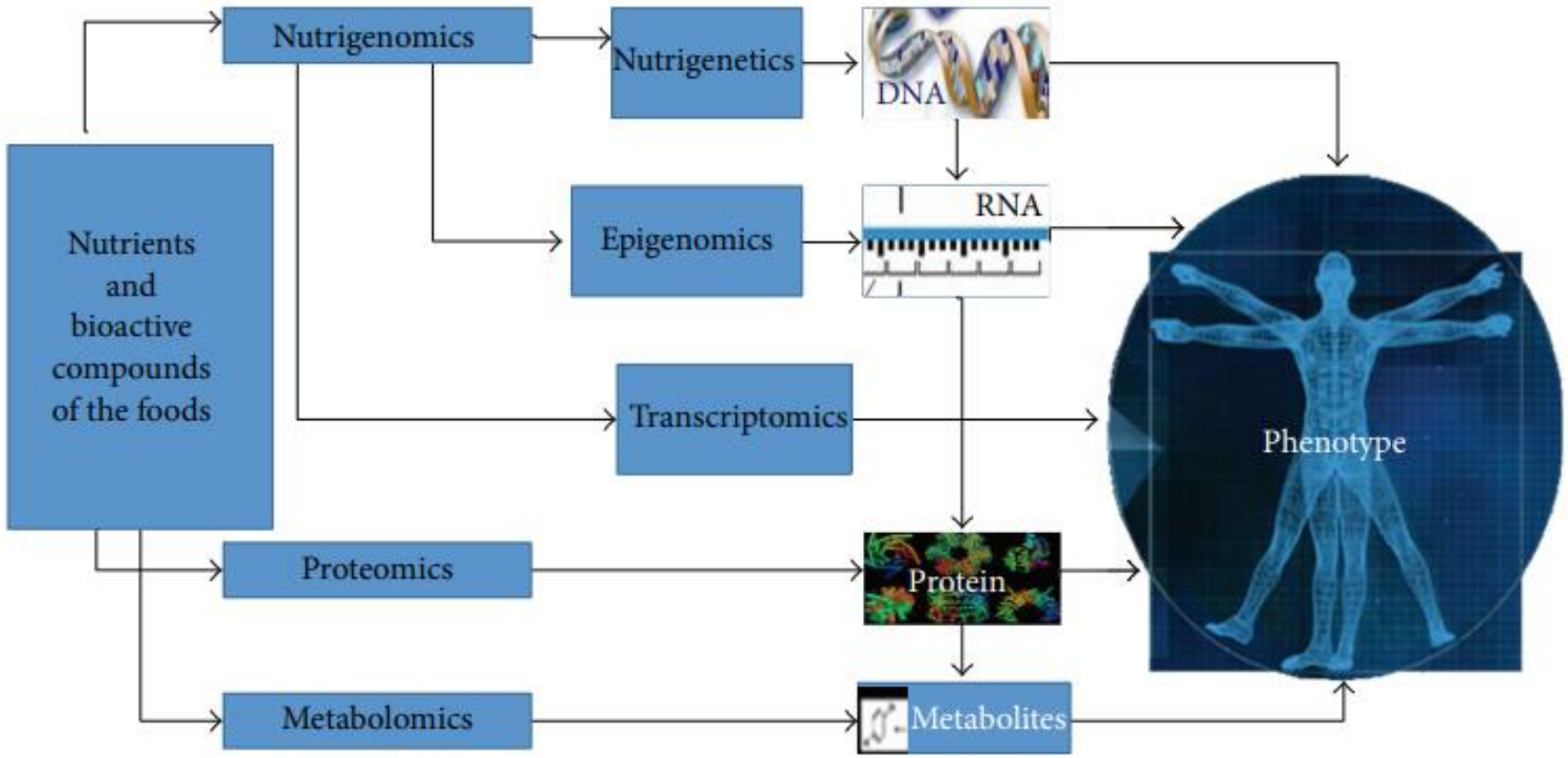
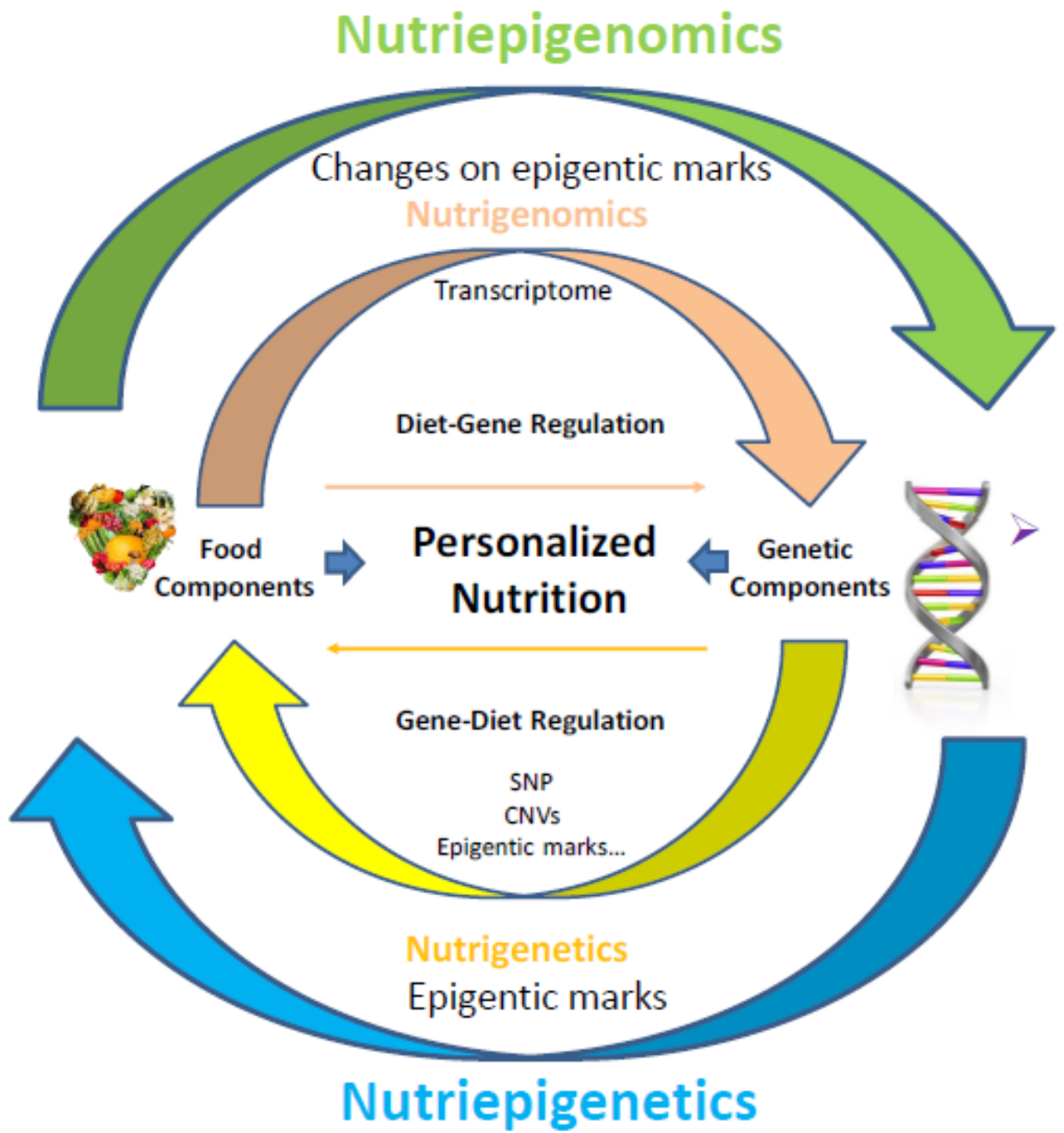
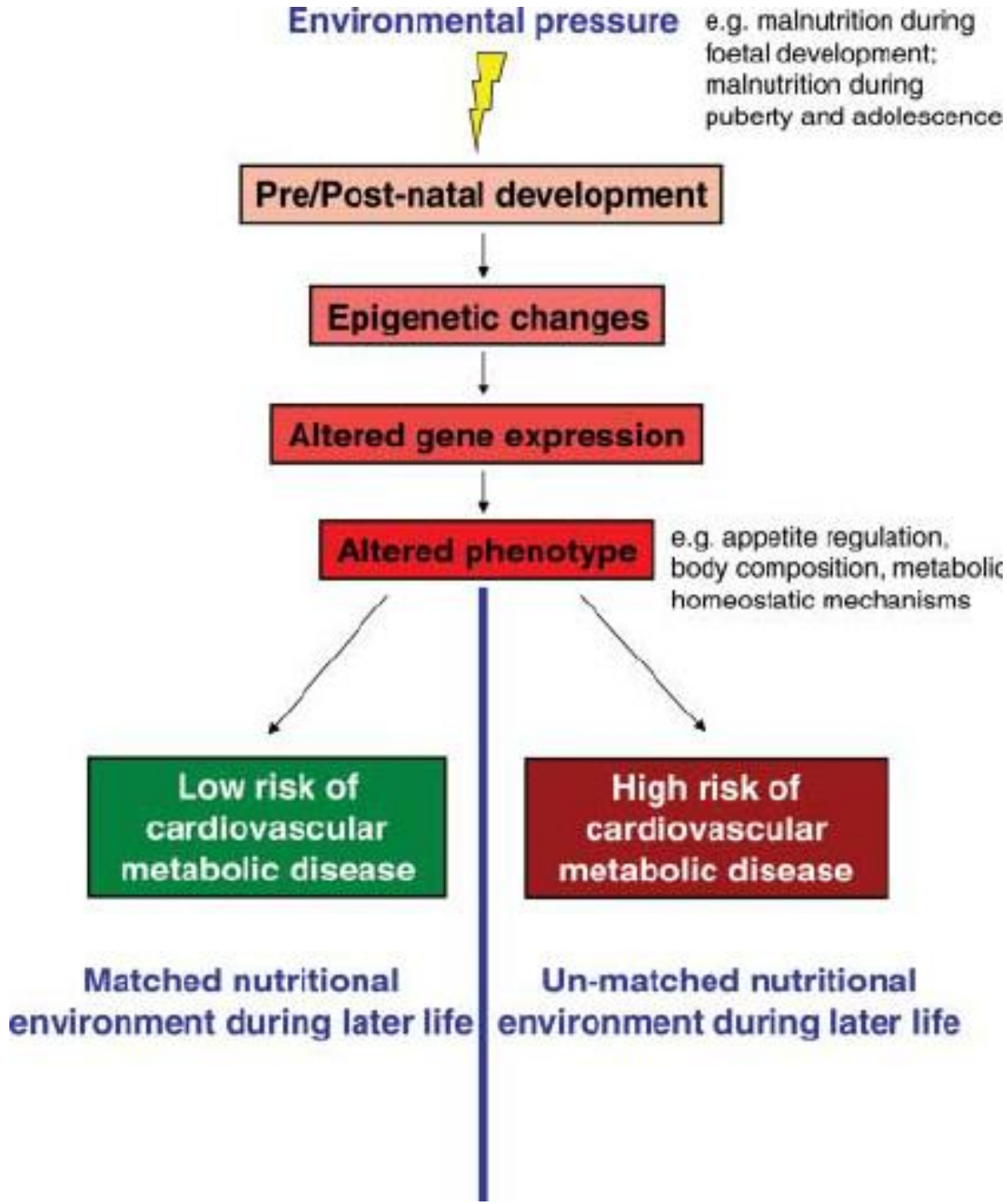
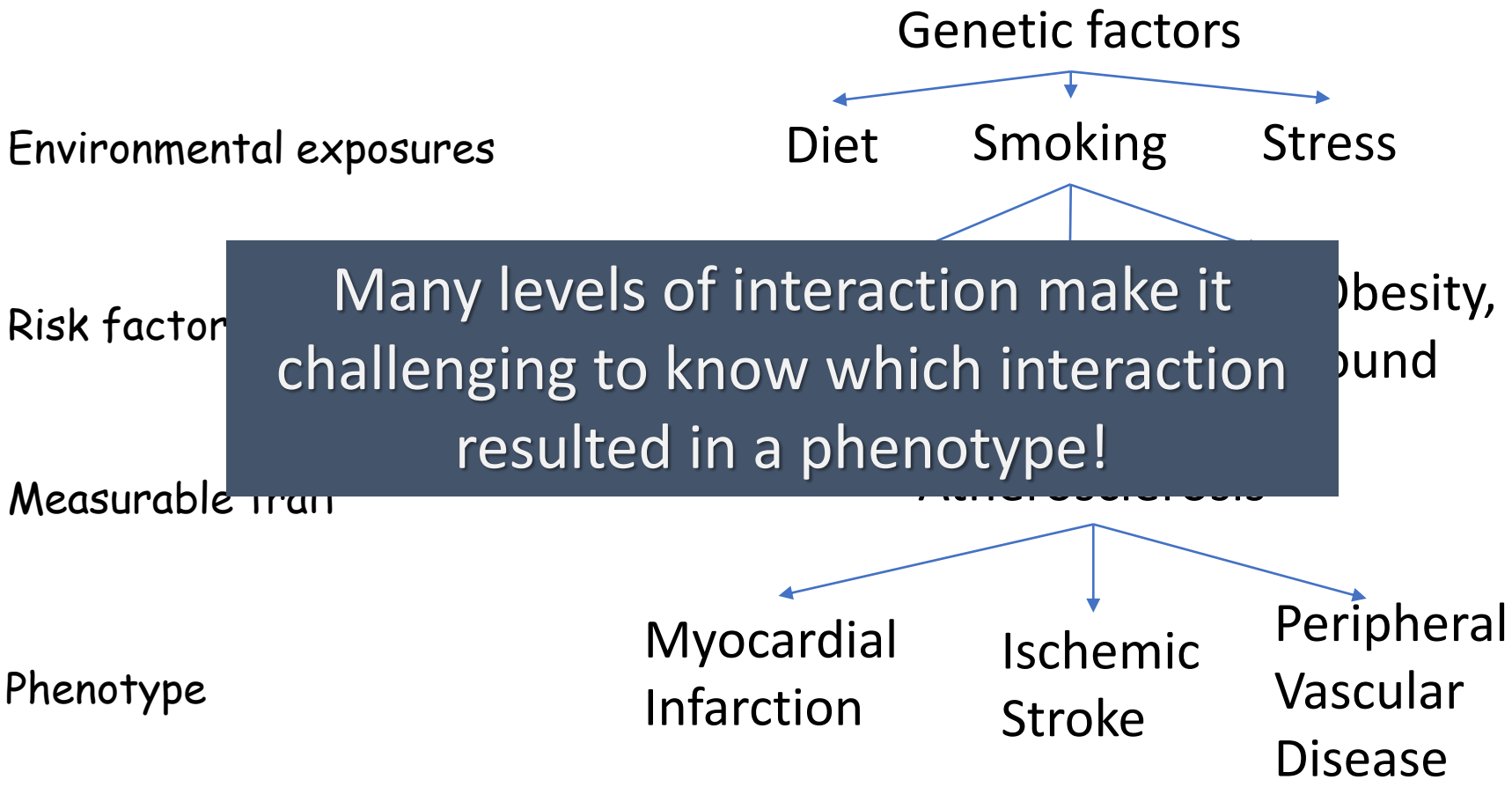


FIGURE 1: "Omics" sciences used in understanding the relationship between nutrition versus health versus disease (source: [4], with modifications; [9] with modifications).


Nutriepigenomics
Changes on epigentic marks
Nutrigenomics
Transcriptome
Diet-Gene Regulation
Food Components
Personalized Nutrition
Genetic Components
Gene-Diet Regulation
SNP
CNVs
Epigentic marks...
Nutrigenetics
Epigentic marks
Nutriepigenetics


Environmental pressure
e.g. malnutrition during foetal development; malnutrition during puberty and adolescence
Pre/Post-natal development
Epigenetic changes
Altered gene expression
Altered phenotype
e.g. appetite regulation, body composition, metabolic homeostatic mechanisms
Low risk of cardiovascular metabolic disease
High risk of cardiovascular metabolic disease
Matched nutritional environment during later life
Un-matched nutritional environment during later life

The complexity of interaction…



Many levels of interaction make it challenging to know which interaction resulted in a phenotype!

Slide adapted from Mente, A.

Pentingnya nutrisi yang adekuat dimasa 1000 hari pertama kehidupan

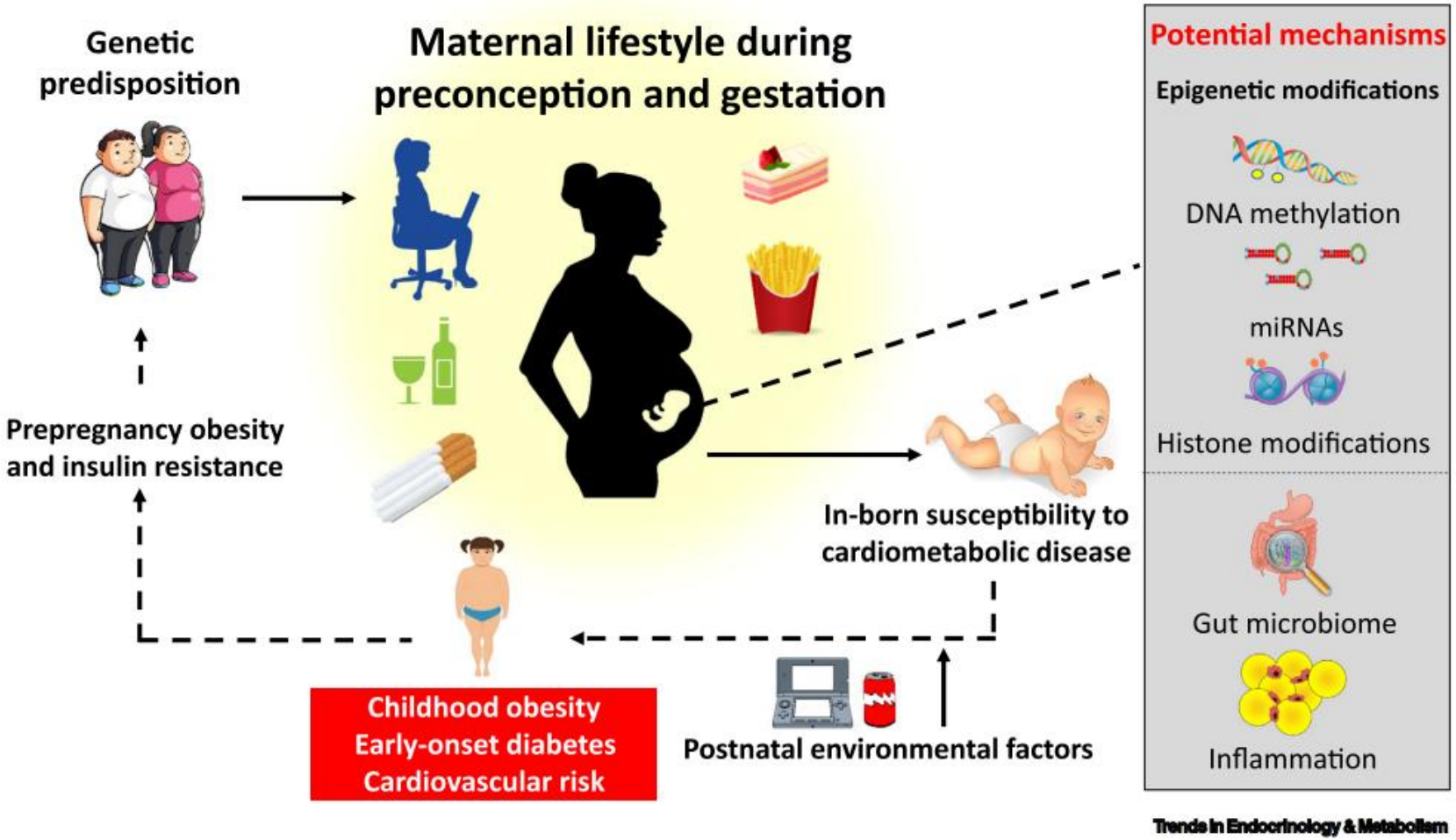
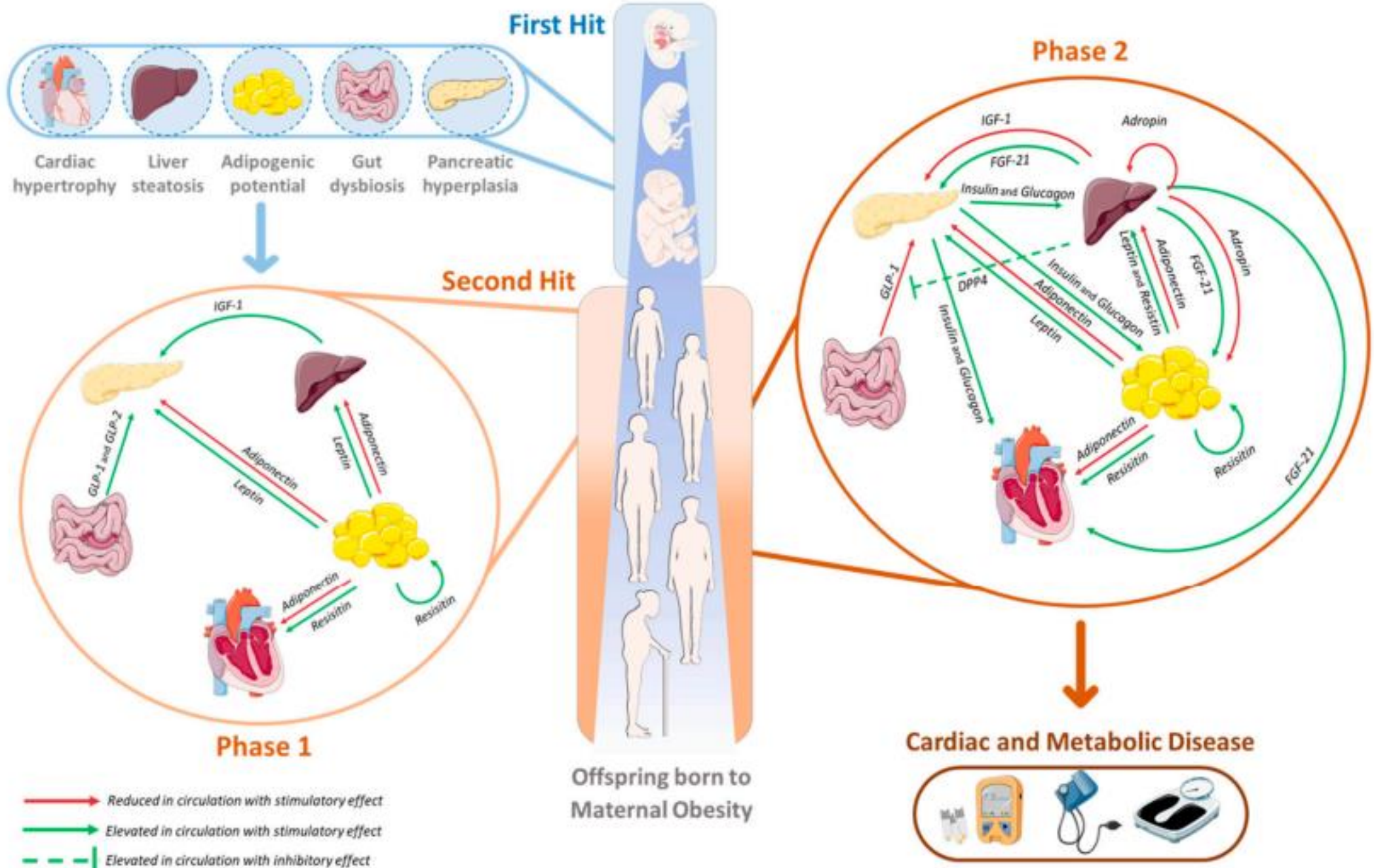


Figure 1. The Intergenerational Cycle of Chronic Cardiometabolic Disorders. Poor preconception and gestational maternal lifestyle predispose both mother and baby to unfavourable pregnancy outcomes, creating an intergenerational cycle of obesity, insulin resistance, and associated disorders.


First Hit
Cardiac hypertrophy
Liver steatosis
Adipogenic potential
Gut dysbiosis
Pancreatic hyperplasia
Second Hit
Phase 1
IGF-1
GLP-1 and GLP-2
Adiponectin
Leptin
Adiponectin
Leptin
Adiponectin
Resistin
Resistin
Offspring born to Maternal Obesity
Phase 2
IGF-1
Adropin
FGF-21
Insulin and Glucagon
GLP-1
DPP4
Insulin and Glucagon
Adiponectin
Leptin
Leptin and Resistin
Adiponectin
FGF-21
Adropin
Insulin and Glucagon
Adiponectin
Resistin
Resistin
FGF-21
Cardiac and Metabolic Disease
Reduced in circulation with stimulatory effect
Elevated in circulation with stimulatory effect
Elevated in circulation with inhibitory effect

Contoh aplikasi: NUTRIGENME

Summary of Results

Nutrient Metabolism

Dietary Component	Gene, rs Number	Risk Variant	Your Variant	Your Risk	Recommendations
Vitamin A	BCMO1, rs11645428	GG	GG	Elevated	Focus on consuming pre-formed sources of vitamin A.
Vitamin B_{12}	FUT2, rs601338	GG or GA	GG	Elevated	Focus on consuming bioavailable sources of vitamin B12.
Vitamin C	GSTT1, rs2266633	Del	Del	Elevated	Meet the RDA for vitamin C daily.
Vitamin D	CYP2R1, rs10741657	Algorithm	GA	Elevated	Consume 1000 IU (25 mcg) vitamin D daily.
	GC, rs2282679		GT		
Vitamin E	COMT, rs4680	GG	AA	Typical	Meet the RDA for vitamin E daily from food sources rich in vitamin E.
Folate	MTHFR, rs1801133	CT or TT	CC	Typical	Meet the RDA for folate daily.
Choline	MTHFD1, rs2236225	AG or AA	AG	Elevated	Meet the AI for choline daily.
Calcium	GC, rs7041	Algorithm	TT	Typical	Meet the RDA for calcium daily.
	GC, rs4588		CA		
Iron Overload	SLC17A1, rs17342717	Algorithm	CC	Low	Follow the recommendations provided in the Low Iron Status section.
	HFE, rs1800562		GG		
	HFE, rs1799945		CC		
Low Iron Status	TMPRSS6, rs4820268	Algorithm	GA	Elevated	Meet the RDA for iron and consume sources of vitamin C with iron-rich foods.
	TFR2, rs7385804		AA		
	TF, rs3811647		GA		

Food Intolerances

Dietary Component	Gene, rs Number	Risk Variant	Your Variant	Your Risk	Recommendations
Lactose	MCM6, rs4988235	CC or CT	CC	Elevated	Limit dairy intake if you experience gastrointestinal symptoms.
Gluten	HLA, rs2395182	Algorithm	GT	Medium	Medium risk for gluten intolerance.
	HLA, rs7775228		TT		
	HLA, rs2187668		CT		
	HLA, rs4639334		GG		
	HLA, rs7454108		TT		
	HLA, rs4713586		AA		
Caffeine	ADORA2A, rs5751876	TT	CT	Typical	Follow the recommendations provided by the CYP1A2 gene section of this report.

Cardiometabolic Health

Dietary Component	Gene, rs Number	Risk Variant	Your Variant	Your Risk	Recommendations
Caffeine	CYP1A2, rs2472300	GA or AA	GG	Typical	Limit caffeine intake to 300 or 400 mg/day.
Glycaemic Index	TCF7L2, rs12255372	TT or GT	GG	Typical	Make at least half of grain products whole grain.
Sodium	ACE, rs4343	GA or AA	GG	Typical	Limit sodium intake to 2300 mg/day.
Omega-6 and Omega-3 Fat	FADS1, rs174547	CC or CT	CC	Elevated	Consume up to 5% of energy per day of omega-6 LA fat and 0.8%-1.2% of energy per day of omega-3 ALA fat.
Physical Activity	LIPC, rs1800588	TT or CT	TT	Enhanced	Aim for at least 150 min/week of cardio and at least 2 days/week of muscle-strengthening activities.

Weight Management and Body Composition

Dietary Component	Gene, rs Number	Response Variant	Your Variant	Your Response	Recommendations
Physical Activity	FTO, rs9939609	Algorithm	TA	Typical	Aim for 150 min/week of cardio and at least 2 days/week of muscle-strengthening activities.
	ADRB2, rs1042713		GG		
Energy	UCP1, rs1800592	GG or GA	AA	Typical	For weight loss, aim for a daily energy deficit of 10-20% from your current energy needs.
Protein	FTO, rs9939609	AA	TA	Typical	Consume 15-25% of energy from protein.
Total Fat	TCF7L2, rs7903146	TT	CC	Typical	Consume 20-35% of energy from fat.
Saturated Fat	APOA2, rs5082	CC	TT	Typical	Limit intake of saturated fat to no more than 10% of energy.
Saturated and Unsaturated Fat	FTO, rs9939609	TA or AA	TA	Enhanced	Limit intake of saturated fat to no more than 10% of energy. Consume at least 5% of energy from polyunsaturated fat.
Monounsaturated Fat	PPARγ2, rs1801282	GG or GC	CC	Typical	Aim for a balance of saturated, monounsaturated and polyunsaturated fats to meet your total daily fat intake.

Eating Habits

Dietary Component	Gene, rs Number	Risk Variant	Your Variant	Your Risk/ Response	Recommendations
Fat Taste Perception	CD36, rs1761667	GG or GA	GG	Enhanced	You have an enhanced ability to sense the fatty taste of foods.
Sugar Preference	GLUT2, rs5400	CT or TT	CC	Typical	Your preference for sugar is typical.
Eating Between Meals	MC4R, rs17782313	CC or CT	TT	Typical	Your tendency to eat between meals is typical.

Exercise Physiology, Fitness and Injury Risk

Dietary Component	Gene, rs Number	Risk/ Response Variant	Your Variant	Your Risk/ Response	Recommendations
Motivation to Exercise	BDNF, rs6265	AA or AG	AG	Enhanced	You have an enhanced innate motivation to exercise.
Exercise Behavior	CYP19A1, rs2470158	Algorithm	GG	Typical	You have a typical likelihood of engaging in physical activity.
	LEPR, rs12405556		TT		
Power and Strength	ACTN3, rs1815739	TC or CC	CC	Ultra	You have a genetic advantage to excel in power sports.
Endurance	NFIA-AS2, rs1572312	Algorithm	CC	Enhanced	You have a genetic advantage to excel in endurance sports.
	ADRB3, rs4994		TC		
	NRF2, rs12594956		CA		
	GSTP1, rs1695		AG		
	PGC1a, rs8192678		AA		
Muscle Damage	ACTN3, rs1815739	TC or TT	CC	Typical	Meet general guidelines for warming up and cooling down.
Pain	COMT, rs4680	GG or GA	AA	Typical	You have a typical pain tolerance.
Bone Mass	WNT16, rs2707466	TC or CC	CC	Elevated	Focus on weight-bearing exercises and ensure adequate amounts of bone-building nutrients.
Achilles Tendon Injury	COL5A1, rs12722	CT or TT	CC	Typical	You have a typical risk for Achilles tendon injury.

CANCER CACHEXIA

Definition

- Cachexia is a debilitating wasting syndrome associated with involuntary weight loss and is derived from the Greek words “kakos,” meaning bad, and “hexis,” meaning condition (Fearon et al. 2012)
- Cachexia occurs in multiple diseases such as chronic kidney, heart and obstructive pulmonary diseases, AIDS, and cancer (Fearon et al. 2013, von Haehling et al. 2016).
- In 1858, the English ophthalmologist John Zachariah first used the term “cancerous cachexia” to describe the wasting syndrome associated with malignancy (Bennani-Baiti & Walsh 2009, Laurence 1858).
- However, a formal definition for cancer-associated cachexia was only recently conceptualized (Fearon et al. 2011) as “a multifactorial syndrome characterized by ongoing loss of skeletal muscle (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment”

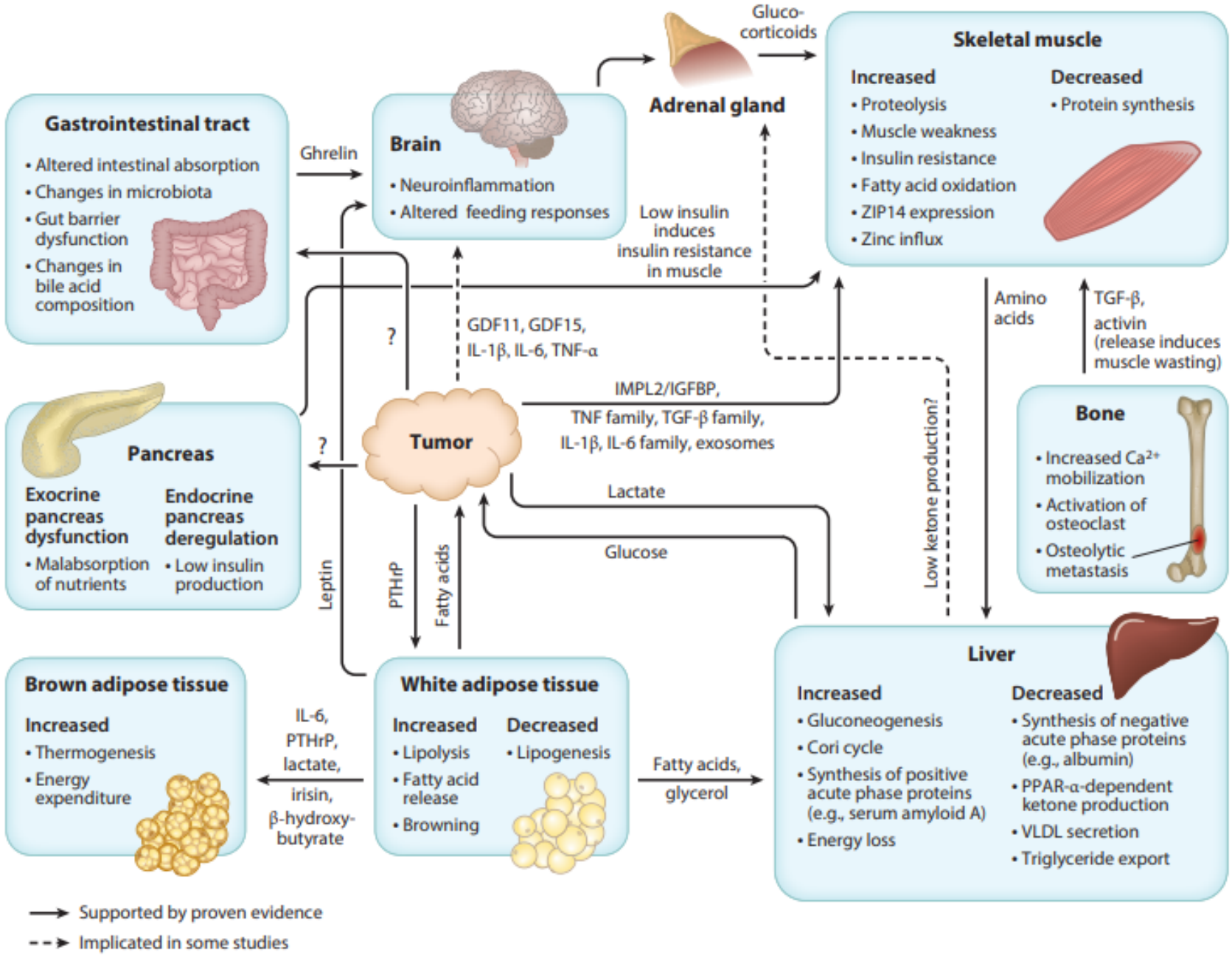

Gastrointestinal tract
• Altered intestinal absorption
• Changes in microbiota
• Gut barrier dysfunction
• Changes in bile acid composition
Ghrelin
Brain
• Neuroinflammation
• Altered feeding responses
Adrenal gland
Gluco-corticoids
Skeletal muscle
Increased
• Proteolysis
• Muscle weakness
• Insulin resistance
• Fatty acid oxidation
• ZIP14 expression
• Zinc influx
Decreased
• Protein synthesis
Low insulin induces insulin resistance in muscle
Amino acids
TGF-β, activin (release induces muscle wasting)
GDF11, GDF15, IL-1β, IL-6, TNF-α
?
Pancreas
Exocrine pancreas dysfunction
• Malabsorption of nutrients
Endocrine pancreas deregulation
• Low insulin production
Tumor
IMPL2/IGFBP, TNF family, TGF-β family, IL-1β, IL-6 family, exosomes
Lactate
Glucose
Low ketone production?
Bone
• Increased Ca2+ mobilization
• Activation of osteoclast
• Osteolytic metastasis
Leptin
PTHrP
Fatty acids
Brown adipose tissue
Increased
• Thermogenesis
• Energy expenditure
IL-6, PTHrP, lactate, irisin, β-hydroxy-butyrate
White adipose tissue
Increased
• Lipolysis
• Fatty acid release
• Browning
Decreased
• Lipogenesis
Fatty acids, glycerol
Liver
Increased
• Gluconeogenesis
• Cori cycle
• Synthesis of positive acute phase proteins (e.g., serum amyloid A)
• Energy loss
Decreased
• Synthesis of negative acute phase proteins (e.g., albumin)
• PPAR-α-dependent ketone production
• VLDL secretion
• Triglyceride export
Supported by proven evidence
Implicated in some studies

Table 1. Cytokines mainly associated with the pathogenesis of cachexia, evidence derived from human studies is italicized

Pro-inflammatory cytokines		
TNFα	Promotes tissue proteolysis and NF-kB activation	Han *et al.*[18]
	Promotes anorexia and fatigue in cancer patients	Jakubowski et al.[17]
IL-1	Promotes anorexia	Uehara *et al.*[23]
	Genetic polymorphisms resulting in increased IL-1β levels are marker of poor prognosis	Graziano et al.[25]
IL-6	Increased circulating levels are poor prognosis markers	Kuroda et al.[28] Mantovani et al.[46]
	It can be produced directly by the tumor and trigger cachexia	Baltgalvis *et al.*[26]
	Increased fat tissue browning	Petruzzelli *et al.*[120]
IFNγ	Synergize with TNFα in promoting muscle wasting	Acharyya *et al.*[21]

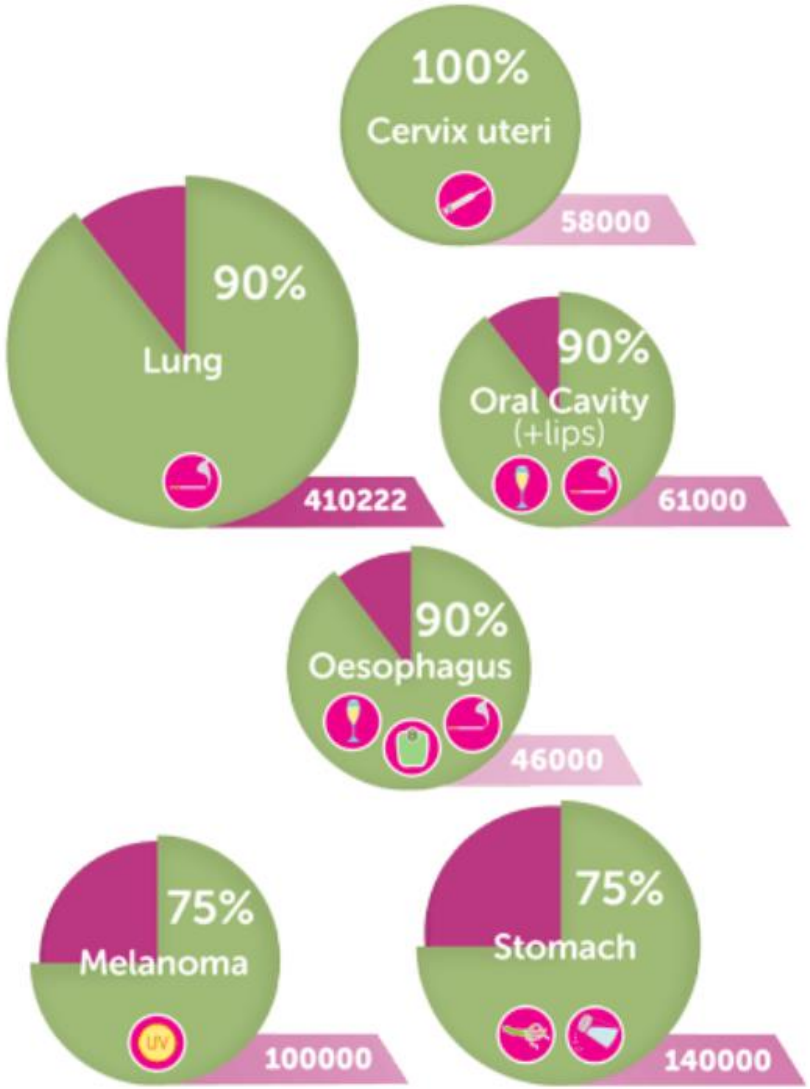
Abbreviations: IFNγ, interferon gamma; IL-1, interleukin-1; IL-6, interleukin-6; TNFα, tumor necrosis factor alpha.

Table 2. Molecular mechanisms driving skeletal muscle atrophy during cachexia, evidence derived from human studies are *italicized*

Skeletal muscle wasting		
UPR	Upregulation of the ubiquitin-proteasome pathway in cancer model	Baracos *et al.*[60]
	Proteasome and NF-kB inhibitors prevent experimental cancer cachexia	Chacon-Cabrera *et al.*[65]
	UPR activation is required for muscle atrophy	Bodine *et al.*[59]
Authophagy	It is induced in the skeletal muscle of cancer patients	Op den Kamp et al.[70] Tardif et al.[71] Boyer-Guittaut et al.[72]
	Promotes muscle wasting during cachexia	Penna *et al.*[68]
ActRIIB	Decoy receptor reverses muscle wasting	Zhou *et al.*[50]
	Cachectic patients present increased circulating levels of ActRIIB ligand, activin	Loumaye et al.[49]
	Myostatin (ActRIIB ligand) knock-out prevents experimental cachexia	Gallot *et al.*[48]
Lipid wasting		
Lipolysis	Adipose Triglyceride Lipase inhibition prevents muscle wasting in experimental cachexia.	Das and Hoefler[117]
	Cachectic cancer patients present increased lipolytic activity	

Abbreviations: ActRIIB, activin receptor IIB; UPR, ubiquitin-mediated proteasome degradation.

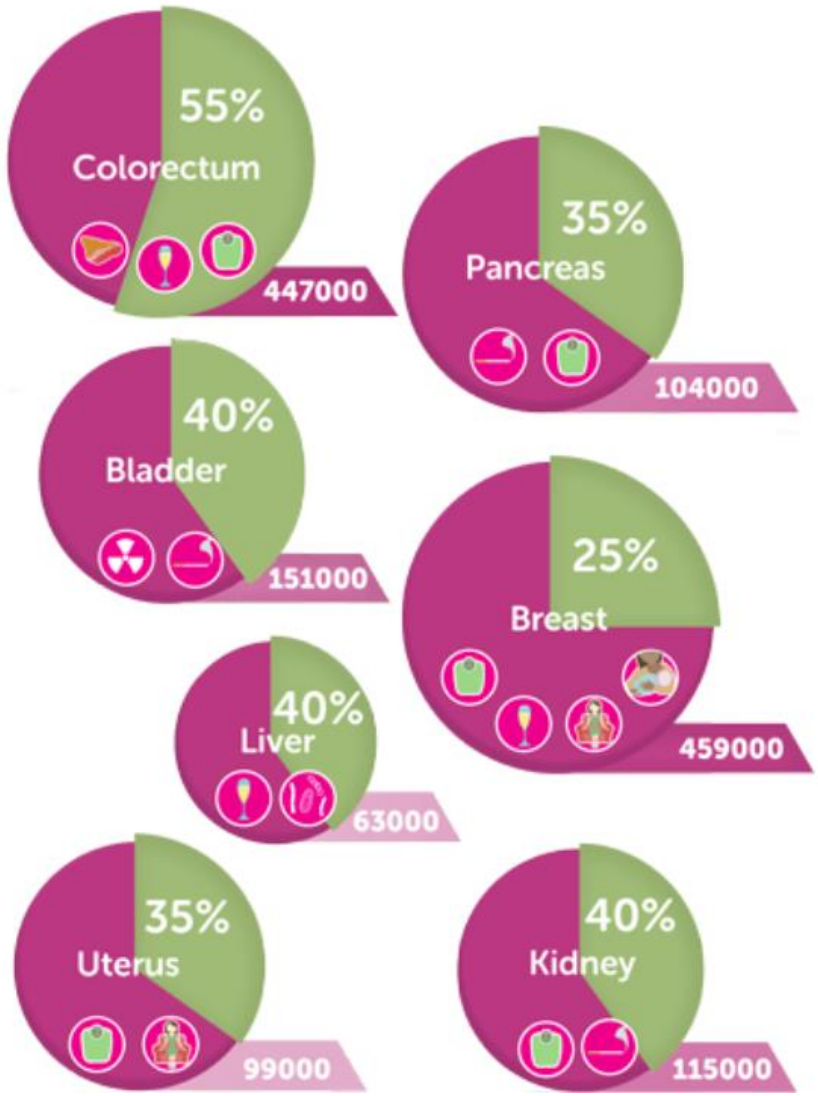
75-100% preventable



Major established modifiable risk/protective factors

- Tobacco
- Body Fatness
- UV Radiation (Sunlight and artificial UV)
- Physical inactivity
- Salt consumption
- Alcohol
- Human papilloma virus infections
- % Preventable (Preventability estimates are for UK)
- Prevention intervention / risk factors
- Processed meat
- Ionising Radiation
- Oral Contraceptives (Protective)
- Breast-feeding (Protective)
- *H. pylori* infections
- Hepatitis B & C infections
- Cancer Type
- Numbers of cancers in Europe

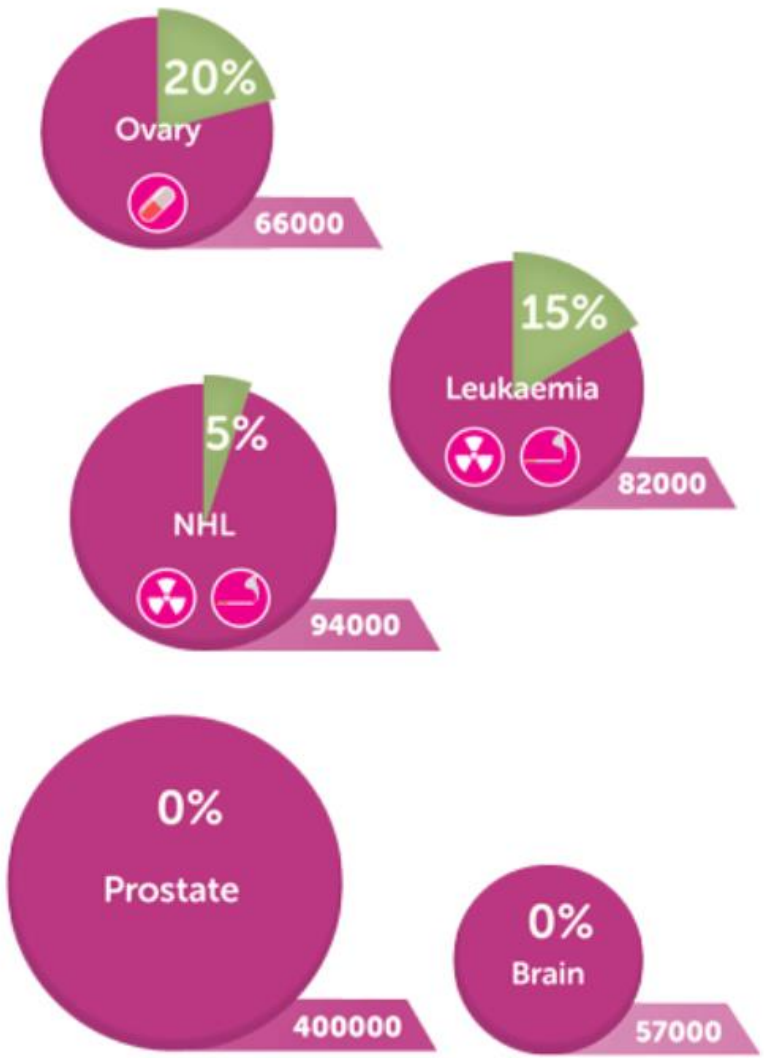
25-74% preventable



Major established modifiable risk/protective factors

- Tobacco
- Body Fatness
- UV Radiation (Sunlight and artificial UV)
- Physical inactivity
- Salt consumption
- Alcohol
- Human papilloma virus infections
- % Preventable (Preventability estimates are for UK)
- Prevention intervention / risk factors
- Processed meat
- Ionising Radiation
- Oral Contraceptives (Protective)
- Breast-feeding (Protective)
- *H. pylori* infections
- Hepatitis B & C infections
- Cancer Type
- Numbers of cancers in Europe

<25% preventable



Major established modifiable risk/protective factors

- Tobacco
- Body Fatness
- UV Radiation (Sunlight and artificial UV)
- Physical inactivity
- Salt consumption
- Alcohol
- Human papilloma virus infections
- % Preventable (Preventability estimates are for UK)
- Prevention intervention / risk factors
- Processed meat
- Ionising Radiation
- Oral Contraceptives (Protective)
- Breast-feeding (Protective)
- *H. pylori* infections
- Hepatitis B & C infections
- Cancer Type
- Numbers of cancers in Europe

IARC Classifications

GROUP	WHAT IT MEANS	EXAMPLES
Group 1 Carcinogenic to Humans	There is sufficient evidence the agent causes cancer in humans.	Solar radiation, processed meats, alcoholic beverages, smoking, asbestos, talc-based baby powder contaminated with asbestos
Group 2A Probably Carcinogenic to Humans	There is sufficient evidence the agent causes cancer in humans.	Anabolic steroids, high temperature frying, HPV, red meat, Roundup (glyphosate), Actos (pioglitazone), N-nitrosodiethylamine (NDMA)
Group 2B Possibly Carcinogenic to Humans	Limited evidence in humans and less than sufficient evidence in animals.	Aloe vera leaf extract, marine diesel fuel, gasoline, engine exhaust, Asian pickled vegetables, progestin, perineal use of talc-based body powder
Group 3 Not Classifiable as to its Carcinogenicity in Humans	Evidence is inadequate in humans and inadequate or limited in animals.	Coffee, low-frequency electric fields, dental materials, ceramic implants, chlorinated drinking water, tea, printing inks

PALIATIVE NUTRITION

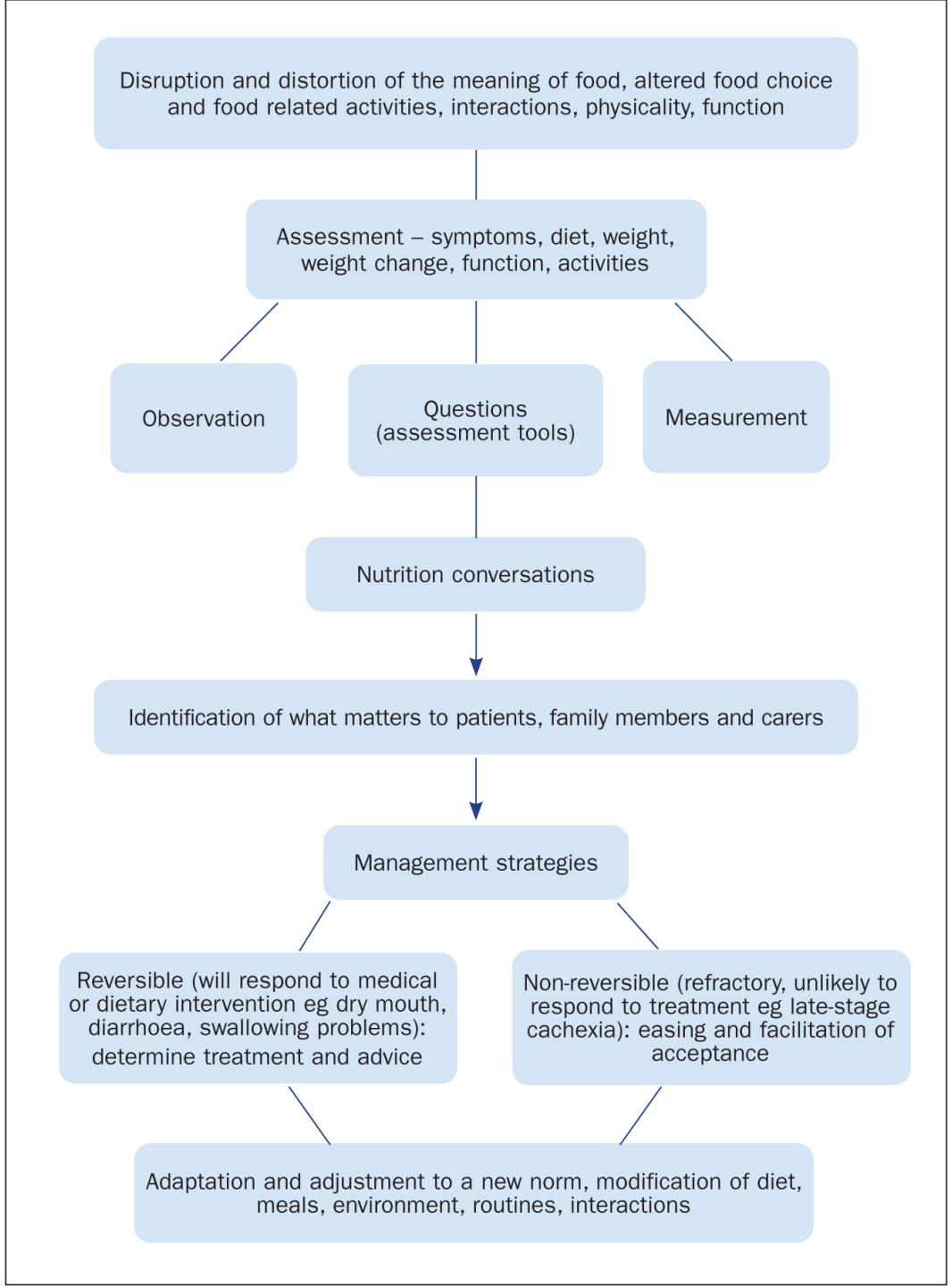

Disruption and distortion of the meaning of food, altered food choice and food related activities, interactions, physicality, function
Assessment – symptoms, diet, weight, weight change, function, activities
Observation
Questions (assessment tools)
Measurement
Nutrition conversations
Identification of what matters to patients, family members and carers
Management strategies
Reversible (will respond to medical or dietary intervention eg dry mouth, diarrhoea, swallowing problems): determine treatment and advice
Non-reversible (refractory, unlikely to respond to treatment eg late-stage cachexia): easing and facilitation of acceptance
Adaptation and adjustment to a new norm, modification of diet, meals, environment, routines, interactions

Table 1. Dietary recommendations according to nutritional impact symptoms.

Symptoms	Dietary Recommendations
Appetite loss, anorexia	• Minimize eating effort by preferring high energy and protein foods through small and frequent snacks throughout the day. • High caloric liquid meals may be useful.
Taste and smell changes	• Adjust diet in accordance with new taste preferences and by avoiding foods that may evoke aversion, such as those with an intense odor (roast meat, fish). • Prefer mildly flavored foods. Cold foods are generally less odorous. • If the oral mucosa is not sensitive, use salt, herbs, spices, and seasonings.
Nausea and vomiting	• Prefer small and frequent snacks throughout the day (crackers, biscuits) in order to avoid stomach emptying. • Take advantage of times when the patient feels less fatigued, or between cycles of chemotherapy. • Less odorous and cold foods may be better tolerated.
Oral mucositis, pain	• Prefer soft, creamy, or liquid foods, and avoid hard ones that could damage the oral membrane (nuts, hard fruit, crusts, hard baked goods). • Prefer foods at room temperature, and avoid hot dishes and beverages. Ice cold foods and fluids may be pleasant. • Avoid extreme tastes, such as spicy and acidic foods, citrus fruits, and very salty products.
Oropharyngeal dysphagia	• Chopping or grinding and moisturizing food (adding cream, gravy, or sauce) allows an adequate thickness to be achieved to facilitate swallowing. • Add a thickener to viscous foods in order to prevent choking. • Avoid mixed consistency foods due to their high choking risk.
Esophageal dysphagia	• Transit of bolus throughout the esophagus can be favored by chopping finely and dipping foods in liquids (drinks, gravy, or sauces). • Chewing well and eating slowly and mindfully are recommended precautions, such as small and frequent meal consumption.
Constipation	• An adequate liquid and fiber intake is aimed at preventing dehydration. • Although 30–40 g of fibers per day is the goal for healthy subjects, this result is difficult to achieve in practice. • Variate different types of fibers.

Table 2. Preferential nutritional routes in different cancer sites.

Tumor Site	Preferential Nutritional Route	Comment
Head, neck	EN	Choose access according to the expected AN duration: • short-term EN: NGT • long-term EN: PEG (RIG or SG when endoscopic procedure is not feasible)
Chest: Esophagus, lung	EN	Choose access according to the expected AN duration: • short-term EN: NGT • long-term EN: PEG (RIG or SG when endoscopic procedure is not feasible) • Self-expandable metal stents: lower survival benefit than PEG
Stomach	EN/PN	Choose access according to the expected AN duration: • short-term EN: NJT • long-term EN: PEJ (SJ when endoscopic procedure is not feasible)In presence of bowel sub-obstruction/obstruction, peritoneal carcinomatosis, severe gastrointestinal symptoms, or EN intolerance: • consider PN
Pancreas, biliary tract, colon-rectum, uterus, ovary, bladder, prostate	PN	In presence of bowel sub-obstruction/obstruction, peritoneal carcinomatosis, severe gastrointestinal symptoms: • consider PN
Others malignancies (e.g., brain, breast, blood)	EN/PN	Choose access according to the expected AN duration: • short-term EN: NGT or NJT (if gastric dysmotility) • long-term EN: PEG or PEJ (if gastric dysmotility) (RIG or SG or SJ when endoscopic procedure is unfeasible)In presence of bowel sub-obstruction/obstruction, peritoneal carcinomatosis, severe gastrointestinal symptoms, or EN intolerance: • consider PN

Legend: AN: artificial nutrition; EN: enteral nutrition; PN: parenteral nutrition; NGT: nasogastric tube; NJT: nasojejunal tube; PEG: percutaneous endoscopic gastrostomy; PEJ: percutaneous endoscopic jejunostomy; RIG: radiologically inserted gastrostomy; SG: surgical gastrostomy; SJ: surgical jejunostomy.