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**INVITED REVIEW**

# Research in nutrigenomics and potential applications to practice

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## Abstract

**Aim:** Nutrigenomics reflects gene–diet interactions. In recent years, the science of nutrigenomics has become more sophisticated. We seek to answer the question as to what this might mean for the dietetics profession.

**Methods:** We have critically reviewed recent developments in the area, and considered the importance of new business opportunities being opened up, which exploit the full potential of nutrigenomics for dietitians.

**Results:** Whereas early business models sold genetic test results through direct-to-consumer testing, new business initiatives move dietitians to a central role. This now provides a robust framework that can inform dietitians in their practice.

**Conclusion:** This field represents an important advance for dietitians.

**Key words:** nutrigenomics, nutrigenetics, molecular nutrition.

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## Introduction

The challenge to a modern dietitian or nutritionist is large. In the hospital clinics, he or she is regularly confronted with problems resulting from poor nutrition. In private practice, consultation may not occur until the nutritional problems become almost insurmountable. In either example, there are inevitably cases who do not respond to conventional dietary interventions. There may be a tendency to focus on the behaviour of the client, and assume there has been non-compliance. However, the possibility exists that this individual is genetically different from the norm in some way, and has some specific nutrient requirements that are not being recognised.

The field of nutritional genomics, or its sub-discipline, nutrigenetics, provides the tools for genetic screening, either of specific areas of the genome or the whole genome, to better understand individual nutrient requirements. It depends upon the recognition that a ‘one size fits all’ approach to defining nutrient requirements is flawed. It has been known for some time that genetic variants in genes encoding key enzymes in nutrient absorption, metabolism

and distribution will influence the dietary requirements for that nutrient.<sup>1</sup> Sensitive modern methods enable rapid and accurate measurement of genetic variants such as single nucleotide polymorphisms (SNPs, which are a variant of a single nucleotide base within a DNA sequence), in a wide range of genes. This knowledge may help guide a dietitian to determine an optimal diet for that individual. For example, if an SNP is identified within a gene encoding a key enzyme for nutrient absorption, and it is known that this SNP results in less effective absorption, then a higher intake of that nutrient would be recommended for the individual carrying that SNP. This approach could be applied across a ‘panel’ of such key genes, with recommended intakes for the relevant nutrients altered accordingly, thus optimising diet on the basis of an individual’s genotype. Table 1 defines some key terms.

Genetic predisposition plays a pivotal role in response to diet and susceptibility to disease. However, we are not alone; within the human gastrointestinal tract can be found approximately  $10^{14}$  bacteria (collectively known as the ‘microbiome’) which are organised into a highly complex, symbiotic community. It is now recognised that the gastrointestinal microbiome makes a significant contribution to human health, and can even influence the expression of the human genome.<sup>2</sup> The number of gene products resulting from microbial metabolism (i.e. encoded by the collective genomes of the bacteria) considerably exceeds that produced by the human genome. Such gene products initiate digestion and the production of nutrients, detoxification and the development of tolerance or host defence against microbes, and are an important component of the complex

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**Table 1** Some definitions of terms commonly used in nutrigenomics

<i>Genome</i> : Collection of genes.
<i>Epigenome</i> : Structural changes to DNA that affect gene expression (gene x environment effects).
<i>Proteome</i> : Proteins expressed at a specific time.
<i>Metabolome</i> : Metabolites expressed at a specific time.
<i>Microbiome</i> : Microbes present in the gut (100 times > human genome).

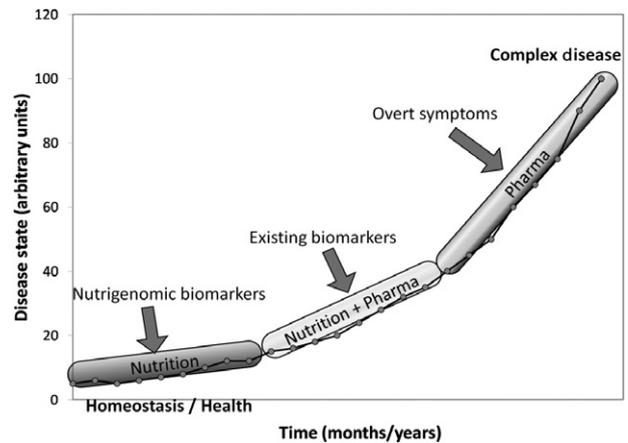
host–microbe symbiotic relationship. Technologies to estimate the influence of the microbial genome, and the interplay between human genes and those of the microbiome, are currently far beyond the scope of an average diet clinic.

The end product of action and interplay of various gene pathways, both human and microbial, is known as the phenotype. The phenotype is usually measured by metabolomic or transcriptomic profiles, which although more complex to interpret, may allow a dietitian to estimate the effect of a given diet on a given individual.<sup>3–5</sup> Metabolomics (or metabonomics) involves the analysis of plasma or urine samples, and enables rapid, high-throughput characterisation of small molecule metabolites, resulting from either human or bacterial metabolism.<sup>3</sup> Transcriptomics may also be referred to as gene-expression profiling.<sup>4,5</sup> It measures the expression level of mRNAs in a given cell population, often using high-throughput techniques. These methodologies may provide sensitive biomarkers to show early signs of effects on health, rather than a need for waiting for early signs of disease to develop, and reliance on pharmaceutical interventions (Figure 1).

Omics technologies may ultimately become more important than genotyping. Genotype refers to the inherited genetic traits, while phenotype refers to observable, physical manifestations. For example, as discussed in more detail next, inheriting a variant in the methylene tetrahydrofolate reductase (*MTHFR* gene) may mean that a given individual requires more folate than the average requirement.<sup>6</sup> Without this, homocysteine levels will rise (a phenotypic effect). However, with genetic tests for *MTHFR* variants, or alternatively with phenotype tests for elevated homocysteine, folate intake can be appropriately adjusted to maintain optimal health (see next).

## Nutrigenetics for the dietitian

The results of a given diet are highly dependent on a complex interaction of lifestyle variables and genetic make-up, and it is difficult to make clear and meaningful recommendations on a population basis. Working with individual patients opens the possibility of basing dietary recommendations on measurement of variants in a relatively small number of genes. While the number of gene variants occurring in an individual may be very large (in the thousands), it is likely that a ‘panel’ of up to 20 variants relating to the metabolism of key nutrients will be sufficient to offer advice



**Figure 1** Health to disease continuum. Progress from health, or homeostasis, to complex diseases, such as metabolic syndrome, can occur over a significant time period. Traditional disease diagnosis relies on the presence of overt symptoms, by which time it is likely that a pharmaceutical or pharmacological intervention will be required to successfully treat disease symptoms. Currently available biomarkers for early disease detection are beneficial, and enable the potential for successful nutritional intervention, although an element of pharma may still be necessary. Nutrigenomics techniques, because of their remarkable sensitivity, can enable detection of the earliest phases of disease pathology or perturbed homeostasis, and will therefore enable effective, early application of nutritional or dietary strategies to prevent disease or to recover homeostasis. Adapted from Afman and Muller.<sup>4</sup>

that can make a real difference in terms of that individual’s diet. There are several commercial entities that provide a genotyping service, and work through dietitians to translate this information into meaningful advice. For example, the newly established Nutrigenomix genotyping service<sup>7</sup> tests for SNPs in a panel of genes relating to uptake and metabolism of vitamin C, folate, whole grains, omega-3 polyunsaturated fatty acids, saturated fat, sodium and caffeine. Nutrigenetics enables us to study people’s responses to the recommended amounts of these nutrients and how their metabolism manages the nutrients. An example here would be different responses of HDL cholesterol levels to long chain omega-3 fatty acids depending on the person’s SNP in one particular gene. The apolipoprotein E (APOE) gene shows genetic variation, with three common alleles in the population, E2, E3 and E4, all of which are seen in significant levels in European populations.<sup>8</sup> There is good evidence from population studies that carrying the APOE4 isoform leads to increased plasma cholesterol and LDL cholesterol, while the APOE2 isoform leads to the lowest, irrespective of diet.<sup>9</sup> However, the APOE4 carriers will benefit the most from reduction of saturated fat and alcohol intake.<sup>9</sup> A nutrigenetics testing service will comprehensively analyse such findings, and send their recommendations to a dietitian, who will interpret the results for an individual. Testing may

be done using a saliva or buccal swab sample, from which DNA can be extracted.

The common genetic variants measured in the Nutrigenomix toolkit are known to affect human response to major groups of foods and beverages, a selection based on robust human evidence. For example, although other genes affect folate requirements, the enzyme coded for by the *MTHFR* gene is central to the effective functioning of this nutrient. The *MTHFR* 677C→T variant strongly modulates folate status. Those people carrying the CT or TT variant at this position of the gene are at greater risk of folate deficiency when folate intake is low, as compared with those with the CC variant.<sup>10</sup> The amount of folate absorbed into the blood can differ among individuals, even those having the same dietary folate intake.<sup>11</sup> Those people who do not utilise dietary folate as efficiently as others are at a greater risk of folate deficiency. *MTHFR* is essential for the production of 5-methyltetrahydrofolate from 5,10-methylenetetrahydrofolate. 5-methyltetrahydrofolate is a co-substrate in the production of methionine, through re-methylation of homocysteine. Thus, if the *MTHFR* enzyme is not functioning effectively, homocysteine can accumulate in the blood. High blood levels of homocysteine have been associated with an increased risk of developing chronic diseases, such as heart disease or cancer.<sup>11</sup>

Coffee is a widely consumed stimulant beverage, prepared from roasted seeds of the coffee plant. Coffee is the world's most widely traded tropical agricultural commodity, accounting for exports worth an estimated US\$ 15.4 billion in 2009/2010.<sup>12</sup> According to legend, the origins of coffee can be traced to an Ethiopian goat herder, who observed that his goats were restless and agitated after consuming wild coffee berries.<sup>13</sup> This is presumably because of their response to the active ingredient, caffeine, an alkaloid found in a variety of plant species, where it acts as a natural pesticide. This response also occurs in humans (and caffeine has been described as 'the most widely consumed behaviourally active substance in the world'<sup>14</sup>), and its effects on neurotransmitter release via binding to adenosine receptors are well established.<sup>14</sup>

It is noteworthy that not all people respond to caffeine in the same way, and this is largely determined by how long it remains in their system. It is metabolised in the liver by the cytochrome P450 oxidase enzyme system, primarily CYP1A2.<sup>14</sup> Individuals who are homozygous for the *CYP1A2*\*1A variant are 'rapid' caffeine metabolisers for whom caffeine has little effect due to its rapid clearance, whereas carriers of the variant *CYP1A2*\*1F are 'slow' caffeine metabolisers, and the longer time that caffeine is active in their systems means it has a greater effect. This is one example of how an SNP within a gene encoding a key enzyme can have a significant influence on the metabolism of a nutrient, with phenotypic consequences, and is indeed the gene used by Nutrigenomix to assess dietary requirements with respect to caffeine.

While increased alertness may not be seen as a major drawback, increased risk of a heart attack is more serious. Cornelis and El-Soehy<sup>15</sup> worked with a Costa Rican popu-

lation, and reported that while there were no overall changes in risk associated with slow or fast metabolisers, this changed with high intake of coffee. High coffee consumption was associated with an increased risk of non-fatal myocardial infarction, but only among individuals who are slow caffeine metabolisers. Thus, while moderate consumption may be of benefit for the majority of people, an understanding of the gene variants associated with caffeine metabolism may be important in order to give appropriate dietary advice with respect to higher levels of coffee consumption. These data also suggest that it is the caffeine in coffee which increases cardiovascular risk, and that another compound may mediate its beneficial effects. There is evidence from animal studies that a component of coffee other than caffeine may be responsible for certain of its beneficial effects,<sup>16</sup> although other studies suggest that the caffeine component itself is of benefit,<sup>17</sup> and there is still controversy regarding the beneficial effects of coffee consumption on human health.<sup>18</sup>

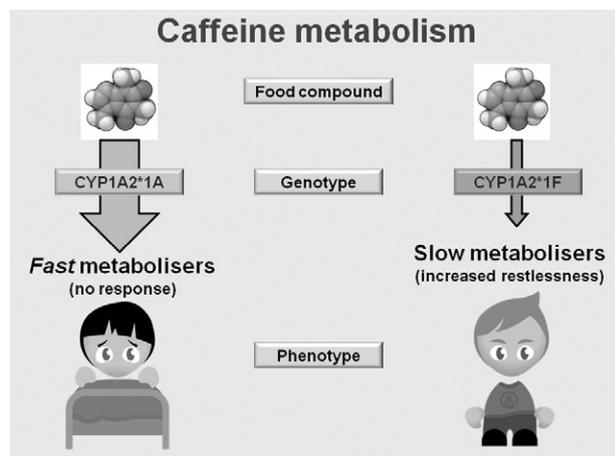
## From genotype to phenotype

The approach used by Nutrigenomix and by other testing companies provides an important step towards optimal nutritional status, thereby helping in the prevention of nutrition-related chronic disease. By detecting more subtle changes in the pathways towards disease as compared with standard biomarkers, nutritional interventions may be instituted before pharmaceutical interventions are required<sup>3-5</sup> (Figure 1). However, as there are more than 23 000 functional genes in the human genome, it will be apparent that although SNPs in seven genes may indicate some key nutritional requirements, they will not provide all the relevant information. Attention is turning to phenotyping as a complementary tool, or in preference to genotyping, a limited number of genes.<sup>3</sup> A phenotype is determined by both genetic and environmental influences, and appears as physical and/or biochemical characteristics of any given individual. Another set of tools is necessary to exploit these characteristics (Table 2). In the caffeine example given previously, most people are aware of their own response to caffeine. Thus, increased restlessness or no response provides a phenotypic indicator of the metabolic genotype (Figure 2).

A second example may further illustrate the potential utility of phenotyping. This is provided by the way in which vitamin D supplementation was optimised for protection against metabolic syndrome.<sup>19</sup> A double-blind, randomised, placebo-controlled dietary intervention trial assigned subjects with markers of metabolic syndrome to receive 15 mg vitamin D3 or placebo daily. Serum 25-hydroxyvitamin D (25(OH)D) and a range of biochemical markers of the metabolic syndrome were measured at baseline, and again after a four-week dietary intervention. Nuclear magnetic resonance-based metabolomic analysis, stratified using k-means clustering, was used to study the response. Although vitamin D supplementation significantly increased serum 25(OH)D, there was no overall effect of supplementation on the metabolic syndrome biomarkers. However, five discrete

**Table 2** The scope of integrated personal –OMICs. This table illustrates the wealth of personal information that is now accessible using –OMICs technologies

Tissue sampled	Method	Analyses
Peripheral blood monocytes	Whole genome sequencing	Variant calling/phasing
	Whole transcriptome sequencing (mRNA and miRNA)	Heteroallelic and variant expression
Serum	Proteome profiling	RNA editing
	Untargeted proteome profiling	Quantitative differential expression and dynamics
	Targeted proteome profiling (cytokines)	Variant confirmation in RNA and protein
	Metabolome profiling	Quantitative differential expression and dynamics
	Autoantibody profiling	Quantitative expression
Medical/ laboratory tests	Dynamics	Differential reactivity
		Glucose, lipids, HbA1c, CRP, Telomere length

**Figure 2** Genotypic and phenotypic differences between fast and slow caffeine metabolisers. Those individuals with a 'fast metaboliser' genotype can partake of caffeinated foods at all hours, without detriment to their sleeping ability. In contrast, slow metabolisers can only tolerate a very limited caffeine intake, and even this has detrimental effects on sleep modes and restlessness.

biomarker clusters were revealed, one of which was characterised by lower serum 25(OH)D and higher levels of metabolic biomarkers prior to supplementation. That is, this technology enabled identification of a group of people whose metabolic syndrome symptoms would be likely to benefit from vitamin D supplementation. These promising data suggest that metabolic phenotyping will be a useful tool in human intervention studies.<sup>20</sup>

### Clinical trials of novel foods, new diets and dietary supplements—current status

Nutrient reference values of both macro- and micronutrients are regularly revised as new information becomes available on the optimal levels for maintaining genomic stability.<sup>21</sup> The advice of dietitians can help to implement these. However,

most healthy individuals prefer their own dietary selections, and there are a number of nutrients that are at suboptimal levels in the normal human diet. An example of this is provided by long chain omega-3 polyunsaturated fatty acids.<sup>22</sup> Rather than making major dietary changes, many will turn to dietary supplements or functional foods to raise the levels of such nutrients.<sup>23</sup> Functional foods are foods claimed (with varying degrees of proof) to have increased levels of nutrients and/or are associated with health claims. As such, they need to be accompanied by some sort of clinical trial data, to have credibility. In their present form, however, such trials are expensive and may be beyond the budget for all but the largest food companies.

Characteristics of clinical trials in their most widely used form are that they:

- Typically require large numbers of volunteers
- Are usually looking for some measurable effects such as reduction in serum cholesterol or reduction in the frequency of colds/infection
- Usually pre-select subjects with an elevated disease risk

However, the most desirable time to develop appropriate dietary regimes is before disease symptoms, or even early biomarkers, start to appear. This is where nutrigenomics technologies are increasingly becoming appropriate<sup>22–24</sup>

### Clinical trials of novel foods, new diets and dietary supplements—future status

The toolkit provided by nutrigenomics does not require that disease symptoms are already present, albeit at an early stage. Both metabolomics and transcriptomics allow some measure of the flux of metabolites, and the implication of the given food or dietary regime for the expression of genes and gene pathways relevant to disease susceptibility. The methods can be applied to excreta or blood samples, making them non-invasive and predictive.

The word 'health' includes a large variation in normality, and the effects of nutritional interventions may remain hidden in this 'diversity of robustness', if incompletely analysed.<sup>25</sup> This suggests that a comprehensive multi-parameter nutrigenomics analysis may identify biomarkers of health

with greater sensitivity than tests more commonly used (Figure 1). Gene expression arrays may reveal key drivers of health, including metabolism, oxidation, inflammation and psychological stress. This important new approach may be instrumental in maintaining health and developing the most effective dietary intervention to prevent disease through appropriate nutrition. The importance of this is that the sensitivity of these markers picks up very early warnings of potential future disease development, enabling more effective nutritional intervention.

## Conclusions

Nutrigenetics and nutrigenomics are relatively new disciplines for the dietitian. Used appropriately, they have the potential to open up some important new information in relation to dietary optimisation. Linkages with academia will be essential to maintaining a competitive advantage in this important new field.

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