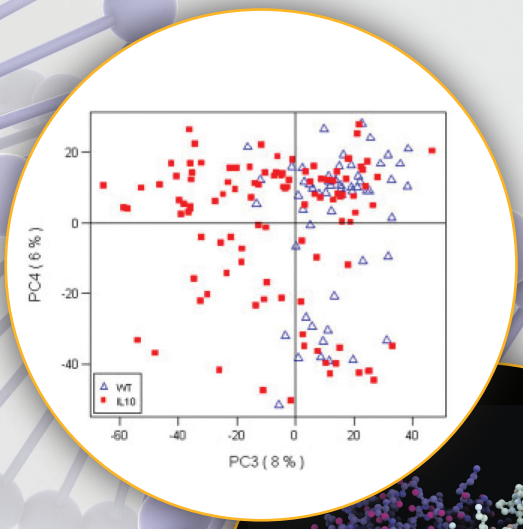
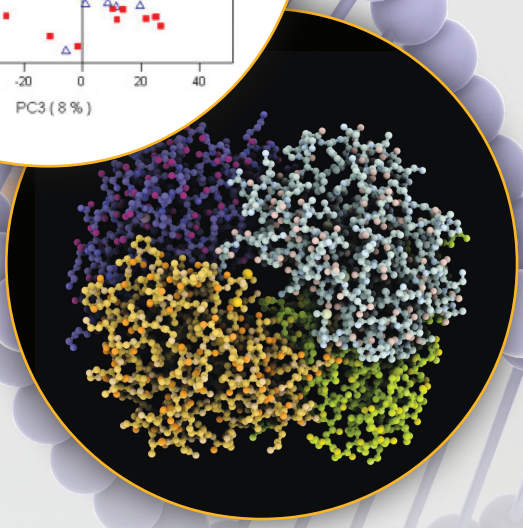
# Nutrigenomics and Nutrigenetics in Functional Foods and Personalized Nutrition



Lynnette R. Ferguson

CRC Press
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# Contents

# Preface

A balanced diet, with a good range of foods to cover the population nutrient requirements and thereby optimize metabolism, is generally considered to equate to good population health. By these means, the risk of disease and its progress may be effectively reduced. Food should not only be nutritious but also enable satiation without excess energy and weight accumulation that is now so prevalent, especially in Western societies. But a food that is tasty, attractive, and beneficial to one individual may not be so for another. There are clear examples of some people who appear to thrive on a particular diet and lifestyle, while others may be disadvantaged. Nutrigenetics, that is, the way in which genotype determines nutrient requirement, may explain some of these individual differences.

If a food company wishes to bring a new food onto the market, or a new dietary regime is being developed, there are increasing pressures to prove human efficacy. This is increasingly an area where the aligned discipline of nutrigenomics (sometimes called foodomics if it is primarily food orientated) comes into its own. Omics technologies can be used as endpoints of cell culture, animal model, or human studies. They enable relatively accurate and cost-effective studies, which do not require a starting hypothesis, and can be done with small study numbers in a relatively short time. While not yet directly acceptable for human-orientated European Food Safety Authority health claims, they can point efficiently to the way forward. That is, they can suggest, but cannot definitively prove, an appropriate biomarker for a larger and more rigorous clinical trial.

While functional foods have become a reasonably well-established concept, especially in countries such as Japan, personalized nutrition is still being treated with skepticism by certain populations and population groups. The recognition that some people would have different nutrient requirements, and/or perceive different foods in different ways, raises several concerns, some real and some not so real. This is a logical follow-on from the recognition that nutrients will be absorbed, utilized in biochemical reactions, metabolized, and excreted to varying extents among different individuals.

This book addresses nutrigenetics and nutrigenomics from a range of perspectives, ranging from purely scientific to ethical, consumer-driven, and public health aspects. It contains up-to-date information in a number of areas that are becoming essential for those trained in nutrition, including both nutritionists and dieticians, as well as other health professionals, including pharmacists and clinicians. It will also provide useful background information for those in the food business and food regulators.

Section I covers some of the best characterized examples of key gene–diet interactions. While referencing nutrigenomics, nutrigenetics is especially important in this section. An overview example of several key genetic variants that influence dietary response and how this might impact the teaching of the dietary pyramid is

covered in Chapter 1. Chapters 2 and 3 focus on some transporter mutations that are particularly likely to influence micronutrient requirements, and some apolipoprotein gene variants that affect the amount and nature of fat that is desirable. Chapter 4 takes an interesting example to show how nutrigenomic tools, this time being applied to studies of a novel fat, can reveal a novel mechanism of action thereby leading to intellectual property that can benefit the food industry.

Several examples of the way in which studies on nutrigenetics and nutrigenomics can help modulate disease risk are described in Section II. Four important chronic diseases are singled out here—cardiovascular disease, obesity, diabetes, and inflammatory bowel disease (IBD)—initially as good examples, where relevant gene variants can respond to very specific nutritional interventions. The latter example is also a very good one in which another environmentally responsive factor—the microbiome—also interacts in a number of gene–diet interactions. Indeed, this is increasingly recognized as a major factor in several key diseases. That is, nutrients influence the expression of bacterial genes, which then in turn affect human gene expression. Chapter 9 also focuses on IBD, this time showing how transcriptome profiling studies can significantly augment an understanding as to how nutrients affect the expression of genes of particular importance for IBD susceptibility.

Chapter 9, arguably, could have been included in Section III, which focuses on technologies. Transcriptomics is an increasingly valuable tool, whose cost has decreased and efficiency increased over the past 10 years. An example of its application to a human dietary intervention study is provided in Chapter 13. One of the increasing challenges in nutrigenomics research is the size and complexity of the datasets generated. Data mining and network analysis are of increasing importance to this field. Other technologies of importance are metabolomics, epigenetics, and genotyping.

Section IV of the book considers some of the benefits—and challenges—of taking nutrigenetics and nutrigenomics beyond being largely science-led endeavors. They are now moving out of the laboratory and into the food industry, as well as out to health professionals and the public. The dangers of going directly to industry and the importance of industry–academia partnerships are emphasized as necessary, but nevertheless, something of a challenge.

As described in Chapter 16, commercialization of these fields is increasingly occurring with a range of different models prevailing. In terms of nutrigenetics, many of the initial ventures that used direct-to-consumer testing have floundered. While some had genuine bases, others were little more than costly excuses for price premiums on micronutrient supplements or functional foods. Those companies that continue to flourish are those that include a health professional, such as a dietician or physician (Chapter 18). There is an increasing number of demonstrable benefits—both to individual health and company finances—of such ventures.

Chapters 19 through 21 consider the implications of these new fields to the public and to the individual. The original title for Chapter 19 was "Is Contemporary Society Ready for Nutrigenomics?" This reflects the degree of skepticism being shown by individuals as to whether or not they want to understand their genotype or effects of

their favorite foods on the expression of those genes. Chapters 20 and 21 consider these questions more generally, in the context of public health.

I hope you enjoy reading this book and that it gives you the same amount of pleasure it gave me in receiving chapters from many of the key players in these developing, and extremely important, fields.

# Editor

**Lynnette R. Ferguson, DPhil, DSc, QSO, FNZIFST** earned her DPhil from Oxford University, working on the subjects of DNA damage, DNA repair, and mutagenesis in yeast. After her return to New Zealand, she began working as part of the Auckland Cancer Society Research Centre, using mutagenicity testing as a predictor of carcinogenesis, with particular focus on the New Zealand situation. In 2000, she took on a 50% role as head of a new discipline of nutrition at the University of Auckland. In more recent years, Dr. Ferguson has considered the interplay between genes and diet in the development of chronic disease, with particular focus on inflammatory bowel disease, a cancer-prone condition, and also in prostate cancer. As program leader for the multidisciplinary, multiorganization Nutrigenomics New Zealand, she is working with a range of others to bring nutrigenomics tools and potential to the New Zealand science scene.

Dr. Ferguson has supervised more than 30 students to the successful completion of a BTech, MSc, or PhD. Her laboratory regularly supervises two to three summer students each year. She is the author or coauthor of more than 300 peer-reviewed publications as chapters in books or articles in international journals. She serves as one of the managing editors for *Mutation Research: Fundamental and Molecular Mechanisms of Mutation*, as well as on the editorial boards of several other major journals.

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# Section I

## Examples of Some Key Gene–Diet Interactions

# 1 Nutrigenetics and Nutrigenomics
## *Importance for Functional Foods and Personalized Nutrition*

*Lynnette R. Ferguson*

### CONTENTS



### INTRODUCTION

Classic research on nutrition considered the effects of macronutrients (lipids, proteins, carbohydrates), or micronutrients (vitamins, minerals), defining physiological requirements for these, and determining the implications of either a deficiency or excess. The primary objective of these studies was to prevent signs of either nutrient deficiencies or of dietary excess. However, it is now apparent that nutrient intakes at levels that prevent classic symptoms of nutrient deficiency may still be inadequate for long-term health

and wellness. As new methods for judging these optimal levels are developed, the recommended daily amounts (RDAs) of many nutrients are changing, and are likely to continue to do so [1]. Most studies on nutrient requirements are limited by studying effects of nutrients one at a time. Nutrient–nutrient interactions and effects of the food matrix are also critical. Furthermore, much of the research to date has implied that all people have the same dietary requirements. It is increasingly clear that not all individuals will benefit from an identical dietary regime, that is, they have a different nutritional phenotype. Although this may be partly a result of early dietary exposures and enzyme induction, as for example, with lactase deficiency [2], or other factors such as stress or concomitant disease, it may also relate to individual genetic variations.

"Nutrigenetics" describes how human genetic variation results in distinct nutritional requirements. Interindividual differences in genetics, resulting in different effects of nutrients on metabolism, were recognized early in nutrition research. A classic example of this may be folate metabolism, whereby a common single nucleotide polymorphism (SNP) exists for the gene that encodes the enzyme, methylenetetrahydrofolate reductase (MTHFR). Around 10% of the human population is homozygous for this SNP. Such individuals require higher than average amounts of dietary folic acid to minimize blood levels of homocysteine [3]. Other examples are given in Chapters 3 and 6 through 8. Although some key genetic variants are likely to be amenable to personal genotyping, practically, many will not. Even if they are, nutritional remedies may not also be immediately obvious. The general principle in setting RDAs has been to ensure that these have a sufficient margin of error to cover population variability.

For nutrients such as folate, there are probably wide gaps between the minimum level required and an excessive dose, so that the approach described earlier is appropriate. But there are several nutrients that have a relatively narrow window of efficacy, below or above which is deleterious to human health. Selenium (Se) provides such an example [1,4]. This micronutrient is important for DNA repair and enabling the cell to cope with oxidative stress. However, there is a relatively narrow window where it is effective, and too much is as damaging as too little. Furthermore, this window changes according to variants in a number of genes. How to combine information on the various affected genes may be beyond the current scope of knowledge in nutrigenetics.

Although the term "nutrigenomics" describes how diet modulates the expression of genes, it is often conceived as the application of high-throughput genomic tools in nutrition research. When such high-throughput screening is applied to nutrition research, it enables the study as to how nutrients affect the expression of the thousands of genes comprising the human genome. This field is increasingly being acknowledged as essential for understanding the role of diet in maintenance of homeostasis (wellness), prevention of risk of chronic disease, or slowing of disease progression. Its considerable potential for the future of food may currently be underrated.

## HUMAN GENETIC VARIATION

No two humans are genetically identical. Even monozygotic twins, developed from a single zygote, have occasional genetic and epigenetic differences occurring during development. SNPs are a common source of genetic variation among people (Table 1.1).

**TABLE 1.1**
**Some Useful Terms in Describing Human Variation**

Allele: a particular configuration of a locus with a particular DNA sequence (can be many alleles for a particular locus, depending on its size)
Genotype: measured DNA sequence at a locus
Haplotype: a set of SNPs on a single chromosome of a chromosome pair that are statistically associated
Locus: an arbitrary region of the genome that can have mutations/polymorphisms
Mutations: differences in DNA sequence in an individual that are rare and may be unique to the individual (or their family line)
Polymorphisms: differences in DNA sequence that are found in many individuals, at a specified frequency (usually 1% or greater of a population)
Single nucleotide polymorphisms (SNPs): DNA sequence variations occurring when a single nucleotide, that is, adenine (A), thymine (T), cytosine (C), or guanine (G), differs between individuals or paired chromosomes in an individual. An SNP is defined as occurring at least in 1% of the population. There are several types of SNPs:

- Synonymous SNP: one in which both forms lead to the same polypeptide sequence (sometimes called a silent mutation)
- Nonsynonymous SNP: one that leads to a different polypeptide sequence (may either be missense or nonsense)
- Missense change: results in a different amino acid
- Nonsense change: results in a premature stop codon

SNPs occur once in every 300 nucleotides on average, making approximately 10 million SNPs in the human genome. Commonly, these variations are found in the DNA between genes. When SNPs occur within a gene, or in the gene's regulatory region, they may affect the gene's function. Most SNPs have no direct effect on health or development, but somewhere between 3% and 5% are functional, influencing phenotypic differences between humans [5]. Knowledge of SNPs may help predict an individual's response to certain diets or drugs, susceptibility to environmental toxins, and risk of developing particular diseases. Genome-wide association studies are becoming increasingly important in identifying SNPs associated with susceptibility to complex chronic diseases, such as cancer or cardiovascular disease (CVD).

Recent evidence suggests that non-SNP variation accounts for even more human genetic variation than SNPs. This variation includes copy number variation (CNV), and results from deletions, inversions, insertions, and duplications [6]. It has been estimated that approximately 0.4% of the genomes of unrelated people differ with respect to copy number. Including this figure, human-to-human genetic variation is estimated to be at least 0.5%, implying 99.5% similarity. CNV may be inherited or may arise during development. A variable number tandem repeat is a chromosomal location where a short nucleotide sequence is repeated in a tandem manner. Tandem repeats are found on many different chromosomes and often show variations in length, even between closely related individuals.

Epigenetics is another major source of genetic variation (Chapter 12). This is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence. Examples of such changes are DNA methylation and histone modification [7]. It is also becoming increasingly important to recognize the interplay between human and microbial genes (Chapter 5). Microorganism genomics is redefining our previous understandings of microbial food safety and the role of microbes in human health [8].

## DESIRABLE HUMAN DIET

Most people, in most countries, will turn to their health department–approved dietary pyramid for healthy eating advice. In 2001, the epidemiologist, Walter Willett, debunked the U.S. Department of Agriculture (USDA) food guide pyramid, which serves as a model of desirable eating behavior for many Western countries. "At best, the USDA Pyramid offers wishy-washy, scientifically unfounded advice on an absolutely vital topic—what to eat. At worst, the misinformation contributes to overweight, poor health and unnecessary early deaths. In either case, it stands as a missed opportunity to improve the health of millions of people." With the help of his Harvard coworkers, he developed his own Healthy Eating Pyramid (Figure 1.1). The main recommendations of this are as follows [9,10].

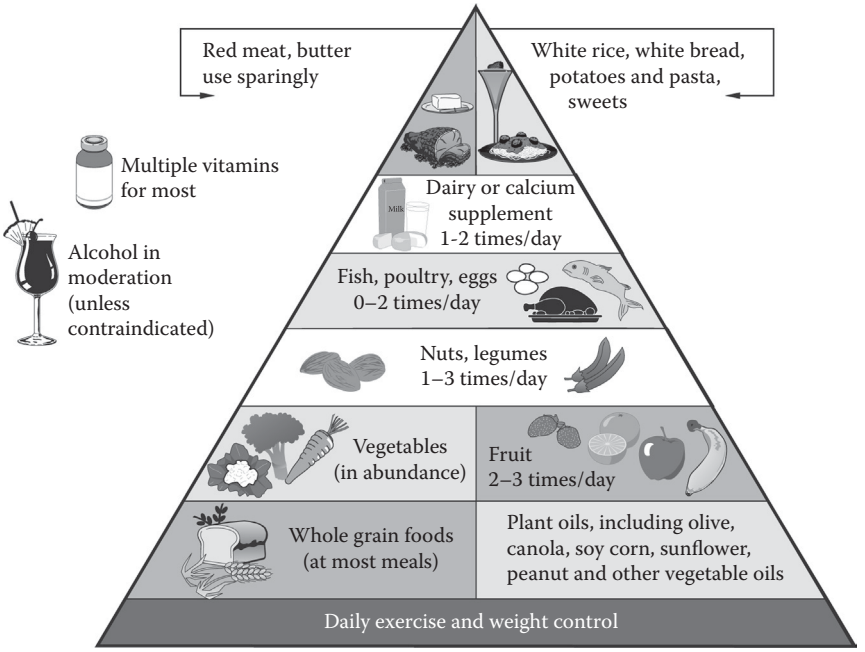


**FIGURE 1.1** Healthy eating pyramid. (From Willett, W.C. et al., *Eat, Drink and Be Healthy: The Harvard Medical School Guide to Healthy Eating*, 299, Simon & Schuster Source, New York, 2001.)

At the base of the Healthy Eating Pyramid is regular exercise and weight control. In practice, this will usually involve conscious caloric restriction. Restriction of fats is commonly recommended as a means of caloric reduction. While recognizing their high energy density, Willett also points to the importance of certain types of fat in the diet. That is, he claims that, providing total energy balance is attained, nonhydrogenated plant oils are desirable in the diet, and indeed come low in his pyramid. He acknowledges some confusion about the benefits of carbohydrates and concludes that instead of recommending complex carbohydrates, the pyramid should reinforce the choice of minimally refined whole grains (WGs) in preference to refined starches and simple sugars. Vegetables and fruits should be consumed in abundance, with green leafy and orange vegetables being consumed daily. Red meat should be consumed rarely, with nuts, legumes, fish, and poultry being consumed in moderation as alternative protein sources. Dairy products may be optional and calcium (Ca) may be conveniently supplied as a supplement. Salt intake should be low, while regular intake of a multivitamin tablet and moderate alcohol consumption may be desirable.

Although several versions of this pyramid are now available, a generally agreed version appears in Figure 1.1.

## EVIDENCE FOR A DESIRABLE HUMAN DIET

A major advantage of the Healthy Eating Pyramid is its strong evidence base, which is continually being reevaluated. The basis of the Healthy Eating Pyramid is mostly epidemiological and clinical studies, in particular, access to data from several large prospective cohort studies, such as the Nurse's Health study in the United States or the European Prospective Investigation into Cancer and Nutrition (EPIC) study across Europe [11]. Although the sheer size of these studies helps in statistical power, they suffer from well-recognized problems of imprecision of dietary recall. In addition, people tend to eat in patterns, so establishing the importance of a single food or nutrient becomes difficult.

The most compelling evidence that a certain level of a certain food or supplement benefits health comes from a controlled clinical trial that feeds large numbers of people, in two comparable groups, either the nutrient in question or a placebo, over enough time for disease to develop. However, the perils of such an approach have been brought into focus by large studies such as the SELECT (the Selenium and Vitamin E Cancer Prevention Trial) [12].

Animal and epidemiological studies had suggested that Se and vitamin E (alone or in combination) might reduce the risk of developing prostate cancer (PC). The randomized, placebo-controlled SELECT trial studied 35,533 men from 427 participating sites in the United States, Canada, and Puerto Rico, randomly assigned to four groups (Se, vitamin E, Se + vitamin E, and placebo) in a double-blind manner, between August 22, 2001 and June 24, 2004. However, an initial analysis of data at 5 years showed that, instead of the predicted and desired trends, there was a small increase in the number of PC cases in men taking only vitamin E and the number of cases of diabetes in men taking only Se [12]. After an average of 7 years (5.5 years on supplements and 1.5 off supplements), there were 17% more cases of PC in men taking only vitamin E than in men taking only placebos.

Surrogate biomarker endpoints to such trials provide a compromise that enables a smaller number of subjects to be used, over a shorter time. The important point is that if the dietary item being tested has an opposite effect to that desired, it is still possible to stop taking it in time to reverse the trend. For example, many recommendations on diet typically recommend that total fat intake should be 30% of energy, or less, to decrease CVD and cancer. Many studies on which these recommendations are based have assumed that total serum cholesterol levels predict CVD risk, thus serum cholesterol functioned as a surrogate biomarker. For example, much data were summarized in the early 1980s [13], suggesting that compared to carbohydrates, saturated fat increases and polyunsaturated fat decreases serum cholesterol, while monounsaturated fat has no effect. However, differentiating high-density from low-density lipoprotein enables more precise predictions of risk, pulling out more accurate and predictive descriptions of dietary desirability [9]. Biomarkers continue to be developed, providing increasingly more accurate dietary feedback. Nutrigenomics is one approach to biomarkers that may further refine current information.

## DESIRABLE HUMAN DIET AND HUMAN GENETIC VARIATION

One disadvantage of the Healthy Eating Pyramid is that it still assumes a "one size fits all" approach to nutrition. Genetic polymorphisms will affect the relative importance of the various nutrient classes, at the level of an individual. Thus, going through the key points identified in the Healthy Eating Pyramid:

- Regular exercise and weight control: The effects of exercise and attempts at portion control will be affected by several genes that have been associated with obesity. For example, carrying certain variants in the *FTO* gene affects dietary selection and the amount of food needed for satiety, especially in children [14]. This may in part be overcome by substantial increases in physical activity levels [15]. The influence of the selection and total intake of fats in the diet will also interact with these polymorphisms. Red meat and dairy products make those individuals carrying an *FTO* variant even more likely to have a high body mass index [16].
- Rational selection of lipid source: In terms of risk of chronic disease, it is the nature of the lipids and their concentration in plasma that is likely to be more important than their overall intake in determining the risk of chronic disease. Variants in a number of genes, such as *PPARa*, *PPARg*, or others identified in Chapters 3, 6, and 7, will substantially modify the nature of the lipid being transported through the body [17].
- Rational selection of carbohydrate source: Varma et al. [18] used a data mining approach to suggest a significant role of various genes in carbohydrate metabolic pathways in the risk of obesity and, to a lesser extent, T2DM. This suggests that the implications of high-carbohydrate diets will vary among the population. The efficacy of high WG consumption in protecting against T2DM has been shown to interact with variants in the transcription factor 7-like 2 (*TCF7L2*) gene [19].

- Abundant fruits and vegetables, with daily consumption of green leafy and orange vegetables: Many green leafy vegetables are in the family Cruciferae. As well as containing a range of recognized nutrients, these vegetables have other phytochemicals, such as glucosinolates, with recognized roles in prevention of chronic diseases, especially cancer. The enzyme coded by the glutathione S-transferase mu 1 (*GSTM1*) gene functions in the detoxification of electrophilic compounds, and a high intake of glucosinolates is associated with upregulation of this gene. However, this function will not occur in individuals carrying a *GSTM1* null variant [20]. The particular value of orange vegetables is that the color indicates significant levels of the micronutrient, beta-carotene. Again, the efficacy of this nutrient will be determined by circulating levels of carotenoids in the plasma, and these levels depend not only on total intake, but also on the presence or absence of a common SNP in the beta-carotene 15,15′-monooxygenase 1 gene [21].
- Occasional or no red meat and dairy product consumption: Both red meat and dairy products are major dietary sources of saturated fatty acids, which are considered as one of the most undesirable types of fat in the human diet. Phillips et al. [22] concluded that dietary saturated fat and gender predict the development of metabolic syndrome when certain genetic variants in the *TCF7L2* gene are taken into account. The other concern relating to high red meat consumption is in relation to a possible iron overload. This would be a particular problem for individuals carrying variants in the hemochromatosis (*HFE*) gene, who are prone to iron overload, liver cirrhosis, and cardiomyopathy.
- Nuts, legumes, fish, and poultry as preferred protein sources: A particular justification for using these as protein sources, as opposed to red meat and dairy products, is that they have a more desirable lipid profile. The interactions of these lipid sources with common genetic variants in a number of genes are detailed elsewhere (Chapters 2, 3, 6, and 7). The interactions between dietary fish oil intakes and common variants in a number of genes are also reviewed in relation to the response of biomarkers of CVD risk [23].
- Ca supplied as a supplement: A variant in the Ca-sensing receptor A986S is associated with higher serum Ca and higher urinary Ca excretion [24]. In addition, Ca supplements have been associated with an increased risk of CVD [25].
- Salt intake should be low: Although there is general agreement on this principle as a preventive measure against CVD risk, there is considerable variability among the population in terms of salt sensitivity, partly through polymorphisms in genes related to the renin–angiotensin–aldosterone system [26].
- Regular intake of a multivitamin tablet: Simple single gene–single nutrient examples, such as that given previously for MTHFR/folate, are probably rare. Even for that example, knowing that an individual is homozygous for a functional SNP in the *MTHFR* gene will indicate a dietary requirement for

higher than average levels of folate, but not the exact amount. Other genes and dietary factors impact on this pathway (Figure 1.2).

- There is good evidence linking key genes with multiple effects on micronutrient and lipid handling in the body. Genetic variations in the genes involved in folate metabolism have multiple effects. Micronutrient and macronutrient interactions are also important. SNPs in MTHFR increase the risk of chronic diseases such as cancer and CVD through more than one mechanism, and respond to nutrients other than folate, albeit indirectly. The micronutrient genomics project provides a range of examples [27].
- Minerals: Although vitamins often have a relatively wide range of tolerances, a number of minerals are also considered to be essential micronutrients because of their role as cofactors for key enzymes. Typically, these have a somewhat narrow dose range of efficacy, as compared with toxicity. Examples include Ca, for which high-dose supplementation has been associated with increased risk of CVD [25], Se, and zinc (Zn). For each of these examples, SNPs in key genes may significantly affect the appropriate dose range for efficacy, and the desirability of supplementation may be disputed. Se provides a well-characterized example. Glutathione peroxidase (GPx) is the general name of an enzyme family whose main biological role is to protect the organism from oxidative damage through peroxidase activity. Their biochemical functions are to reduce lipid hydroperoxides to their corresponding alcohol and free hydrogen peroxide to water. Since the human GPxs are Se-containing, their function and activity depend significantly on the body Se level. SNPs in the genes for GPx can modify GPx4, GPx1, and GPx3 protein expression or activity, in response to Se supplementation. Thus, depending on the particular variants carried by an individual, as well

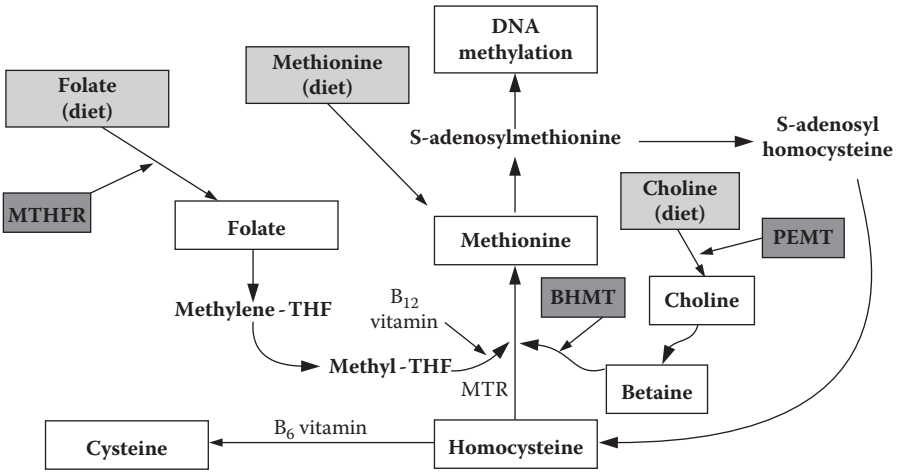


**FIGURE 1.2** Examples of genes and gene products, and their effects on dietary items, in the pathway leading to accumulation or removal of homocysteine and DNA methylation. *Note*: PEMT: phosphatidylethanolamine N-methyltransferase; BHMT: betaine–homocysteine S-methyltransferase; MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase.

as the starting plasma Se level, Se supplementation may be beneficial, have no effect, or be detrimental [4,28]. Similar examples can be found for Zn.

- Alcohol consumption may be desirable in moderation: Certain groups may find even low levels of alcohol to be undesirable, and alcohol may exacerbate the effects of other known genetic variants. For example, a high alcohol intake may increase still further the need for extra folate in those carrying variants of the *MTHFR* gene [29].

A more striking example, relevant to functional foods, is where knowledge of SNPs in a gene has been used to tailor remedial dietary preparations to specific groups. Kornman and coworkers [30,31] stratified subjects by genotype before a nutritional intervention. Their proof-of-concept trial considered the effects of a specifically formulated botanical mixture on inflammation in individuals stratified according to genetic variations that predispose to overexpression of interleukin-1β (IL-1β) and early CVD. They selected healthy adults with elevated C-reactive protein (CRP), a biomarker of inflammation, and genotyped them for variations in the *IL-1* gene that have previously been found to have a higher risk of heart disease. These subjects were then randomized to the candidate botanical formulation that included rose hips, a blueberry and blackberry mixture, and a grapevine extract, or placebo. The participants supplemented their normal diet with this mixture for 12 weeks, then provided samples for the study of *IL-1β* gene expression in stimulated peripheral blood mononuclear cells. The botanical mixture significantly reduced expression of this gene, and the effect was greater in higher risk than lower risk subjects. There was, however, no significant change in serum CRP levels. This study was important, not only in showing the effects of stratifying subjects for such trials, but also in justifying nutrigenetic and nutrigenomic approaches to study endpoints.

The gut microbiota also adds another dimension to individual dietary requirements. For example, the desirable human levels of vitamin H (biotin) are contentious. The U.S. dietary guidelines claim that biotin deficiency is rare because, in general, intestinal bacteria produce biotin in excess of the body's daily requirements [32]. For that reason, they do not prescribe an RDA of biotin. This conclusion neglects, however, the variations in microflora known to occur between healthy individuals and those with certain diseases, such as inflammatory bowel diseases [33], or between population groups with different dietary practices. It also neglects the impact of infections and use of antibiotics. Thus, biotin deficiency may be a significant problem in certain population groups.

## NUTRIGENOMICS TOOLKIT

Although genomics has successfully identified associations between genetic variants and the risk of specific diseases, the biological mechanisms by which gene variations interact with one another and with the environment, including diet, to influence disease development and severity, are often not fully understood. It is important to realize that there are possibly thousands of genetic polymorphisms that may result in minor deviations in nutritional biochemistry, where only marginal or additive effects would result from these deviations. The tools to study the

physiological impact were not available until now and are only now becoming available enabling the development of nutrigenomics. Such tools include those that measure the transcriptome—DNA microarrays, exon arrays, and tiling arrays. Methods to measure the proteome are less developed. These include methods based on gel electrophoresis, chromatography, and mass spectrometry (MS). Finally, the tools that measure the metabolome include methods based on nuclear magnetic resonance (NMR) spectroscopy and MS, often in combination with gas chromatography (GC) and liquid chromatography (LC).

### Transcriptomics

As an example, the demonstration of functional effects due to variations in the concentrations of micronutrients in our diet is difficult, unless they are at such low levels as to lead to a risk of deficiency disease. It is even more complicated to estimate optimal levels of bioactive food components. The transcriptome, that is, the total set of RNA transcripts in a given organism, may be helpful. Transcriptomics measures the expression level of RNAs in a given cell population, providing information on relative amounts of RNA. Increasingly sophisticated methods to estimate gene expression, including whole-genome transcriptome analysis, are highly suitable to obtain unbiased information on potentially affected biological processes, at a whole-genome level. Transcriptome analysis is playing an increasingly important role in benefit–risk assessments, helping to identify functional effects and appropriate levels of micronutrients and bioactive food components.

### Proteomics

Unfortunately, RNA levels are not directly proportional to the expression level of the proteins. In addition, transcripts may be translated into more than one protein. Proteomics reveals more details of molecular processing, and thereby potentially leads to a more comprehensive molecular understanding of the health benefits of micronutrients and bioactive food components. Identification and quantification of bioactive proteins and peptides, using proteomic technologies, can more precisely address questions of nutritional bioefficacy. However, a given cell type may produce different proteins at different times, and under different conditions. Also, any protein can undergo a wide range of posttranslational modifications. Thus, although genomics, transcriptomics, and proteomics may suggest a potential phenotypic response to a given dietary intervention, they cannot definitively predict this.

### Metabolomics

Metabolomics (or metabonomics) may provide an answer to the problem. The metabolome consists of all the low-molecular-weight molecules or metabolites in a cell, tissue, or organism, thereby providing a functional readout of cellular biochemistry. Thousands of metabolites can now be measured quantitatively from relatively small amounts of biological material. Global metabolite profiling (untargeted metabolomics) enables new discoveries linking cellular pathways to biological mechanism

in ways not previously suspected. In contrast, targeted metabolomics is defined by the identification and quantification of sets of structurally characterized and biochemically annotated metabolites, utilizing current knowledge of most biochemical pathways. Most enzymatic reactions and their end products are relatively well characterized, allowing early signs of disease processes to be identified, and targeted remedies, including tailored diets, to be developed. Targeted metabolomics generally provides quantitative information on the molar concentrations of metabolites in a pathway. Thus, deviations from normal are relatively easy to interpret, whether the study considers healthy versus diseased or treated versus untreated. Such methodology is well suited for high-throughput and routine applications. It has at least three important applications:

- Stratifying population groups (phenotyping): Metabolomics technologies are often appropriate to distinguish those individuals most likely to respond positively to a dietary intervention from those who will not.
- Biomarkers of disease risk: Many diseases, including cancer and inflammatory bowel diseases, have distinctive metabolomic signatures that increase as the disease progresses. In this case, metabolomics can provide a biomarker to consider whether a given dietary intervention can enable a reversal of the progression to advanced disease, or at least a slowing of the disease process.
- Validating dietary intake: It has been repeatedly found that many human subjects show a selective memory for dietary intake. There is no perfect method of dietary assessment in human populations. Metabolomics technologies, using sensitive measurements, such as GC–MS, LC–MS, capillary electrophoresis, or NMR, may help to characterize markers of nutrient exposure or detect relatively subtle shifts in dietary patterns.

The large multidimensional datasets that result from such studies must be processed and analyzed to render the data meaningful. Thus, bioinformatics tools are essential for the efficient processing of huge datasets, the characterization of the detected signals, and to align multiple datasets and their features.

Next-generation sequencing technologies are cost-effective ways of producing millions of short DNA or RNA sequence reads in a high-throughput manner. Their applications include whole-genome sequencing and resequencing, SNP and structural variation discovery, noncoding RNA profiling, and protein–nucleic acid interaction assays. Case studies in structural, functional, and comparative genomics, including metagenomics and epigenomics, provide a comprehensive picture of genomic structures and functions. They are highly appropriate for solving complex biological problems in diet and nutrition.

## NUTRIGENOMICS AND THE MAINTENANCE OF HOMEOSTASIS

Nutrients are detected by cellular signaling molecules and may be seen as signals that tell a specific cell in the body how to react to a specific dietary factor. By this means, the cell obtains information about its environment, which is the diet. The sensory

system that interprets information from nutrients about the dietary environment includes transcription factors together with many additional proteins. Once the nutrient interacts with such a sensory system, it modulates gene, protein expression, and metabolite production in accordance with the level of nutrient it senses. As a result, different diets elicit different patterns of gene and protein expression and metabolite production. Nutrigenomics describes the patterns of these dietary signatures. This enables an understanding as to how nutrition influences homeostasis.

Maintenance of homeostasis is essential to the prolongation of good health and prevention or delay of disease. Although we have biomarkers for disease risk, biomarkers to quantify health are necessary. Quantifying homeostasis is a significant challenge. However, it has been suggested that measuring responses to a challenge to homeostasis may be more informative than a static measure [34]. Perturbation tests might use known detrimental nutritional challenges, such as high fat or high glucose, over a short time frame, then consider the ability of the body to restore itself to normal functioning. Comprehensive multidimensional, omics-based analyses provide a route to identifying key biomarkers, as well as leading to a greater understanding of health.

Metabolic flexibility is the capacity for an individual to adapt fuel oxidation to fuel availability. This concept is further developed as phenotypic flexibility, involving fundamental mechanisms essential for optimal metabolic health. The European FP7-funded NutriTech project will apply an integrated series of methods to assess the underlying and related cell biological and genetic mechanisms, and multiple physiological processes of adaptation when homeostasis is challenged in an integrated series of human intervention studies (http://www.nutritech.nl).

We have long considered most genetic states to be somewhat stable in the absence of the extreme physiological challenges described earlier. However, a recent study of a single individual over 14 months, using state of the art extremely high-coverage genomic analyses, described as an integrative personal omics profile, showed significant fluxing [35]. Extensive heteroallelic changes occurred, during both healthy and diseased states, as well as an unexpected RNA editing mechanism. The analysis combined genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles, revealing various medical risks, including a higher than normal susceptibility to type 2 diabetes. It also revealed extensive, dynamic changes in diverse molecular components and biological pathways.

## NUTRIGENOMICS AND PREVENTIVE HEALTH

PC is the most common cancer in the Western world. After lung cancer, it is the second most important cancer causing male deaths in the United States and Britain. Dietary and lifestyle changes are recommended for men diagnosed with early-stage PC, but the evidence base for these has not been as strong as would be desirable. PC provides a good example on which gene-expression profiling, before and after dietary interventions, has led to a rationale for disease prevention.

Men with a diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN), the preinvasive in situ stage of prostatic adenocarcinoma, are known to be at increased risk of developing PC. Epidemiological studies have suggested that consumption of more than one portion of cruciferous vegetables (such as broccoli) per week may

reduce both the incidence of PC and the risk of developing aggressive PC. Traka et al. [36] quantified and interpreted changes in global gene-expression patterns in the human prostate gland before, during, and after a 12 month broccoli-rich diet, as compared with a pea-rich diet. Volunteers with a diagnosis of HGPIN were randomly assigned to either of these two diets. Comparison of biopsies obtained pre- and post-intervention revealed more changes in gene expression occurred in individuals on a broccoli-rich diet than in those on a pea-rich diet, and this stratified according to genotype. The authors suggested that regular consumption of broccoli interacts with GSTM1 genotype to result in complex changes to signaling pathways associated with inflammation and carcinogenesis in the prostate. That is, broccoli consumption shifted the gene-expression profile to a less cancer-prone state. This study, therefore, provides experimental evidence in humans to support observational studies that diets rich in cruciferous vegetables may reduce the risk of PC and other chronic disease.

## NUTRIGENOMICS AND THE SLOWING OF DISEASE PROGRESSION

There are a number of examples whereby nutrigenomics technologies have given information relevant to the slowing of disease progression. PC again provides an exemplar.

In vitro studies, considering effects of nutrients on gene-expression profiles, may provide preliminary evidence for effective dietary intervention strategies. Friedrichs et al. [37] suggested that progression of PC to androgen independence is a key turning point in the progression of the disease. They had reason to believe that long-chain omega-3 polyunsaturated fatty acids (*n*-3 PUFA) could be effective at preventing and treating refractory PC. Thus, they used an in vitro model of androgen ablation to determine the effects of two *n*-3 PUFA, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), on progression of the LNCaP PC cell line to an androgen-independent state. Treatment with these PUFA was able to prevent progression of LNCaP cells, whereas the omega-6 PUFA, arachidonic acid (AA), promoted cell growth under conditions of hormone depletion. These results correlated with a decrease in the expression of the androgen receptor, as well as suppression of an important cancer-related signaling pathway.

In vivo studies are essential to confirm the efficacy of nutrient interventions. Thus, Magbanua et al. [38] considered the effects of supplementation with fish oil (which contains high levels of EPA and DHA) on prostate gene expression, in a double-blind placebo-controlled randomized clinical trial. They studied men with low-grade PC, stratified based on self-reported dietary consumption of fish, and then randomly assigned to a 3-month intervention of fish oil ($n = 27$) supplementation or placebo ($n = 28$). cDNA microarray analysis was used to study gene expression in morphologically normal prostate tissue at baseline and at 3 months. Differential gene expression and pathway analyses were then used to identify genes and pathways modulated by these dietary components. Pathway analyses of rank-ordered genes showed modulation of androgen and estrogen metabolism in men who routinely consumed more fish compared to men who ate less. In addition, modulation of AA metabolism and oxidative stress response was significantly different between the supplemented and nonsupplemented group.

Metabolomics approaches have also been used in dietary intervention studies to slow cancer progression. For example, they have been used to study the mechanism by which a diet rich in WG rye reduces the progression of early-stage PC [39]. This study compared changes in the plasma metabolic signature of patients with early-stage PC, after a 6-week intervention with a diet rich in WG rye and rye bran product (RP), as compared with a similar intervention with a diet rich in a refined white wheat product (WP). Seventeen PC patients received 485 g RP or WP in a randomized, controlled, crossover design. At the end of each intervention period, fasting plasma samples were collected and studied using $^{1}$H NMR-based metabolomics technologies. The data showed an increase in five metabolites, including 3-hydroxybutyric acid, acetone, betaine, *N*,*N*-dimethylglycine, and dimethyl sulfone, after the RP but not the WP intervention. The data suggested a shift in energy metabolism from an anabolic to a catabolic status, which could explain some of the beneficial health effects of WG rye. These would support the use of RP in dietary regimes for slowing cancer progression.

## FUNCTIONAL FOODS

In the 1980s, Japan proposed the terminology and concepts of 'functional food', stimulating a considerable amount of basic and applied studies on food functionality across the globe. Although there are several definitions, an agreed working definition is "a food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond nutritional effects in a way which is relevant to either the state of health or well-being or the reduction of the risk of a disease." Functional foods are typically created to enhance the levels, bioavailability, or palatability of various nutrients and/or bioactive compounds.

### How to Produce a Functional Food

Several methods can be used.

1. Eliminating or reducing the levels of a given food compound: This is appropriate to components known to cause a deleterious effect when consumed (e.g., an allergen).
2. Increasing the concentration of a component naturally present in food: For example, foods might be fortified with a micronutrient to reach a daily intake compatible with the dietary guidelines for reducing risk of disease.
3. Adding a novel component not normally present in most foods: Examples here would include probiotics or nonvitamin antioxidants.
4. Replacing a component whose intake may be at dietary excess levels: For example, starches may be replaced by dietary fibers in fiber-enhanced foods such as breads.
5. Increasing bioavailability or stability of a functional component: Examples here include studies on polyphenolic compounds.

Examples of typical ingredients added, and the claims associated with them, are provided in Table 1.2.

**TABLE 1.2**
**Examples of Functional Food Ingredients, the Claims That Are Made or Implied, and the Evidence for the Efficacy of These Ingredients in Maintaining Health and/or Preventing Disease**

| Ingredient | Examples of Products | Claim | Strength of Evidence in Humans |
|---|---|---|---|
| | | **Macronutrients** | |
| Carbohydrates as dietary fiber | Fiber-enhanced breads | Relieves constipation | ++ |
| Lipids as *n*-3 PUFA | Breads, eggs | Reduces risk of heart disease | ++ |
| Soy protein | Drinks, bars | Reduces cholesterol and risk of heart disease | +– For cholesterol lowering<br>+– For reduction of heart disease |
| | | **Micronutrients** | |
| Folic acid | Breakfast cereals | Protects against neural tube defects | ++ |
| Folic acid + vitamin $B_6$ (pyridoxine) | Breakfast cereals | Decreases homocysteine and risk of CVD | ++ For homocysteine<br>– For CVD |
| Vitamin D | Milk, breakfast cereals, and margarines | Immune function, bone health, and a decrease in mortality in elderly women | + For all |
| Vitamin E | Supplements | Antioxidant, prevents CVD | – For CVD |
| Vitamin C | Drinks, sweets | Protects against CVD | +– In observational studies<br>– In clinical trials |
| Calcium | Cereals, fruit juices, milk products, spreads | Protects against osteoporosis, helps maintain bone density | + For consumers with a low calcium intake |
| Zinc | Sweets, lozenges | Prevention/cure of common cold | +– |
| | | **Novel functional food ingredients** | |
| Plant stanols and sterols | Margarine, yogurt, cereal bars | Lower cholesterol and risk of coronary heart disease | ++ For low-density lipoprotein cholesterol lowering<br>+– For coronary heart disease<br>No data on coronary heart disease |
| "Probiotic" live bacteria, plus fermentable sugars (prebiotics) | Yogurts | Enhance immunity | Some effects on biomarkers |

(*Continued*)

**TABLE 1.2 (*Continued*)**
**Examples of Functional Food Ingredients, the Claims That Are Made or Implied, and the Evidence for the Efficacy of These Ingredients in Maintaining Health and/or Preventing Disease**

| Ingredient | Examples of Products | Claim | Strength of Evidence in Humans |
|---|---|---|---|
| Isoflavones | Soy products | Reduce menopausal symptoms, osteoporosis, and CVD | – For hot flushes<br>+– For osteoporosis and heart disease |
| Catechins | Tea | Reduce CVD | +– Some epidemiological evidence<br>No trial data |
| Conjugated linoleic acid | Supplements (small amounts occur naturally in milk, beef, and lamb) | Anti-inflammatory effects reduce cancer and CVD risk | No data on cancer in humans<br>– For blood lipids in humans |

Whether the food itself will have a similar effect depends on the amounts and bioavailability of the claimed active ingredients.
++, Proven efficacy, consistent effect seen in multiple high-quality studies; +, reasonable evidence for efficacy, effect seen in a limited number of studies, or some inconsistency between studies; +–, evidence for no effect, absence of an effect evident from a limited number of studies; –, proven not to work, absence of an effect evident. More detailed references can be found in References [40–42].

Why might nutrigenomics be important for functional foods?

It is important to recognize that just adding a so-called functional ingredient to a food matrix does not prove that the food will benefit health. Theory does not always extrapolate to practice, and hitherto standard chemical, biochemical, or physiological methodologies may not be adequate to fully describe functional effects. Despite their increasing popularity, few functional foods are currently accompanied by scientifically supported health claims. The aims of nutrigenomics include being able to demonstrate the effect of known nutrients and bioactive food compounds and health foods on health, independent of the biological matrix which these are presented in. The technologies should lead to the development of functional foods that will keep people healthy according to their individual needs. Additional variables to be considered include the question as to whether the food is unprocessed and processed, the food matrix it is in, the amount that is actually eaten, and the eating-related behaviors of consumers. The studies are large and complex, and international cooperation in nutrigenomics research is highly desirable [43].

Functional foods are being designed for personalized nutrition, based on genetic information relevant to health risk profiles. An example might be functional food products designed to reduce the risk of CVDs. Despite excellent hypotheses for their design, effects induced by functional foods are hard to identify and prove, let alone

to establish a recommended daily intake. Thus, defining the optimal intake and the upper limit of both functional foods and dietary supplements poses a technical challenge. Whole-genome transcriptome analysis can provide unbiased information on potentially affected biological processes, on a whole-genome level [40].

## PERSONALIZED NUTRITION

A human phenotype is the composite of observable characteristics or traits, including appearance, behavior, development, and biochemical or physiological properties. Phenotypes result from the interaction between genes and environment, which ultimately determines the personalized nutritional requirements for an individual. As discussed earlier, there are a considerable number of genes that affect individual dietary requirements. However, we are not yet sufficiently in control of bioinformatics manipulation of that genetic information to understand how to optimally combine information on gene pathways and epistasis, thereby determining individual nutritional requirements. Alternative approaches (Figure 1.3) may provide answers to this dilemma. The identification of responders from nonresponders to diet must be a primary goal of personalizing nutrition, based on genetic and metabolic information.

The response of an individual to the combined effects of nutrient and caloric intake, genetic and epigenetic background, lifestyle choices, and environmental exposures, provides a sensitive indicator of nutritional and metabolic status, increasingly being measured as a metabolic phenotype [44]. Such information enables a rational basis for the selection of foods, including functional foods, and supplements,

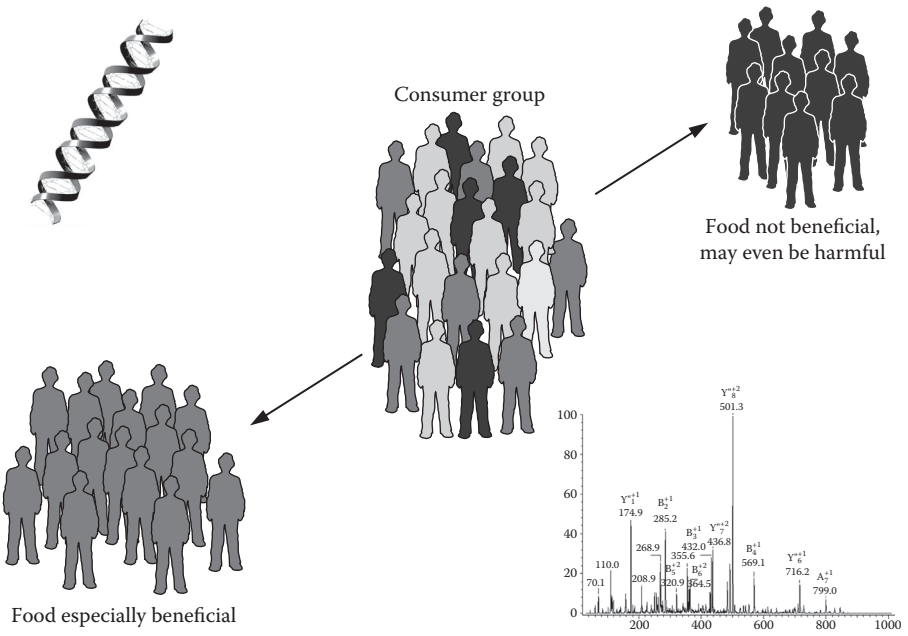


**FIGURE 1.3** Both genetic and metabolomics methods may be appropriate for stratifying individuals for dietary benefits, in a comparable manner to pharmacogenomics.

along with lifestyle modification, to move an individual's health in a more personally beneficial direction. The ultimate goal is to develop a dietary pattern for each individual to maximize health and wellness, and prevent disease. This will also depend on age, activity level, and other lifestyle and environmental factors.

In addition to variations in the human genome, it is important to recognize the role of variation in the gut microbiota on human health [45]. These microbes and their by-products have been shown to alter the host genome, transcriptome, proteome, metabolome, and health status. Urinary metabolites reflect not only human metabolism, but also gut microflora metabolism. For example, distinctive urinary metabolites have been associated with the obesity phenotype [46]. Urinary metabolite profiling using $^{1}$H NMR spectroscopy and pattern recognition methods has distinguished children with autism from closely related individuals without the disease [47]. The data suggest perturbations in sulfur and amino acid metabolism, as well as biochemical changes associated with an altered gut microbiota in the autistic children. Such distinctive metabolic profiles could be of potential value in monitoring the success of therapeutic interventions. This means that modulating the gut microbiota must be considered as an essential component of personalized nutrition. It becomes important to distinguish how different dietary components can enhance the selective growth of one microbial population over another. Metabolomics-based technologies have provided convincing evidence that regular consumption of synbiotics (a combination of probiotics and prebiotics) can lead to significant shifts in microbial flora [48].

## TAKING PERSONALIZED NUTRITION TO THE PUBLIC

Surveys have generally shown consumers to have a positive attitude toward personalized foods. They would also be responsive to the use of their genetic profile, especially if guided by a dietician, and would be willing to buy the resulting product [49] (Chapter 18). However, there are still several challenges to targeted nutrition advice and functional food marketing according to genetic advice. Despite the promise of nutrigenomics to personalize diet, there have not yet been the large-scale nutrition intervention studies to prove the efficacy of the concept. The technology is now sufficiently sensitive and poised to make a significant difference to long-term human health.

Personalized nutrition uses familial, genetic, or metabolomics information to interpret an individual's health risk profile. The derived nutritional recommendations are claimed to help maintain wellness and/or reduce disease risk. Various Internet surveys have questioned consumers regarding their attitudes to such testing, if they would buy functional foods relevant to their individual nutrigenetic profile, or more generally use personalized nutrition. For example, such an Internet survey was conducted in December 2007 using a sample of 452 randomly selected adults in Germany [41]. The survey also considered the potential acceptance of functional food products claimed to reduce the risk of CVDs. In general, this group of consumers was positive toward the testing of their genetic profile, if it would lead to specific advice on beneficial nutrition. In addition, more than 40% would be willing to buy derived functional food products.

Ethical and practical considerations for various consumer groups can be found in Chapters 15 through 20.

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