The Radial: Integrative and Functional MNT

Kathie M. Swift, Elizabeth Redmond, and Diana Noland

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5.1 Background

Radial (rā′dē-əl)
radiates from or converges to a common center.
American Heritage Medical Dictionary, 2007

As the field of integrative and functional nutrition took root, a concrete model to help practitioners gain a deep understanding of this approach was needed. The ability to connect, synthesize, and apply information coherently using an integrated, whole systems-based lens to nutrition care led to the development of the Integrative and Functional Medical Nutrition Therapy (IFMNT) Radial [1]. Recent updates to the IFMNT Radial (referred to as the Radial) were based on emerging data on nutritional science, systems biology medicine, omics technologies, and the microbiome.

5.2 Overview

The Radial is a conceptual framework for critical thinking and clinical investigation that graphically depicts the multidimensional facets of a systems-based nutrition assessment in delivering medical nutrition therapy (MNT). The term medical nutrition therapy is defined as "nutritional diagnostic, therapy, and counseling services for the purpose of disease management, which are furnished by a registered dietitian or nutrition professional" [2]. The counseling component of MNT has been described as a "supportive process to set priorities, establish goals and create individualized action plans which acknowledge and foster responsibility for self-care" [3]. The circular architecture of the Radial depicts a person-centered process that allows for the evaluation of complex interactions and interrelationships. The Radial purposefully integrates the evidence-based Nutrition Care Process (NCP) for clinicians to apply an integrative and functional methodology to provide high-quality nutrition care. The radial is the core, five sphere, and four potential triggers.

The five primary spheres of influence in the Radial are as follows:

- Food, lifestyle, and environment
- Nutrition physical, signs, and systems
- Biomarkers
- Metabolic pathways and networks
- Systems (Fig. 5.1)

5.3 Core of the Radial: Personalized Nutrition Care

Personalized nutrition care highlighting the NCP is featured at the core of the Radial. It is centrally positioned and shows the four distinct, interrelated NCP steps including nutrition assessment, diagnosis, intervention, and monitoring/evaluation. Applying the NCP ensures that nutrition care is individualized and holistic using the highest quality information

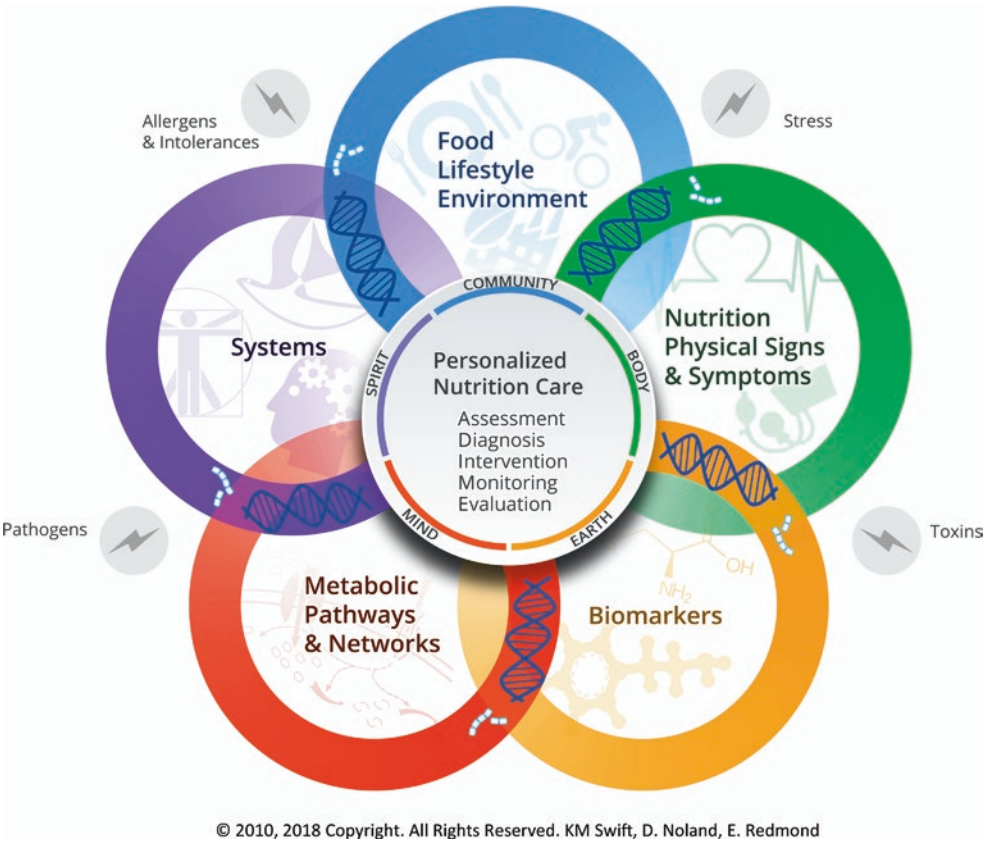

Fig. 5.1 The Radial. (Courtesy of Kathie Madonna Swift, Diana Noland, Elizabeth Redmond)

available to the clinician providing the service. A more detailed description of the NCP can be explored elsewhere [4].

A holistic approach to nutrition care embraces the assimilation of multiple components that influence one's well-being. Health is viewed as a dynamic quality where mind, body, and spirit are engaged in the fullness of life [5].

5.4 Mind, Body, Spirit, Community, and Earth

The Radial core illustrates the intermingling of mind, body, spirit, community, and earth and its association with personalized nutrition care, since all of these factors influence one's health and healing. Mind, body, and spirit are viewed as wholeness versus distinct and separate physiological, psychological, and spiritual units. The value of community and social networks as a component of health and wellness must be considered since social contexts influence biological systems [6]. An appreciation of our intimate connection to the earth and the healing power of nature to foster one's health is also valued as an integrative concept of food and sustainable nutrition.

5.5 DNA Strands and Microbes

The sequencing of the human genome and growing knowledge regarding genetic variation and biotechnological omics advances is contributing to the development of personalized nutrition. The Radial depicts genetic influence by the strands of DNA that surround the core. Personalized nutrition is an application of nutritional genomics and seeks to enhance health through the understanding of "the functional interaction between bioactive food components with the genome at the molecular, cellular, and systemic level in order to understand the role of nutrients in gene expression and… how diet can be used to prevent or treat disease" [7]. Diversity in the genetic profile among individuals impacts nutrient requirements, metabolism, and response to dietary, nutritional, and lifestyle interventions [8].

The microbiome revolution has established that microbial signatures vary between individuals far more than genetics [9]. Dietary habits and lifestyle affect the gut microbiota composition in dramatic ways. This vital influence must be taken into account and is represented by the microbes in the graphic that, like the DNA strands, radiate to all five spheres of the Radial. The composition of the microbiome and its diverse activities are involved in most, if not all, of the biological processes, and thus, it is a key player in health and disease at all stages of the life cycle [9].

The concept of "food as information" influencing genetic expression, manipulating the microbiome and, consequently, supporting or hijacking the patient's physiological systems is cardinal to the integrative and functional model. The Systems sphere radiates from the core of the Radial and underscores the imbalances that are created by poor diet, unhealthy lifestyle behaviors, and environmental exposures such as chronic inflammation, oxidative stress, digestive and detoxification disturbances, metabolic chaos, neuro-endocrine-immune disruption, and nutritional depletion.

5.6 Food, Environment, and Lifestyle

Food is the ideal starting point in an IFMNT assessment since it is a powerful determining factor in health and disease. Hippocrates is credited with the "food as medicine" philosophy, although scholars debate the origin of this theme since nutrition has been a central premise in ancient, traditional forms of medicine [9, 10]. A modern, integrated concept of food as medicine emphasizes scientific understanding of nutrition with lifestyle behaviors in relation to a person's ability to realize vital goals of healthy living. Food is valued as an instrument for vibrant health and an essential tool to kindle healing by restoring nutritional integrity.

Changes in the human diet and food systems have altered crucial nutritional attributes that impact biological systems including glycemic and insulinogenic load, carbohydrate quality, fiber content, fatty acid composition, macronutrient balance, micronutrient density, phytonutrient richness, sodium-potassium ratio, and acid-base balance [11]. A theme of healthful eating that considers these nutritional factors has been described with the strength of evidence supporting a plant-based diet with foods close to nature [12]. Other elements of diverse diets and healthy dietary patterns include limited refined starches, added sugars including fructose, avoidance of ultra-processed foods, and limited intake of certain fats.

Personalized nutrition extends beyond these general principles of healthy eating and targets the underlying root causes of system imbalances, is specific to the individual's unique nutrient requirements, and is designed with biological compatibility and lifestyle in mind [13]. It seeks to understand how diet and lifestyle-related modulators act together and coconspire to create the perfect storm of complex, chronic disease. For example, personalized nutrition recognizes that following general nutrition guidelines may result in high glycemic responses in some individuals, accelerating metabolic decline and that there can be unique dietary responses because of biochemical uniqueness. Thus, consideration of personal variables including sex, age, genetics, biomarkers, lifestyle, and environmental factors must be taken into account in tailoring a personalized nutrition prescription [14]. Food intolerances such as gluten, fructose, FODMAPs, food chemicals, and histamine are other examples of the dietary discord that can impact the health of some individuals while not affecting others. The age-old saying, "one person's meat is another person's poison," is now viewed in light of the scientific revelation that the multi-tasking, metabolically active microbes play a significant role in the unique interpretation by the body of food as friend or foe [15].

To be effective, personalized nutrition care must integrate the scientific approach with cultural, emotional, ethical, spiritual, social, and sensual understandings of food [16]. The

science of nutrition and the *art* of dietary behavior change are indispensable partners in personalized nutrition care that is relational in nature. The heart of nutrition assessment lies in a therapeutic relationship that values the patient's story (see ▶ Chap. 39). This means that the nutrition professional is able to listen reflectively to the patient's narrative, absorb what the person is sharing, and understand their concerns. It must go beyond root-cause analysis of medical history, anthropometrics, symptomatology, testing, and other metrics and focus on the patient's humanity and their desire to shape their well-being. This requires skills and competencies in addressing health behaviors and engaging the patient in self-care management of mind, body, and spirit. It implies attention of the patient on their personal health goals, increased self-awareness, and commitment on ways to achieve and maintain optimal health. Shared decision-making by both the clinician and patient is essential in the design of a nutrition intervention plan that is truly personalized, actionable, practical, sustainable, and, ultimately, successful.

Integrative health questionnaires can assist the clinician in the personalized nutrition care process. Supportive tools include food records, activity journals, circadian patterns, timeline of significant medical events, medication and dietary supplement lists, symptom appraisal forms, nutrition-focused physical findings, and biomarker results from both conventional and functional laboratory testing. Individual health risks of diet, physical activity, substance abuse, excess stress, sleep deprivation, environmental toxins, pathogens, food allergens, and intolerances must also be unearthed. Open-ended questions can reveal aspects of the patient's story that may not have been revealed in specific data collection tools and techniques. These questions can help the clinician and patient as co-investigators in uncovering unique and deeply personal themes that affect an individual's health:

- *Did something trigger a change in your health?*
- *What makes you feel better?*
- *What makes you feel worse?*
- *Have you made any changes in your eating habits or lifestyle because of your health?*
- *What do you think would make the most difference in your health and well-being?*
- *In your own words, tell me your story…*

The personalized nutrition care process, when delivered skillfully, engages the patient in self-care to attain their highest health potential. A thorough understanding of how the trilogy of food, environment, and lifestyle impact physiological systems must be realized for the clinician to apply this in practice and support the patient with a truly personalized care plan.

5.7 Nutrition Physical Exam and Signs and Symptoms

Most patient encounters begin by hearing the patient's story with appropriate history taking, identifying the signs and symptoms with which they are presenting, and the nutrition physical exam (NPE). Universally, basic anthropometrics are measured: blood pressure, height, weight, and calculating BMI. For the IFMNT approach, the NPE can be expanded with tools that add more detailed information for assessing the nutritional and body composition status. These tool options to consider collecting nutrition data are:

- Tape measure: measures waist circumference
- Bioelectric impedance analysis (BIA) (full body): measures several parameters described in ▶ Chap. 22 on Body Composition. One of the measurements most commonly appreciated is percentage of body fat/lean mass and BMI.
- Fingertip Pulse Oximeter Blood Oxygen Saturation Monitor: measures oxygen saturation and pulse rate
- Oral/axillary thermometer: measures body temperature
- Calipers: measures body fat

Signs and symptoms can be documented by patient questionnaires completed prior to the client visit, or upon arrival at the appointment. The medical symptoms questionnaire (MSQ) commonly used in integrative and functional medicine practice measures symptoms based on systems biology, according to body systems. The practitioner's assessment of the questionnaire can be done quickly to easily see where the system priorities are to consider for diagnosis and intervention for the client. The systems and related symptoms often included on the questionnaire are:

- *HEAD*: headache, faintness, dizziness, insomnia
- *EYES*: Watery or itchy eyes; swollen, reddened/sticky eyelids; bags, dark circles; blurred or tunnel vision (does not include near or far-sightedness)
- *EARS*: Itchy ears; earaches, ear infections; drainage from ear; ringing/hearing loss
- *NOSE*: Stuffy nose, sinus problems, hay fever, sneezing attacks, excessive mucus
- *MOUTH/THROAT*: Chronic coughing; gagging/throat clearing; sore throat, hoarseness; swollen/discolored tongue, gums, lips; canker sores
- *HEART*: Irregular/skipped beats, rapid/pounding beats, chest pain
- *SKIN*: Acne; hives, rashes, dry skin; hair loss; flushing, hot flashes; excessive sweating
- *LUNGS*: Chest congestion; asthma, bronchitis; shortness of breath; difficulty breathing
- *DIGESTIVE TRACT*: Nausea, vomiting; diarrhea; constipation; bloated feeling; belching, passing gas; heartburn; intestinal/stomach pain
- *JOINTS/MUSCLE*: Pain or aches in joints, arthritis, stiffness/limited movement, pain or aches in muscles, feeling of weakness or tiredness
- *WEIGHT*: Binge eating/drinking, craving certain foods, excessive weight, compulsive eating, water retention, underweight
- *ENERGY/ACTIVITY*: Fatigue/sluggishness; apathy, lethargy; hyperactivity; restless leg; jetlag
- *MIND*: Poor memory; confusion, poor comprehension; poor concentration; poor physical coordination;

difficulty making decisions; stuttering or stammering; slurred speech; learning disabilities
- *EMOTIONS*: Mood swings; anxiety, fear, nervousness; anger, irritability, aggressiveness; depression
- *OTHER*: Frequent illness; frequent or urgent urination; genital itch or discharge; bone pain
- *PAST SURGERIES AND DATES*: See ▶ Chap. 56 for a sample questionnaire.

5.8 Biomarkers

Nutrition-related biomarkers are biological indicators. While a nutrition assessment is essential to assess what nutrients the diet is providing, an evaluation of biomarkers may provide a more detailed picture of what the client is actually digesting, absorbing, and utilizing. Diet assessments may not always coordinate with laboratory values of individual nutrients. This may be due to many factors, such as an individual having a greater need for a nutrient than the RDA, poor-quality food or supplements, a genetic variation, impaired absorption, exposure to a specific toxin whose detoxification requires specific nutrients, etc.

5.9 Laboratory Testing

Most clinicians are familiar with conventional laboratory testing of standard markers. In addition to conventional lab testing, integrative and functional clinicians also often utilize specialty diagnostic laboratories, which are often early adopters of new testing. Functional medicine was an early adopter of the concept of utilizing organic acid measurements for assessment of biochemical pathways and metabolomics. Functional medicine clinicians also incorporate a systems-based interpretation of standard laboratory tests.

There are two primary types of laboratory tests: indirect (also referred to as functional) or direct.

A functional test is an evaluation of an analyte that is dependent on the marker. For example, levels of methylmalonic acid (MMA) measure functional need for vitamin B12. Vitamin B12 is a nutrient cofactor needed for the enzyme methylmalonyl-CoA mutase. It breaks down L-methylmalonyl-CoA to succinyl-CoA, which then goes into the Krebs cycle. If vitamin B12 is not available in adequate amounts, the pathway will stall and MMA will build up. Thus, elevated MMA levels in both urine and blood have been correlated to vitamin B12 deficiency [17].

Direct laboratory testing identifies levels that are actually there, such as serum 25-hydroxy vitamin D. Though there has been significant disagreement on the "ideal" vitamin D level, as the level needed for an individual may vary significantly, there is strong consensus on the specimen selection of serum 25-hydroxy vitamin D.

Specimen selection should generally be based on what literature has identified. For example, urine amino acids can identify what a person has eaten over the last few days, while serum amino acids can tell more about overall amino acid status. Additionally, whole blood lead may not be the best way to assess lead levels, but it is the way public health organization and researchers check lead levels, and thus if you are evaluating lead levels, it is best to check whole blood lead so comparisons can be made.

Beyond specimen selection, clinicians should be aware of reference ranges and how they are set. While some biomarkers have medical decision points identifying what each level means, such as levels of A1C, other markers do not have a standard accepted reference range or decision point. For many markers, the reference range is represented by what has been noted within a "normal" population. A patient is considered abnormal if they are more than 2 standard deviations (>95.4%) from the mean within the population utilized to set the reference range. Researchers may correlate values with disease status, but if comparisons are made to research studies, the laboratory technique and reference range population must be compared. For example, elevated alpha-hydroxybutyrate has been associated with insulin resistance, but the specific level is not established.

Integrative and functional clinicians look at several areas of laboratory assessments, including metabolism, inflammation and immune reactions, nutrition, nutrigenomics, digestion and absorption, biotransformation, etc.

Metabolism: Metabolism includes energy metabolism and metabolomics. Metabolomics accesses metabolite profiles to detect which biomarkers or biomarker patterns are associated with a disease in the hope of better defining a specific metabolic profile for each condition or disease. It has also been referred to as the specific metabolic "fingerprint" that is unique to each person and disease. In other words, metabolomics takes into account the impact of lifestyle factors like diet, movement, and the environment to illustrate overall health.

Inflammation: Evaluation of inflammation can identify systemic inflammation, such as hsCRP, or it can be site-specific, such as fecal calprotectin to evaluate gastrointestinal inflammation. Different specimen types can identify the type of inflammation, lipid peroxides identify fatty acid membrane oxidation, and 8-hydroxy-2-deoxyguanosine evaluates oxidative damage to DNA. Oxidative stress and inflammation are key markers of nutrient deficiencies [18]. Nutrients are the substrates for many immune reactions, such as fatty acids and immune cytokines. Nutrients can also modulate the immune system, for example, antioxidants tempering immune responses to inflammation. While classic inflammation is short term, chronic "metaflammation" is a low-level long-term inflammation that is associated with inflammation-related diseases. Chronic inflammation differs because there is only a small rise in immune markers (i.e., a four- to sixfold increase versus a several hundred-fold increase seen in acute reactions) which can lead to systemic effects and is associated with a reduced metabolic rate [19].

Testing can also identify the immune system's reaction to components in foods, such as proteins, toxins, and other bioactive components. Functional medicine evaluates a patient's

Table 5.1 Micronutrient laboratory assessment

Minerals	IOM assessment [22–24]	Possible functional or other testing options
Magnesium	A serum magnesium concentration of less than 0.75 mmol/liter (1.8 mg/dl) is thought to indicate magnesium depletion.	Serum/plasma magnesium concentration, red blood cell (RBC) magnesium concentration, and urinary magnesium excretion appear to be useful biomarkers of magnesium status in the general population [25].
Zinc	Factorial analysis was used to set the Estimated Average Requirement (EAR).	Physical growth response to zinc supplementation [24]. While both plasma and serum zinc concentrations are used as indicators of zinc status, plasma zinc concentration is preferable because of the lack of contamination of zinc from the erythrocyte [26].
Copper	The primary criterion used to estimate the EAR for copper is a combination of indicators, including plasma copper and ceruloplasmin concentrations, erythrocyte superoxide dismutase activity, and platelet copper concentration in controlled human depletion/repletion studies.	Low serum copper. Serum copper and ceruloplasmin levels may fall 30% in deficiency [27]. An elevated homovanillate/vanilmandelate has been reported to identify copper need since the conversion of dihydroxyphenylalanine (DOPA) to epinephrine requires copper, though research is limited. Homovanillate is the breakdown product of DOPA and vanilmandelate is the breakdown product of epinephrine and nor-epinephrine. The ratio has been used as a screening for Menkes [28].
Vitamins	**IOM assessment**	**Possible functional or other testing options**
Vitamin K	Due to insufficient laboratory values to estimate levels, an Adequate Intake (AI) was set based on representative dietary intake data from healthy individuals.	A direct measure of vitamin K is not of value as both serum and plasma phylloquinone reflect recent intakes (24 hours) and do not responds to changes in dietary intake [24]. Carboxylated Gla (Gla) or undercarboxylated osteocalcin (uc-OC) may be used. A deficiency of vitamin K upregulates the level of serum undercarboxylated osteocalcin (ucOC), and serum ucOC has been found to correlate with fracture risk [29].
Folate	The primary indicator used to estimate the RDA for folate is erythrocyte (RBC) folate in conjunction with plasma homocysteine and folate concentrations.	Serum folate, without a concurrent vitamin B12 deficiency, is a useful biomarker for folate deficiency [30]. Formiminoglutamic acid (FIGLU) is an intermediate metabolite in L-histidine catabolism in the conversion of L-histidine to L-glutamic acid. It may be an indicator of vitamin B12, folic acid deficiency, or liver disease [31]. Measurement of urinary FIGLU excretion after a histidine load has been used as a marker of folate in those with adequate B12 levels [32].
B3 Niacin	The most reliable and sensitive measures of niacin status, also used to set the RDA, was urinary excretion of the two major methylated metabolites, N1-methyl-nicotinamide and its 2-pyridone derivative (N1-methyl-2-pyridone-5-carboxamide).	An increase in urinary excretion of kynurenic acid and a decreased in quinolinic acid were found in pellagra that was corrected with niacin supplementation [33]. Urinary branched chain keto acids (organic acids) positively identified subjects with B vitamin-complex deficiency; those with the highest level of urine branched chain amino acids (BCAA) were more likely to be B vitamin deficiency [34].

reaction to foods or environment. By definition, IgE reactions are true allergic reactions, while other reactions are food intolerances or sensitivities, measured with immunoglobulins (IgG) or white cells, and have significantly less literature support. IgG testing (ELISA) includes IgG1, IgG2, IgG3, and IgG4. IgG testing is controversial, as limited evidence from peer-reviewed research has found correlations with migraines and IBS [20]. Some researchers believe IgG is identifying exposure, since "healthy" people can have elevated levels. Leukocyte testing includes both the mediator release and the leucocyte activation test. Though both evaluate changes in white blood cells, they are different processes. Both are also controversial with limited peer-reviewed literature, though, like IgG, many clinicians claim to find them helpful in clinical practice [21].

Nutrition: As noted, personalized nutrition is specific to the individual's unique nutrient requirements. Table 5.1 identifies examples of both laboratory markers used by the IOM in setting recommended levels, and functional or other testing options. Though there is often controversy with the specific tests selected by the IOM, it is important to know the technique and specimen used, and how other testing options compare to it.

- Micronutrients are common enzyme cofactors. Identifying inadequate levels of individual micronutrients may also identify possible blocks in biochemical pathways (Table 5.2).

Nutrigenomics: Nutrigenomics is the study of the interaction of nutrition and genes and has been shown to personalize

Table 5.2 Functional nutrition approach to macronutrients

Protein	Functional assessment goes beyond total protein evaluation and identifies individual amino acids and types of protein (plant or animal). Plasma assessment of individual amino acids helps to identify overall level of protein intake and processing. Plasma identifies longer term status and use. Urine identifies intake in the last 24 hours and some metabolic issues. Both plasma and urine assessments are best done in a stable dietary intake. Blood amino acids can be measured with a blood draw or from a finger stick.
Fat	Functional assessment goes beyond evaluating standard blood lipids such as TAG, LDL, and HDL and includes individual fatty acids, such as the polyunsaturated fats omega-3 and omega-6, as well as monounsaturated fats and saturated fats. Specimen types include whole blood, plasma, or RBC and are available in blood draw or finger stick. Fatty acids are measured as a percentage of total or as a concentration, and direct comparisons should not be made. Further, the different methods of expressing fatty acids can lead to dissimilar correlations between blood lipids and certain fatty acids [35]. Evaluation of fatty acids of varying carbon chain length and degree of saturation can help to identify dietary intake and have been noted as biomarkers of various conditions. A review of individual fatty acids helps to evaluate function of desaturase and elongase enzymes, which can impact treatment. For example, the conversion of alpha-linolenic acid (ALA) to eicosapentaenoic acid (EPA) is not always efficient and supplementation with flax, high in ALA, may not result in expected increases in EPA. Testing would aid in identifying those who are not making the conversion.
Carbohydrates	Conventional assessment of carbohydrates is generally the assessment of the body's blood sugar response and includes glucose and A1c. Functional medicine also evaluates additional early markers of biochemical disruption using metabolomics, such as identifying alpha-hydroxybutyrate or impaired plasma levels of branched-chain amino acids, which may identify risk of T2D and CVD [36]. The composition of the microbiome can also identify the impact of carbohydrate and fiber intake. Plant-focused diets high in fiber are associated with greater microbial diversity and higher levels of *Prevotella* over *Bacteroides*. Low levels of SCFAs (acetate, propionate, butyrate) in stool can identify poor carbohydrate (fiber) intake or inadequate gut bacterial function [37]. Additionally, high-protein diets can increase the level of bacterial products of protein breakdown, including the short-chain proteolytic fatty acids, valerate, iso-butyrate, and iso-valerate [38, 39].

For comparison, the IOM Recommended Dietary Intake (RDI) for macronutrients in adults is 45–65% of their calories from carbohydrates, 20–35% from fat, and 10–35% from protein [40]

treatment. Test profiles are often buccal swabs and packaged to evaluate a specific area such as weight loss, immune function, nutrient absorption, etc. Previously, the US Food and Drug Administration raised concerns about the validity of the information and the potential for inappropriate medical actions, highlighting the need for practitioners to be aware of the literature of individual single nucleotide polymorphisms (SNPs) [41].

Digestion and Absorption: Functional assessment of digestion and absorption includes tests related to the gastrointestinal tract and its function. Assessment of a patient's digestion and absorption can be assessed in a variety of tests. Two examples are pancreatic elastase 1 (PE1) and fecal fats. PE1 is a proteolytic enzyme that identifies the function of the exocrine pancreas (not to be confused with the endocrine pancreas). The exocrine pancreas produces 3 types of enzymes: amylase, protease, lipase. If it is impaired, digestion may be impaired. Exocrine pancreatic insufficiency is identified with an elastase level < 200 μg/g stool [42]. Fecal fats are used to evaluate fat malabsorption. The gold standard for fat malabsorption is a 3-day quantitative determination of fecal fat. It is cumbersome and takes significant dietary preparation, so a single fecal assessment is often done as an initial evaluation [43].

Assessment of gut bacteria or the microbiome can aid clinicians understanding of the impact of individual bacteria and overall diversity. Assessment is generally done with fecal samples, though breath tests can also identify levels of some gut bacteria. The microbiome is a primary player in the immune system and is heavily impacted by diet, lifestyle, and environment. There are many culture-independent techniques in use, such as fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR), next- and third-generation sequencing, etc. While each technique is valid, the results are not comparable. Even laboratories that do the same stated process such as PCR assessment are generally not comparable due to a lack of standardization. Evaluation of microbiome levels with disease associations or conditions needs to be done using comparable testing.

Intestinal permeability is another concern that functional clinicians evaluate in a full assessment. The intestine is lined with a single layer of epithelial cells held together with tight junctions (TJ), which coordinate exchange between lumen and tissues. Disruption of the intestinal barrier impairs function and may increase the risk of specific disease. Zonulin is a physiologic modulator of intercellular intestinal tight junctions. An increase in zonulin has been proposed to identify a "leaky gut" and has been related to autoimmune disease, metabolic disorders, heart disease, and intestinal disease such as IBS, IBD, and non-celiac gluten [44, 45]. Unfortunately, zonulin has been difficult to test accurately in commercially available tests [46].

Detoxification (also known as biotransformation): Biotransformation refers to the process of transforming tox-

ins, hormones, etc. through the phases of detoxification. Functional clinicians can support the process by ensuring adequate nutritional status of detoxification pathways and identifying toxin levels when needed. There is no single test to evaluate detoxification phases. Phase I is generally done with genetic SNP testing and phase II includes status of amino acid substrates and nutrient co-factors. Detoxification is heavily reliant on enzymes, such as cytochrome P450 oxidase enzymes (CYP450) and nutrient status. Diet can significantly impact the ability to detoxify because it provides both needed nutrients and is a leading contributor of body toxins. Testing for the presence of toxins is available from several laboratories. The ability to compare toxin levels to population data, such as NHANES, allows clinicians to compare client's levels to the general population.

5.10 Metabolic Pathways and Networks

Understanding biochemical pathways and how they function is essential in functional medicine. Biomarkers are not just levels of individual analytes; they include markers of status and pathway function. Individual nutrients often work as nutrient cofactors, and can impact the ability of a pathway to flow smoothly. In order to fully evaluate a patient's biochemical status, clinicians must know the key pathways and networks, such as methylation, conjugation, nutrient breakdown, urea cycle, etc., including substrates, products, enzymes, and cofactors. After a full evaluation of a patient's history, signs and symptoms, anthropometrics, diet assessment, and laboratory evaluations, clinicians can take the next step of identifying key pathways that could be impaired. Several examples are listed below, including vitamin B12 and MMA, and breakdown of fatty acids and BCAA.

Vitamin B12 and Methylmalonic Acid (MMA): When MMA levels are elevated, it may identify a need for vitamin B12 due to inadequate intake or increased need. If diet assessment identifies an adequate intake, there may be increased needs due to other factors, such as decreased stomach acid or increased methylation issues. As seen in the simplified diagram below, L-methylmalonyl-CoA (substrate) is converted to succinyl-CoA (product) via the enzyme methylmalonyl-CoA mutase. The enzyme requires a nutrient-cofactor, adenosylcobalamin (vitamin B12). If the enzyme function is decreased, the L-methylmalonyl-CoA will build up and be excreted as MMA. The enzyme may have decreased function due to a genetic SNP or decreased levels of its nutrient cofactor, vitamin B12. As with most pathways, it is important to know that there are additional related pathways that can also be impacted. For example, converting homocysteine to methionine (methylation) may also be increased with a need for B12 (Fig. 5.2).

Fatty Acid Breakdown Eicosanoids are signaling molecules that result in a range of processes generally related to immune and inflammation. They are derived from omega-3 and omega-6 fatty acids, as seen in Fig. 5.2. Diet provides the fatty acids and nutrients support the breakdown pathways.

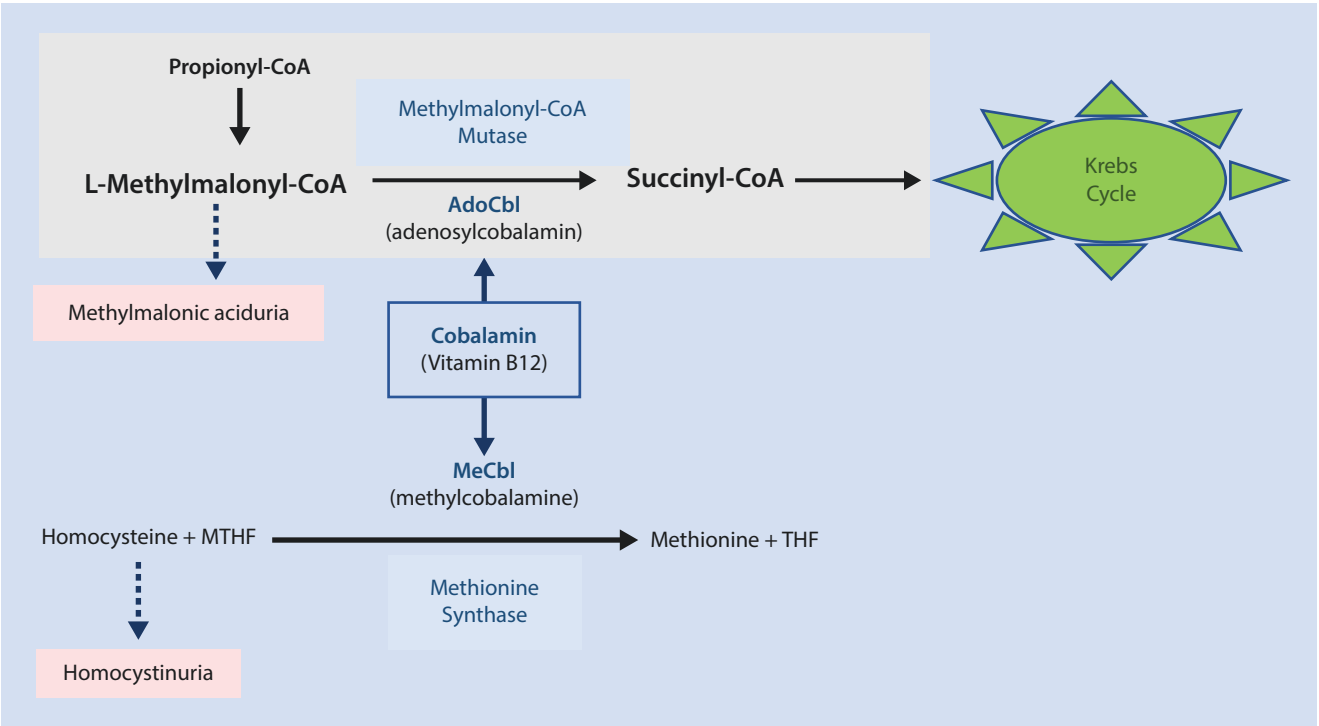

Fig. 5.2 Methylmalonic acid (MMA) pathway. (Courtesy of E. Redmond, PhD, RDN)

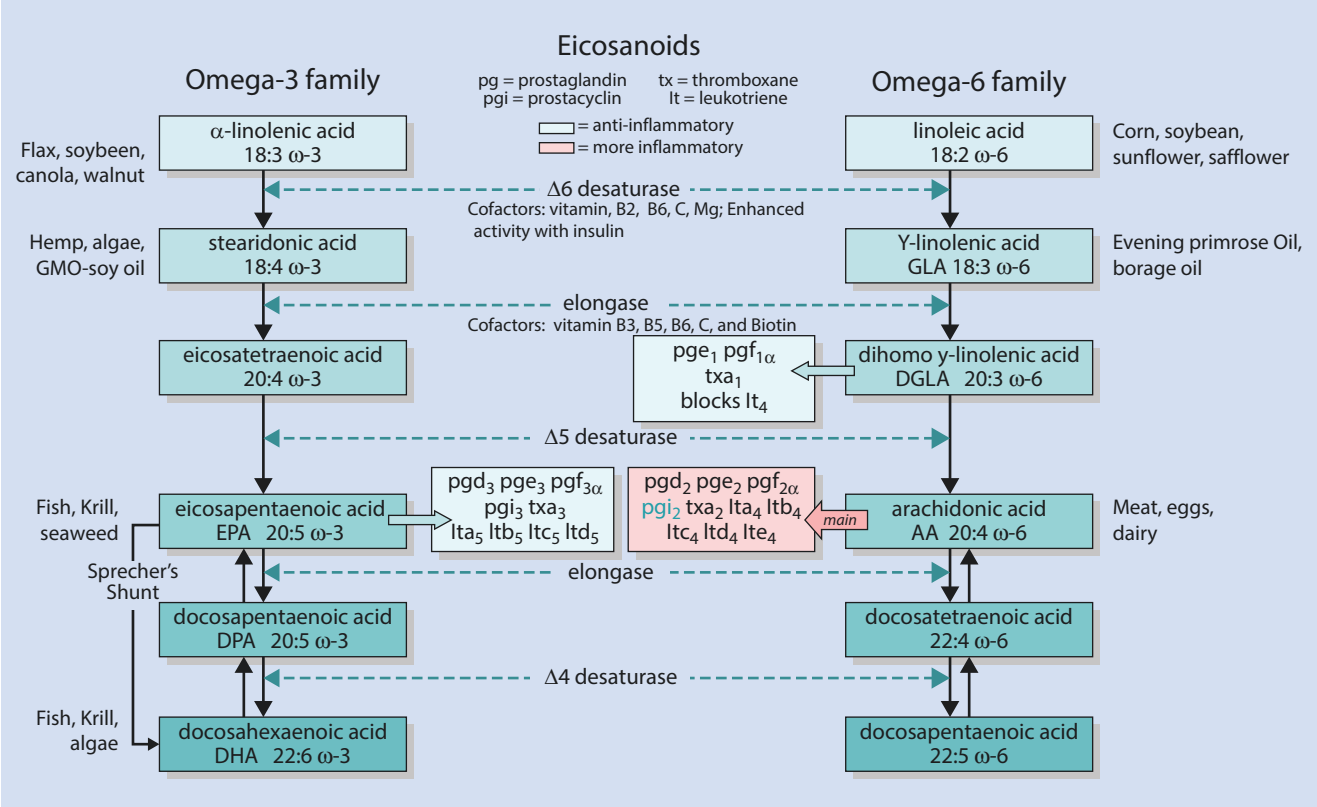

Fig. 5.3 Eicosanoid pathway [47]. (Adapted with permission from: ▶ https://commons.wikimedia.org/wiki/File:EFA_to_Eicosanoids.svg)

Altered fatty acids have been associated with several metabolic diseases, including diabetes, metabolic syndrome, hypertension, alcohol, radiation exposure, and others. The eicosanoid pathway is heavily reliant on elongase and desaturase enzymes, which are dependent on adequate nutrient cofactors. Though a conclusive list has not been developed the following are thought to play a role in desaturase and elongase enzyme function, vitamins B2, B3, B5, B6, C, and biotin, and minerals zinc and magnesium. Additionally insulin is believed to impact function [48–50] (Fig. 5.3).

Furthermore, evaluations of specific monounsaturated and saturated fatty acids can also identify functional impairments. The Δ9-desaturase enzyme or stearoyl-CoA desaturase (SCD) catalyzes the synthesis of monounsaturated fatty acids, primarily oleate (18:1) and palmitoleate (16:1), from saturated fatty acids, palmitate (16:0), and stearate (18:0). Stearic acid is correlated to cholesterol level and Δ9 may be impacted by insulin; thus, an evaluation may help to identify early biochemical function and possible increased risk [51, 52]. A decrease in insulin activity reduces the activity of desaturase enzymes that convert saturated to monounsaturated fats, which can be identified by increases in blood saturated fat levels.

Branched-chain Amino Acids (BCAA) Breakdown: Leucine, isoleucine, and valine are BCAAs. The BCAAs differ from other essential amino acids in that the liver lacks the enzymes to break them down or catabolize them. They are broken down to their keto-acids with transaminase enzymes and the nutrient cofactor vitamin B6. If vitamin B6 is not in adequate supplies, the BCAA amino acids may build up. The next step utilizes a dehydrogenase enzyme and its required nutrient cofactors, vitamins B1, B2, B3, B5, and lipoic acid (LA), which then flow into the Krebs cycle in the mitochondria. Identification of elevated keto-acids may signal a need for B-complex vitamins [34]. Thus, an impairment in the BCAA process has been proposed to impair basic mitochondrial function. Research has found that levels of BCAAs were higher in some individuals with obesity and have been associated with worse metabolic health and future insulin resistance or type 2 diabetes mellitus (T2DM). Insulin resistance may increase protein degradation since insulin normally suppresses it. In clients with metabolic issues, functional clinicians may evaluate plasma BCAAs as well as their keto acids to identify issues in the pathways (Fig. 5.4 and Table 5.3).

The evaluation of pathways and metabolites is continuously being researched. Key resources include the following

- The Scripps Center for Metabolomics: METLIN metabolites database ▶ https://metlin.scripps.edu/index.php
- Expasy: omics scientific databases and tools ▶ https://www.expasy.org/
- Canada's Human Metabolome Database (HMDB) site for the human metabolome markers: ▶ http://www.hmdb.ca/

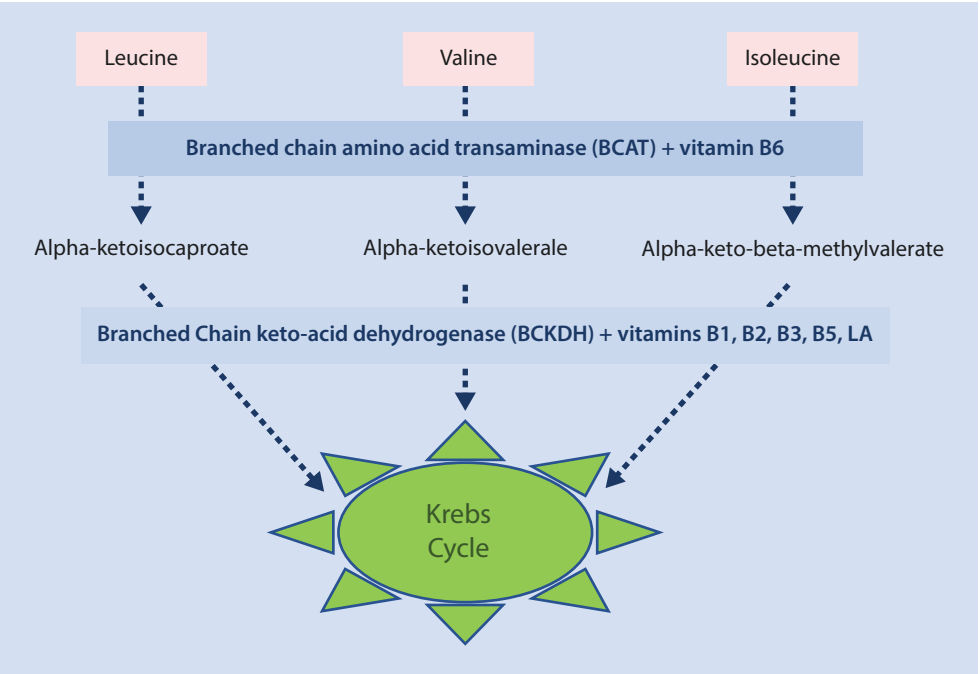

Fig. 5.4 Krebs cycle. (Courtesy of E. Redmond, PhD, RDN)

5

Table 5.3 Branched-chain amino acids (BCAA)

BCAA)	Enzyme plus cofactors	BCAA keto-acid	Enzyme plus cofactors
Valine	*BCAA transaminase + vitamin B6*	Alpha-ketoisovalerate	*Branched-chain keto-acid dehydrogenase + B1, B2, B3, B5, LA*
Leucine		Alpha-ketoisocaproate	
Isoleucine		Alpha-keto-beta-methylvalerate	

5.11 Systems

The foundation of integrative and functional medicine is systems biology [53]. There is a broad consensus as to the definition of systems biology. The biological systems described in IFMNT recognize that the whole human organism is comprised of systems working together contributing to total function. The systems included in assessment of the whole patient story are those where disease can be promoted with the individual's identified pathophysiological symptoms and imbalances. In systems biology, of three primary principles, the first is *diversity*, where there is the appreciation of the complex molecular and genetic uniqueness of each individual. The depth of grasping uniqueness has been enhanced with the discovery and identification of the human genome.

The second key characteristic of systems biology is the recognition of the *complexity* of biological systems and the perturbations of those systems that can promote disease. In contrast to the reductionist medical acute-care model of quickly finding the diagnosis and applying a standard of care, a systems biology-based medicine and medical nutrition therapy applies a whole-systems approach to identification of "root causes" that is a better fit to treatment of chronic diseases.

Thirdly, *simplicity* reflects the application of systems biology to manage the complexity of metabolism to create manageable healthcare procedures that can be applied clinically. Simplicity refers to prioritizing the systems that most impact the individual. Once systems of concern are ranked in importance, they enable a realistic analysis of "root" causes of a chronic disease condition. Prioritizing and simplifying systems that need modulation increases the possibility of successful outcomes for such patients. Prioritized systems require practitioner skills in modulating the systems' biochemical networks, especially in the use of nutrients as cofactors and structural components. This knowledge is foundational for simplifying the development of effective interventions addressing "root causes" with food, dietary supplementation, and lifestyle education. This knowledge depends on the principle that one disease can have multiple influences, with nutrient cofactors being primary when searching for "root causes."

Chronic diseases are diet- and lifestyle-related with the influence of an individual's unique genotype. Thirty years ago, the Institute for Functional Medicine (IFM) was the first to provide a framework, "The IFM Matrix," for how to harness the complexity of chronic diseases into a manageable

clinical tool that simplifies primary priorities needing metabolic correction (see ▶ Chaps. 7 and 47). Later, IFMNT practitioners implemented the conceptual diagram, The Radial (see ◘ Fig. 5.1), to target the nutrition component in the practice of patient care. For a systems biology approach to be effective, the uniqueness of each individual becomes "patient-centered care" [54], using tools like the Radial to "extract simplicity out of chaos" [53].

Working knowledge of the following systems equips the IFMNT practitioner with advanced skills in "metabolic correction" once an imbalance is identified (see ▶ Chap. 7).

As we review the systems below, it is obvious that there is interaction among all the systems to produce a personalized phenotype, but at any time, there are usually two or three of the systems raising a flag indicating dysfunction and needing restoration back to wellness.

5.12 Gastrointestinal System

» All disease starts in the gut. –Hippocrates

The gastrointestinal tract provides the largest interaction of the human with the environment primarily through ingested food, water, and beneficial fermented bacteria to promote a healthy gut ecology. The gut houses more than 70% of the immune system in its lymphoid tissues. It is also the secretor of many neurotransmitters and other life-giving metabolites like the short-chain fatty acid butyric acid, the primary repair fuel for colonocytes (colon cells), which promotes increased energy and cell proliferation and may protect against colon cancer. Key GI tract interventions are based on a whole foods low-antigen diet, with adequate prebiotics of soluble fiber and fermented foods or supplemental probiotics. A common thoughtful functional medicine approach to gut restoration is the 5R program [55]. It begins with *removing* the offender – whatever is in excess or an antigen for an individual; then *replacing* digestive secretions/enzymatic activity and fiber if indicated, repletion of insufficient or deficient nutrients; next, *reinoculating* to restore the balance of good bacteria, pre- and probiotics, adequate hydration; *repairing* the gut barrier that may be compromised from long-standing insults like antibiotics, antigen exposure, toxins, and emotional conflicts; and finally *rebalancing*. This type of protocol provides a significant tool to provide treatment for an individual who is experiencing gastrointestinal distress [56].

5.13 Immune System: Defense and Repair

With chronic systemic inflammation being a common denominator with all chronic diseases, it is important to focus on the condition of a person's immune system. This system, when perturbed, responds with inflammation that can lead to recoverable illness like flu and autoimmunity, as well as life-threatening cancer. The IFMNT practitioner can assess if the immune system is a priority for an individual by using the tools of nutrition physical exam, laboratory biomarkers of inflammation like C-reactive-protein-high sensitivity, sedimentation rate, differential with hearing the patient's history, and diagnosis/symptoms. Dietary history can reveal a diet of pro-inflammatory character that can be modulated to improve the immune response for the individual. Recent recognition of genomic polymorphisms that may increase risk of inflammation includes people with HLA DQ2 and DQ8 who have increased predisposition to celiac disease-related inflammation (see ▶ Chap. 49 Autoimmune).

5.14 Cardiovascular System: Cardiometabolic Comorbidities

According to the World Health Organization, heart and cardiovascular diseases are the most common chronic diseases worldwide. The bigger picture is the pathophysiology of the cardiometabolic system that underlays the trend toward the high risk of cardio diseases for an individual.

Inflammation is foundational to the early stage development of atherosclerosis, along with contributing chronic infections, pro-inflammatory dietary choices, poor sleep, endocrine-disrupting chemical toxins, etc. Nutritional and lifestyle interventions provide powerful change agents to modulate the cardiovascular system.

5.15 Endocrine System: Hormonal Health Influences

The endocrine system's response to our environment to message cellular activity is important to consider when assessing a patient. Two glands in jeopardy today are the adrenal and pancreatic glands. The adrenal gland responds to stress and lack of quality sleep-producing cortisol (stimulatory) elevations. The concerns for the hormones produced by the pancreas are the influence of insulin which, when in excess, is involved in promoting sarcopenic obesity (loss of muscle, gain of body fat) and metabolic syndrome. The pancreas also has an important influence by secretion of the digestive enzymes: lipases, amylases, and proteases to digest the dietary intake of the macronutrients fat, carbohydrate, and proteins. Other important glandular systems are thyroid, parathyroid, hippocampus, and pineal. All of the glandular hormones dance together, interacting to guide the human body to allostasis – the best metabolic balance to survive (see ▶ Chap. 47).

5.16 Respiratory System: Lung and Sinus Illness

The oxygenation of the body is dependent on the respiratory system exchange of oxygen from the air in the atmosphere with the metabolic waste of carbon dioxide – a rhythm critical throughout life; going without for approximately 6 min or more can result in death. The health of the sinus areas as the

Table 5.4 Genomic considerations for restrictive respiratory diseases

Condition	Gene(s)	Key nutrient considerations [57]
Asthma	Alpha 1 antitrypsin [Smoking increases risk]	Vitamins C, A, D Zinc Biotin Essential fatty acids
Emphysema		
Chronic obstructive pulmonary disease (COPD)		
Cystic fibrosis	Cystic fibrosis transmembrane conductance regulator (CFTR)	Vitamins C, A, D Zinc Biotin Essential fatty acids
Lung cancer	[Smoking increases risk] ROS1 symptoms attributed to a respiratory infection	Zinc Vitamins D, A, E Essential fatty acids Immune support
Sarcoidosis	Small groups of inflammatory cells to grow in lungs	Vitamins D*, A, E Essential fatty acids (*Caution using vitamin D)
Idiopathic pulmonary fibrosis	Scarring in the lungs	Vitamins C, A, D Zinc Biotin Essential fatty acids Phospholipids
Granulomatosis with polyangiitis (GPA) ("Wegener's granulomatosis")	Chronic inflammation of lungs, kidney, and cells usually related to infection; a vasculitis; rare multisystem autoimmune disease	Vitamins C, A, D Zinc Biotin Essential fatty acids Phospholipids Immune support

first air entry point is important as hair filters in the nose protect from most particles being inhaled into the lungs. The lung has nutrient requirements of fats, oils, and proteins to maintain the structure of the lung barrier along with nutrient cofactors vitamin A, zinc, and vitamin C influencing lung metabolism. As the exchange occurs, the oxygen entering the bloodstream connects with the RBC heme to be carried and distributed to cells and tissues throughout the body. With many unique genomics that can affect the lung, knowledge of those increases the skill of the nutrition practitioner to intervene successfully for each individual (see ▶ Chap. 52) (Table 5.4).

Genotype-related risk of metabolic perturbation pathway systems and genes:

- Methylation genomics: the genomic expression related to B vitamins, phospholipids, and vitamin D. Genes: *MTHFR* 677C/1298C, *MMTR*, *MTR*, etc.
- Detoxification genomics: Glutathione-S-transferase genes (*GSTM1*, *GSTP1*, *GST*), *CYP*, and *COMT*
- Vitamin D receptor: *VDR RXR*. Vitamin D is dependent on magnesium status for its function. Vitamin D is a hormone and immune modulator in addition to the other roles in mineral metabolism and inflammation.

Because of the recognition of the unique biochemical phenotype and genotype for each individual, the current trend in medicine is toward personalized medicine [58]. Often referred to as "P4 medicine" (predictive, preventive, personalized, and participatory), the personalized paradigm for chronic disease healthcare is gaining support from practitioners of diagnostic medicine.

Biological systems are groupings of molecules, tissues, hormones, and organs that are affected by lifestyle choices and that work together to perform a common function to express as one whole human organism. Nutrients are basic co-factors for all those systems that determine their function. Common systems, such as the circulatory, respiratory, and nervous systems, need to be appreciated in the context of their interactions. The concept of systems biology focuses on interacting systems, in contrast to conventional acute-care medicine that generally considers systems as isolated entities without appreciating their interrelationships.

5.17 Potential Triggers

The five spheres of the Radial can be impacted by genetics, epigenetics, biochemical uniqueness, and microbial interactions and interplay. Imbalances can be triggered by chronic stress, toxins, pathogens, food allergens and intolerances resulting in a disruption in cells, tissues, and organ systems. These potential biological triggers are illustrated in the exter-

nal section of the Radial and can collude to harm health and fuel chronic diseases such as obesity, diabetes, cardiovascular, neurodegeneration, mental illness, autoimmune conditions, allergies, asthma, and more. Evaluating the five spheres of influence and identifying pathological insults is essential in order to reestablish systems balance, foster metabolic integrity, and promote nutritional resilience.

5.18 Stress

Chronic stress is an antecedent to health issues and is represented in the outside of the Radial. There have been many definitions of stress in the medical literature from Hans Selye's original description as "the nonspecific response of the body to any demand made upon it" to R.S. Lazarus describing stress as "a circumstance external to a person, which makes unusual or extraordinary demands on him, or threatens him in some way" [59]. The detrimental impact of chronic stress has been well documented and causes major disruptions in the neuro-endocrine-gastro-immune and musculoskeletal systems. Chronic adverse life experiences, especially psychosocial stress, have been shown to induce destructive changes to the microbiome [60].

The nutrition professional should assess the role stress plays in a patient's life by incorporating some questions in the health questionnaire that are specific to stress. This can be done with a stress rating scale where the patient scores their chronic stress level (e.g., 1 = no stress to 5 = major stress) in categories such as health, finances, relationships, and work. Referrals to clinical social workers, behavioral psychologists, integrative yoga therapists, or mind body skills groups should be made if the individual is unable to effectively manage chronic stress. In addition, some integrative nutrition professionals have advanced training in behavioral therapies and mind-body medicine and can apply those skills to a person-centered nutrition care process (see ▶ Chap. 47).

5.19 Toxins and Toxicants

It can be difficult to know when a level of a toxin will have a physiologic impact on a single person, as response to toxins is individual. Nutritional interventions have been proposed as a key prevention strategy. The impact of toxins is being identified beyond just those with work-related exposures, and evidence suggests a significant impact in seemingly everyday exposures [61]. Two primary references are the Centers for Disease Control and Prevention's (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) ToxFacts sheets, which address where toxins come from and how to best test for them, and the National Health and Nutrition Examination Survey (NHANES) Fourth Report evaluates toxins assessed by NHANES from population studies, allowing the clinician to make comparisons against population values [62, 63].

Table 5.1 lists a truncated list of the ▶ Box 5.1 ATSDR 2013 Substance Priority List.

Box 5.1 The ATSDR 2013 Substance Priority List [62]

Arsenic
Testing: Urine arsenic is the most reliable test for recent exposure to arsenic (within a few days prior). Tests of hair and fingernails can measure exposure over the last 6–12 months. Most tests measure the total amount of arsenic in urine. This can sometimes be misleading because there are non-harmful forms of arsenic in fish and shellfish, which can give a high reading even if you have not been exposed to a toxic form of arsenic.

Lead
Testing: A blood test measures the amount and estimates recent exposure. Lead in blood is rapidly taken up by red blood cells and referred to as blood lead concentration (PbB) which is the most widely used and reliable biomarker for general clinical use, and reflects recent exposure, <30 days. Venous sampling of blood is preferable to finger prick sampling. Urinary lead excretion reflects, mainly, recent exposure.

Mercury
Testing: Blood or urine samples are used to test for exposure to metallic mercury and to inorganic forms of mercury. Mercury in whole blood or in hair from the scalp is measured to determine exposure to methylmercury.

Polychlorinated biphenyls (PCB)
Testing: There are more than 200 PCBs. Testing can identify if PCB levels are elevated, which would indicate past exposure to above-normal levels of PCBs but cannot determine time and length of exposure.

Benzene
Testing: Measuring benzene in blood is a common test. However, since benzene disappears rapidly from the blood, it is only useful for recent exposures. Benzene is converted to the metabolite S-phenylmercapturic acid in urine, which is a sensitive indicator of benzene exposure. Since benzene is lipophilic, it is preferentially distributed to lipid-rich tissues, so blood tests should be lipid adjusted.

Cadmium
Testing: Cadmium can be measured in blood, urine, hair, or nails. Blood shows your recent exposure to cadmium. Urine shows both recent and past exposure and can reflect the amount of cadmium in the body. However, urine test results can be impacted by kidney function.

This priority list is not a list of the most toxic substances, but rather a prioritization of substances based on a combination of their frequency, toxicity, and potential for human exposure. A biomarker of toxic exposure is a xenobiotic substance, its metabolite(s), or the product of an interaction between a xenobiotic agent.

5.20 Pathogens (See ▶ Chap. 21)

Pathogens, by definition, are a bacterium, virus, fungus, prion, or other microorganism that can cause disease. Parasites are generally larger organisms like worms, ticks, or insects that can also cause disease. The concern for parasites

is often decided based on their level of virulence. Common bacterial pathogens are *Pseudomonas*, *Shigella*, and *Salmonella*. Viral pathogens include influenza, adenovirus, rubella, and others. Examples of pathogenic fungi include *Candida*, *Aspergillus*, and *Cryptococcus*. The best-known prionic pathogen is bovine spongiform encephalopathy, also known as "mad cow disease." Pathogens can be difficult to identify and treat. In 2016, the CDC debuted the MicrobeNet Pathogen database [64], which contains information on pathogens and treatment protocols. Undernutrition puts people at a greater risk of infection and increased severity. Adequate nutritional status helps to support the negative physiologic impact of a parasite, such as increased metabolic rate, loss of appetite, immune responses, and specific nutrient requirements [65].

5.21 Food Allergies and Intolerances

There has been a notable rise in food allergies and intolerances around the globe. A food allergy is defined as an adverse health effect arising from a specific IgE immune response that occurs reproducibly on exposure to a given food. Symptoms can range from urticaria to life-threatening anaphylaxis. A food intolerance is an adverse reaction to a food or food component that lacks an identified immunologic pathophysiology. It results from the body's inability to digest, absorb, or metabolize a food or component of the food. These non-immune mediated reactions are caused by metabolic, toxicological, pharmacological, microbial, and undefined mechanisms [21] (see ► Chap. 20).

5.22 Conclusion

The Radial assimilates all the elements of a systems biology approach to healthcare (also referred to as P4 medicine) [58]. It is a paradigm-shifting model for nutrition professionals to apply in practice to engage and empower patients in self-care to achieve their highest health potential and realize their vital goals. Poor diet coupled with harmful environmental exposures and unhealthy lifestyle behaviors are causative factors driving the global burden of chronic disease.

» The truly competent physician (practitioner) is the one who sits down, senses the 'mystery' of another human being, and offers with an open hand the simple gifts of personal interest and understanding [66].
–Harold S. Jenkins, MD

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