NRC Research Press

INVITED REVIEW

The evolution of nutrition research

Cara K. Isaak and Yaw L. Siow

Abstract: "*The doctor of the future will no longer treat the human frame with drugs, but will rather cure and prevent disease with nutrition*". Thomas Edison's contemplation may come to fruition if the nutritional revolution continues in its current course. Two realizations have propelled the world into a new age of personalized nutrition: (*i*) food can provide benefits beyond its intrinsic nutrient content, and (*ii*) we are not all created equal in our ability to realize to these benefits. Nutrigenomics is concerned with delineating genomic propensities to respond to various nutritional stimuli and the resulting impact on individual health. This review will examine the current technologies utilized by nutrigeneticists, the available literature regarding nutrient-gene interactions, and the translation of this new awareness into public health.

Key words: genome-wide association studies, knowledge translation, nutrigenomics, nutrition, single nucleotide polymorphism.

Résumé : « *Le médecin de l'avenir ne traitera plus le corps humain avec des médicaments mais plutôt, le guérira et préviendra la maladie par la nutrition* ». La réflexion de Thomas Edison peut devenir réalité si la révolution nutritionnelle continue sur sa lancée. Deux observations ont propulsé le monde dans une nouvelle ère de nutrition personnalisée : (*i*) un aliment peut fournir de bénéfices qui vont au-delà de son contenu intrinsèque en nutriment et (*ii*) nous ne sommes pas nés égaux quant à notre capacité à tirer profit de ces bénéfices. La nutrigénomique s'intéresse à définir sur le plan génomique les propensions à répondre à différents stimuli nutritionnels et l'impact qui en découle sur la santé d'un individu. Cet article de revue examinera les technologies actuelles utilisées par les nutrigénéticiens, la littérature publiée sur les interactions nutriment-gène et le transfert de ce nouveau savoir en santé publique. [Traduit par la Rédaction]

Mots-clés : études d'association à l'échelle du génome, transfert de connaissance, nutrigénomique, nutrition, polymorphisme nucléotidique simple.

Introduction

At its inception, nutritional research focused on the nourishment of populations and the relative consumption of generalized food groups. From these humble beginnings, the field has flourished and we now demand not only sustenance from our diet, but also health promotion, disease prevention, and performance enhancement. Only recently, with the explosion of lifestyle-related diseases like obesity, type 2 diabetes, cardiovascular diseases, and certain cancers, have North Americans begun to appreciate the enormous impact our diet has on our health. To avoid the fates of the overindulgent, our response has been to gorge ourselves instead on the feast of scientific research available. We will modify, customize, supplement, and scrutinize our diets to exact the most advantageous combination of nutrients.

Two fields have emerged in the study of the interaction between the genome and diet: (*i*) nutrigenomics, which aims to unravel the influence of diet over the genome, or more specifically, the genetic or cellular response elicited by a nutritional stimulus (Ordovas and Mooser 2004); and (*ii*) nutrigenetics, which aims to understand how genotype influences the genetic or cellular response to a nutritional stimulus (Mutch et al. 2005).

Clearly, these 2 fields, although directionally opposed, are intrinsically linked at the diet–genome interface. Regardless of whether diet or genotype is the more influential force, their interaction is of great importance in the context of common disease states. One may be predisposed to certain pathologies by one's genetics, but empirical evidence indicates that for many complex traits, environmental exposures, nutritional or otherwise, can sway the balance between health and disease.

The study of diet–gene interactions ultimately combines every field of research, from cell biology, to analytical chemistry, to health policy, to sociology, and utilizes every biotechnological advancement currently available. This review will examine the methods and technologies currently being used in nutrigenomic studies, summarize the available nutrigenomic research, and dissect a few examples of the practical applications of their findings.

The "omics"

While the ultimate goal of nutrigenomics is providing personalized nutrition for maintenance of individual health, the current priority is defining a healthy phenotype. This goal can be met by integrating genomics, transcriptomics, proteomics, and metabolomics to create the definitive definition of nutrigenomic health, which is yet enigmatic (Kussmann et al. 2006). These 4 fields are independently complex and still evolving, and therefore require further examination.

Genomics is the study of the sequence and structure of the complete genome, genes, and their mRNA products, as well as the study of epigenetic and evolutionary phenomena. The sequencing of the human genome provided a starting point for human genetic research, but little functional comprehension (International Human Genome Sequencing Consortium 2001). This deficiency was helped by the HapMap project, which generated a list of single nucleotide polymorphisms (SNPs), capturing a large proportion of the common genetic variation in many human populations (International HapMap Consortium 2005). The current

Received 12 October 2012. Accepted 14 January 2013.

C.K. Isaak and Y.L. Siow. Agriculture and Agri-Food Canada, Canadian Centre for Agri-Food Research in Health and Medicine, St. Boniface Hospital Research Centre, 351 Taché Avenue, Winnipeg, MB R2H 2A6, Canada; Department of Physiology, University of Manitoba, 432 Basic Medical Sciences Building, 745 Bannatyne Avenue, Winnipeg, MB R3E 0J9, Canada.

Corresponding author: Yaw L. Siow (e-mail: YawChris.Siow@agr.gc.ca).

goal is to discover the function of the thousands of known genes as well as the intergenic regions of the genome. Common variations are used in nutrigenomic research in the form of genome-wide association studies, which will be discussed later. Genomics may be more suited to nutrigenetics than nutrigenomics, as effects of the diet on the cellular response is more often seen at the mRNA or protein level, rather than at the genomic level.

Transcriptomics is the analysis of genome-wide gene expression, and can provide a comprehensive snapshot of all active genes in a sample. This is extremely useful, as gene expression is a dynamic process, and gene expression profiles can be compared between samples or between time points. Microarray analysis developed in the 1990s is the technology of choice for detecting multiple analytes (Schena et al. 1995), and will be discussed further.

mRNA expression will only reveal the nuclear response to nutrient intake, and this is far from the only way genome function is represented. Additionally, mRNA levels do not necessarily translate into physiological function. Proteomics quantifies the bioactive proteins and peptides so that they may be used as biomarkers of healthy or disease states. This field uses 2-dimensional electrophoresis coupled to mass spectrometry (MS) to identify and quantitate proteins (Kussmann 2009).

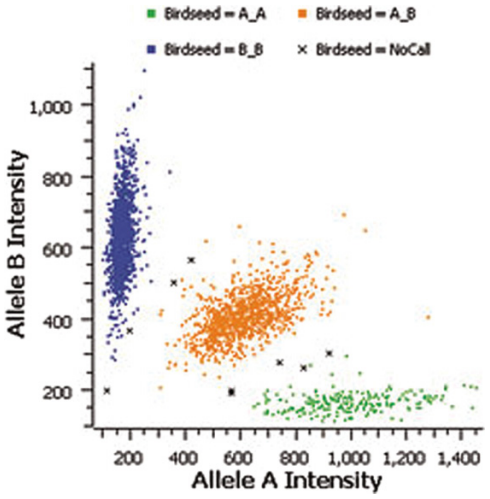
Metabolomics is the study of the changes in the complete set of metabolites in response to nutrient intake. Looking for the intermediates of metabolism or low-molecular weight molecules in bodily fluids using nuclear magnetic resonance spectroscopy, infrared spectroscopy, or high performance liquid chromatography (HPLC) is a less invasive alternative to genomic, proteomic, or transcriptomic analysis of tissues. The metabolic profile can be analyzed using bioinformatics to compare the metabolome in response to different stimuli (Van Der Werf et al. 2001). Screening methods will also improve dietary assessment in clinical trials by replacing highly variable food-frequency questionnaires with a detailed screen for plasma micronutrient concentrations. Metabolomics also has clinical applications for detecting and preventing nutritional deficiencies before health is affected, and it is the only field that takes into account contributions from gut microflora. Metabolism by intestinal bacteria can affect the response to nutrients, but cannot be captured by traditional methods (McNiven et al. 2011).

Genome-wide association studies

A nutrigenomic study will often start with the premise that a polymorphism is associated with a disease state, and from there attempt to uncover how that SNP affects the individuals response to a certain nutrient. SNPs are linked to diseases by genome-wide association studies (GWAS). Essentially, the HapMap project has provided a list of common variations across the genome. Each of these SNPs is captured in an oligonucleotide that is spotted onto a glass slide. DNA from both cases (individuals who have the disease) and controls (healthy individuals) are assayed, or genotyped, so that the degree of hybridization at each spot can be recorded based on the intensity of a fluorescent signal. Currently, 2 main SNP platforms are commercially available: (*i*) the Affymetrix Genome-wide Human SNP Array 6.0, which can detect 906 600 SNPs, including both historically used SNPs and SNPs found on the X and Y chromosomes, in mitochondrial DNA, and in recombination hotspots, as well as 946 000 copy number variants, and (*ii*) the Illumina HumanOmni5-Quad BeadChip, which can detect over 4 million markers, including many SNPs specific to the major histocompatibility complex region associated with autoimmune diseases and regions related to drug metabolism. Both chips can be customized by adding additional SNPs (Affymetrix 2012; Illumina 2012).

The generated data are analyzed first using a scatterplot and a genotype calling algorithm. A useful SNP will give 3 well-defined clusters of individuals with each genotype (Fig. 1). At this point, quality control measures are used to remove uninformative SNPs and subjects with missing or inconsistent data from the analysis.

Fig. 1. An allele intensity plot (from Christensen 2010, reproduced with permission from Golden Helix, Inc., ©2010 Golden Helix, Inc.).

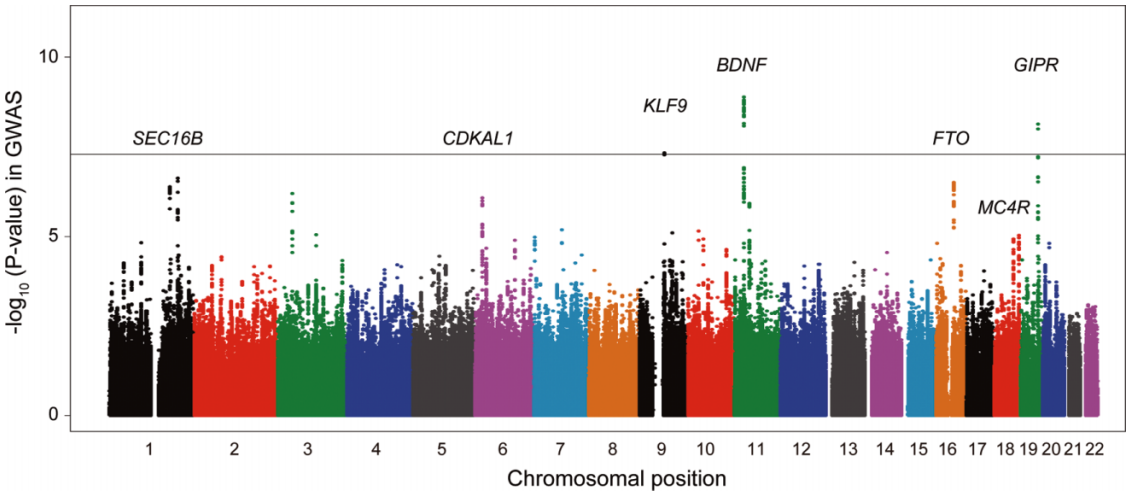


The data are further transformed by logistic regression (not shown) using the disease status (control = 0, case = 1) as the dependent variable, and the SNP genotype (the number of copies of the minor/less frequent allele: 0, 1, or 2) as the independent variable. An additive test with 1 degree of freedom will yield a *p* value for each SNP (Wellcome Trust Case Control Consortium, 2007). The next step is to produce a quantile–quantile plot, or a graph with the $-\log_{10}$ (*p* value) on the *y*-axis and the $-\log_{10}$ (*p* value expected by chance) on the *x*-axis (not shown). For visualization, *p* values are usually shown in a Manhattan plot: a scatter plot with the $-\log_{10}$ of the *p* value on the *y*-axis and the genomic position on the *x*-axis (Fig. 2). In the context of GWAS, only *p* values less than 5×10^{-8} (indicated on the graph by the grey horizontal line) are considered significant, owing to the huge number of statistical tests being performed (Glessner and Hakonarson 2012). In this graph, regions with high significance, or loci falling above the grey line, are extremely clear and can be expanded in more detailed charts.

While this method may seem very straightforward and robust, GWAS is not without its critics or limitations. Detractors are skeptical of both the basic assumptions on which GWAS is founded and their clinical relevance if the results are in fact legitimate. These opinions have been reviewed by Visscher et al. (2012).

A major problem of correlating genetic markers with disease states is that GWAS fail to take into account other possible causative factors like nutrition and lifestyle. It is the task of the nutrigeneticist to sift through these correlations to see whether and how they are modulated by diet (Ioannidis 2010). Table 1 presents a summary of recent nutrigenomic and nutrigenetic studies that make use of genetic variations identified by GWAS. Alternatively, a single GWAS may be conducted using nutritional status to define cases, rather than pathology. For example, Ahn et al. (2010) conducted a meta-analysis of 5 GWAS where circulating vitamin D levels were recorded, regardless of the purpose of the original study. They found significant associations between 3 loci and circulating vitamin D, which is linked to rickets, osteoporosis, multiple sclerosis, and cancer. These findings indicate that some individuals may need to consume more vitamin D to maintain healthy circulating levels than other members of the population. Of course, many investigators find no link between nutrient intake and the polymorphism they set out to observe, and these findings are just as important in forming our insights. So far, very few studies have sought to replicate significant findings, which

Fig. 2. A Manhattan plot from a genome-wide association studies on body mass index in east Asian populations (from Okada et al. 2012, reproduced with permission from McMillan Publishers Ltd., Nature Genetics, vol. 44, ©2012).



may speak more to a lack of resources rather than a lack of recognition of the importance of corroboration.

Since GWAS are only concerned with variants that are common in the population, and, as Table 1 indicates, many are associated with altered nutrient status, then nutritionally relevant variation is common. This means that there may be no such thing as a normal population with respect to nutrient requirements, as was assumed when dietary reference values were established. Rather, specific genetic information is likely needed to define the optimal diet for an individual (Simopoulos 2010).

Microarray analysis

Clearly, GWAS and SNP analysis can be used to study the influence of genotype on the genetic and cellular response to the diet, but nutrigenomicists are also concerned with the influence of diet on the genome. Microarray analysis is the quintessential method for comparing gene expression profiles between 2 samples; for example, before and after taking a nutritional supplement. A microarray is a glass slide or nylon substrate spotted with a known set of gene sequences. mRNA extracted from blood, cells, or tissues is subjected to reverse transcriptase – in-vitro transcription and labeled with a fluorescent probe to create labeled cRNA. The cRNA is hydridized to the complementary probes on the array and unbound cRNA is washed off. The color intensity at each spot on the array can then be captured using a confocal fluorescent scanner or a chemiluminescence reader, and the resulting image can be analyzed for raw data on gene expression. Essentially, the technique allows for determination of up-regulated or down-regulated genes when compared with a control sample. A detailed review of platforms currently used for microarray analysis is provided by Seidel and Niessner (2008).

Two limitations of microarray analysis are as follows: (*i*) the amount of mRNA present in a cell does not necessarily translate into level of gene expression, since transcription is only one step towards functional protein formation, and (*ii*) different platforms and experimental procedures make comparisons between microarray datasets or between data from different labs difficult (Masotti et al. 2010). In an attempt to increase standardization of microarray studies, the Microarray Gene Expression Data Society released a set of minimum standards for microarray experiments, Minimum Information About a Microarray Experiment (MIAME), to ensure ease of interpretation and independent verification (NCBI 2011). Several microarray databases have adopted the MIAME as a requirement for submission. A communication from Saito et al. (2005) outlines the need for more integrated and detailed repositories for microarray data.

As a case study, the Functional Genomics and Nutrition study (FUNGENUT) tested the changes in gene expression in response to 2 different dietary carbohydrate modifications (Kallio et al. 2007). Their hypothesis was that diets rich in whole grains with low glycemic indices can protect against type 2 diabetes (T2DM) caused by the metabolic syndrome (MetS). MetS is characterized by abdominal obesity and insulin resistance, the latter of which is a strong risk factor for T2DM. Two carbohydrate meals were tested for their effect on gene expression in subcutaneous adipose tissue (SAT) in MetS patients: (*i*) a rye bread and dark pasta diet with low post-prandial insulin response, and (*ii*) an oat bread and potato diet with a high postprandial insulin response. The patients replaced their normal breads and baked products with the test meals for 12 weeks. After the intervention, an adipose tissue biopsy was taken, RNA was extracted, and biotin-labeled cRNA was produced using reverse transcription and in vitro transcription kits supplied by Affymetrix. An Affymetrix HG-U133 Plus 2.0 gene chip was incubated with each cRNA sample, stained with streptavidin–phycoerythrin, incubated with biotinylated anti-streptavidin immunoglobulin, and restained with streptavidin–phycoerythrin. The arrays were scanned with the Affymetrix HP GeneArray Scanner 3000 and data was analyzed with the Affymetrix GeneChip Operating Software.

Using the latest microarray technology, the study showed that both modifications induced changes in SAT gene expression in MetS patients, even without changes in body weight and insulin sensitivity. The rye–pasta diet significantly down-regulated 71 genes linked to insulin signaling and apoptosis, and significantly improved the insulinogenic index, while the oat–potato diet significantly up-regulated 62 genes linked to stress, inflammation, and oxidative stress. In a very practical example of nutritional transcriptomics, these findings suggest that long-term consumption of certain carbohydrates may influence the risk for T2DM even if the patients are unable to lose weight.

Future research considerations

The map of the diet–genome interface is far from complete, although broad ideas and interactions are materializing. As more and more laboratories rush to join the hunt for nutrient–gene interactions, however, an unbalance arises between the amount of knowledge being generated and our ability to understand its ramifications. The most urgent need is for improved bioinformatic and data-mining processes. The theoretical aspects of im-

Table 1. Summary of recent nutrigenomic and nutrigenetic studies.

Reference	Pathology	Modulating dietary factor	Associated SNP	Gene–diet interaction
Ahn 2004, LIBCSP	Breast cancer	Fruits and vegetables	MPO G463A	Carriers of the *A* allele are at lower risk for breast cancer than *GG* homozygotes, and fruit and vegetable consumption further reduces this risk (1011 cases, 1067 controls, American women)
Le Marchand et al. 2004, MCS	Breast cancer	Folate	MTHFR C677T	No significant interaction (1189 cases, 2414 controls, multiethnic American women)
		Alcohol	MTHFR C677T	Carriers of the *C* allele are at a nonsignificant but increased risk for breast cancer compared with *TT* homozygotes, and this risk is increased further in women who drink moderately-to-heavily and are taking hormone replacement therapy.
Ahn 2005, LIBCSP	Breast cancer	Fruits and vegetables	CAT C262T	*CC* homozygotes are at lower risk for breast cancer and see greater reduction in risk with fruit and vegetable consumption than *T* carriers. (1008 cases and 1056 controls)
Lee et al. 2012	Breast cancer	β-carotene	NOS3-786 T>C and NOS3 894 G>T	β-carotene consumption is only protective against breast cancer in individuals with the *TG:TG* diplotype (512 cases, 512 controls, Korean women)
		Vitamin E	NOS3-786 T>C and NOS3 894 G>T	Vitamin E consumption is only protective against breast cancer in NOS3-786 *TC* and *TT* individuals and in NOS3 894 *GT* and *TT* individuals.
Hedelin et al. 2006	Prostate cancer	Fatty fish	COX2 rs5275 (+6365 T/C)	Frequent fatty fish consumption lowers risk for prostate cancer in men with the SNP, but not in men carrying the more common *T* allele (1378 cases, 782 controls, Swedish men)
Fradet et al. 2008	Prostate cancer	Omega-3 fatty acids	COX2 rs274557	EPA and DHA intake is inversely associated with risk of aggressive prostate cancer and this protection is stronger in men who carry the *rs274557* variant (1012 cases and controls, American men)
Jung et al. 2008	Colorectal adenoma	Folate and methionine	DNMT3b –149C>T	*TT* homozygotes with low folate and methionine intake have higher risk for colorectal adenoma than similar individuals who carry the *C* allele (732 cases, 649 controls)
		Alcohol	ADH1 C *2	Heavy drinkers with the **2/*2* genotype have increased risk for colorectal adenoma compared with wild-type heavy drinkers
De Vogel et al. 2011, NCS	Colorectal cancer	Folate and methionine	Several in folate metabolizing enzymes	No significant interaction (609 cases, 1663 controls, Dutch)
London et al. 2000	Lung cancer	Cruciferous vegetables	GSTM1 deletion	Isothiocyanate intake in the form of cruciferous vegetables lowers lung cancer risk more in men with the deletion than in men who have the enzyme (18244 Chinese men)
D'Angelo et al. 2000	Atherosclerosis	Folate and vitamin B12	MTHFR C677T	Plasma homocysteine is negatively correlated with folate and vitamin B12, and this association is stronger in *TT* individuals than in *CC* or *CT* individuals (170 cases, 182 controls, Italian men and women)
Rontu et al. 2004	Atherosclerosis	Alcohol	PON1 M55L	*M* carriers are more at risk for atherosclerosis than *LL* homozygotes, but this risk is reduced with increasing alcohol consumption (700 middle-aged Finnish men who died suddenly)
Strandhagen et al. 2004	Atherosclerosis	Coffee	MTHFR C677T	*TT* individuals saw a greater increase in homocysteine levels than *C* carriers when drinking coffee daily, but this increase could be reduced with a folic acid supplement (120 healthy men and women)
Dedoussis et al. 2007	Atherosclerosis	Mediterranean diet	MTHFR C677T	The Mediterranean diet reduced homocysteine levels in healthy *TT* and *CT* individuals, but not in *CC* individuals (574 healthy Greek men and women)
Zee et al. 2007	Atherosclerosis	Folate and vitamin B12	MTHFR C677T	The *TT* genotype increases homocysteine levels, but there is no association between *MTFHR* genotype, dietary folate/vitamin B12, and cardiovascular disease (24968 healthy, white, American women)

Table 1 (*continued*).

Reference	Pathology	Modulating dietary factor	Associated SNP	Gene–diet interaction
Volcik et al. 2008, ARIC	Atherosclerosis	PUFA	PPARα 3-UTR G>A	Among whites only, with high n-6 PUFA consumption, *A* homozygotes have lower total cholesterol and LDL cholesterol than *G* carriers (10134 white and 3480 African Americans)
			PPARα 3-UTR C>T	Among African-Americans only with high n-3 PUFA consumption, *T* homozygotes have lower total cholesterol and LDL cholesterol than *C* carriers.
Nettleton et al. 2009, ARIC	Atherosclerosis	Carbohydrates	ANGPTL4 E40K	High carbohydrate intake is inversely associated with HDL cholesterol levels and positively associated with triglyceride levels. In men, but not women, carrying the *A* allele increases the association between carbohydrate intake and HDL cholesterol levels (~8000 white American men and women)
AlSaleh 2012, RISCK	Atherosclerosis	PUFA	PPARγ2 Pro12Ala	White carriers of the *Ala* allele with the lowest PUFA:SFA intake ratio had higher plasma total cholesterol and LDL cholesterol than noncarriers, but these parameters improved as PUFA:SFA intake ratio increased (549 participants, UK)
Leeson et al. 2002	Cardiovascular disease	Smoking	eNOS Glu298Asp	Male *298Asp* carriers who smoke have lower flow-mediated brachial artery dilation than *298Glu* homozygotes. (248 men and women, UK)
		n-3 fatty acids	eNOS Glu298Asp	n-3 fatty acid consumption is positively associated with FMD in *298Asp* carriers but not in *298Glu* homozygotes
Corella et al. 2009	Cardiovascular-disease-associated inflammation	Mediterranean diet	COX2 –765 G>C and IL6 –174 G>C	A Mediterranean diet reduced inflammation to a similar extent regardless of genotype (721 Mediterannean men and women at high risk for CVD)
Younis et al. 2005, SNPHS	Coronary heart disease	Alcohol	ADH1C γ1>γ2	Moderate alcohol consumption decreases CHD risk in the general population and *γ2* homozygous modest drinkers have a 78% lower CHD risk than *γ1* homozygous modest drinkers (2773 middle-aged men, 220 with CHD)
Bowman et al. 2009, EPIC	Coronary heart disease	Total fat	FVII R353Q	FVII activity is associated with total fat intake for women, and this association is stronger in *RR* homozygotes than in *Q* carriers. The association with genotype was not seen in males. No association was found between PUFA or MUFA intake and genotype in either gender (958 cases, 2009 controls, UK)
Cornelis et al. 2007	Myocardial infarction	Cruciferous vegetables	GSTT1*1	Increased isothiocyanate intake from cruciferous vegetables decreased risk of MI in GSTT1*1 individuals but not in GSTT1*0*0 individuals. This protective effect is greater in smokers than in nonsmokers (2042 cases, 2042 controls, Costa Rica)
Pérez-Martínez et al. 2008*a*	Ischemic heart disease	MUFA	PAI-1 -675 4 G/5G	4 *G* allele carriers respond to dietary intake of MUFA with lower levels of PAI-1 but 5 *G* homozygotes do not (59 healthy Spanish men and women)
Zhang et al. 2006	Hypertension	Salt	ACE I/D	In the general population, ACE I/D is not associated with hypertension, but among men with high salt intake the *ID+II* genotype increases risk for hypertension over *DD* individuals. This association is stronger in overweight men than normal-weight men (284 Japanese men)
Norat et al. 2008, EPIC	Hypertension	Salt	AGT M235T	Salt intake is correlated with blood pressure but this association is less significant in *MM* homozygotes than in *MT* or *TT* individuals. (11384 middle-aged men and women, UK)
Freitas et al. 2009, EPIC	Hypertension	Salt	HMGCR rs17238540	Men who carry the *G* allele show stronger correlation between blood pressure and salt intake than *TT* men, but the opposite is observed in women (23011 men and women, UK)
Yu et al. 2007	Type 2 diabetes	Protein	adipoQ G276T	Protein intake is inversely associated with BMI in *GG* individuals with diabetes (351 Korean cases with no known CVD)
		Carbohydrates	adipoQ G276T	Carbohydrate intake is positively associated with BMI in *GT* individuals with diabetes.

Table 1 (*continued*).

Reference	Pathology	Modulating dietary factor	Associated SNP	Gene–diet interaction
		Total macronutrient	adipoQ G276T	*TT* individuals have no association between macronutrient intake and anthropometric measurements so they may need different dietary interventions to lower CVD risk with type 2 diabetes.
Pérez-Martínez et al. 2008*b*	Type 2 diabetes	Fat	adipoQ –11377 C>G	Among men, but not women, *CC* homozygotes show a greater decrease in resting plasma glucose when they switched from a high saturated fat diet to either a MUFA-rich diet or a carbohydrate-rich diet than carriers of the *G* allele, indicating greater benefit from dietary interventions (59 healthy men and women)
Fisher et al. 2009, EPIC	Type 2 diabetes	Whole grains	TCF7L2 rs7903146	Whole-grain intake is inversely associated with diabetes risk in *CC* homozygotes but not in carriers of the *T* allele (724 cases, 2318 controls, UK)
Fisher et al. 2011, EPIC	Type 2 diabetes	Fat	CAV2 rs2270188	Rare *T* homozygosity increases type 2 diabetes risk by 100% when combined with an increase in fat intake from 30% to 40% energy. If saturated fat intake increases from 10% to 20% energy, the risk is increased by 200% (614 cases, 2248 controls, UK)
Lamri et al. 2012, DESIR	Type 2 diabetes	Fat	PPARγ Pro12Ala	High fat consumption increases type 2 diabetes risk in *Pro* homozygotes only (4676 from French general population)
			PPARγ C1431T	High fat consumption increases type 2 diabetes risk in *C* homozygotes only.
Rubin et al. 2012	Insulin resistance	Conjugated linoleic acids	PPARγ2 Pro12Ala	Carriers of the *Ala* allele had increased body weight and higher insulin resistance after taking t10c12 CLA for 4 weeks while *Pro* allele homozygotes had decreased body weight (39 middle aged men)
Smith et al. 2012	Insulin resistance	Saturated fat	PLIN1 11482 G<A	Carriers of the minor allele will have higher insulin resistance as the ratio of dietary saturated fat to carbohydrate increases, but this association is not seen in noncarriers (462 men and 508 women, USA)
Luan et al. 2001	Obesity	PUFA	PPARγ2 Pro12Ala	*Ala* carriers with a low dietary PUFA:SFA ratio have higher BMI than similar *Pro* homozygotes. *Ala* carriers with a high dietary PUFA:SFA ratio have lower BMI than similar *Pro* homozygotes. *Ala* carriers may be more sensitive to the PUFA:SFA ratio (592 non-diabetics)
Tai et al. 2005, FHS	Obesity	PUFA	PPARα L162 V	*V* allele carriers who consume a low PUFA diet have higher plasma triglycerides and ApoC3 concentrations than *L* homozygotes. However, on a high PUFA diet, *V* carriers have lower plasma triglycerides and ApoC3 concentrations than *L* homozygotes (1003 men, 1103 women)
Kourlaba et al. 2008, 2009, GENESIS	Obesity	Total energy	ACE I/D	Among toddlers and preschoolers, only carriers of the *D* allele showed correlation between total energy intake and waist circumference (2374 Greek children)
		Protein	ACE I/D	Among toddlers and preschoolers, only carriers of *D* allele showed correlation between protein intake and BMI and weight.
Moleres et al. 2012	Obesity	PUFA	FTO rs9939609	Children who carry the *A* allele and have high SFA intake or low dietary PUFA:SFA ratio have increased risk for obesity compared with *TT* homozygotes. (354 Spanish children and adolescents)
Phillips et al. 2010	Obesity	Fat	ACC2 rs4766587	Carriers of the *A* allele are at increased risk for metabolic syndrome, and this risk is exacerbated by a high-fat diet (1754 cases and controls)
Dedoussis et al. 2011	Obesity	PUFA	PPARγ Pro12Ala	In children, a low dietary PUFA:SFA ratio is more strongly associated with higher BMI in *Ala* carriers than in *Pro* homozygotes. (2896 Greek children)
Santos et al. 2011, NUGENOB	Obesity	Hypoenergetic diet	MC3 R, several	There is no effect on weight loss after a 10 week hypoenergetic diet by MC3 *R* variants in obese individuals (760 obese patients)

Table 1 (*concluded*).

Reference	Pathology	Modulating dietary factor	Associated SNP	Gene–diet interaction
de Luis et al. 2012	Obesity	Hypocaloric diets	CB1 G1359A	Wildtype G1359 *G* obese individuals respond to both low-fat and low-carbohydrate diets with decreased blood glucose, total cholesterol, and insulin levels while G1359 *A* and A1359 *A* obese individuals saw weight loss but no metabolic improvement after 3 months (249 obese men and women)
Qi et al. 2012	Obesity	Fat	GIPR rs2287019	Overweight individuals who carry the *T* allele and consumed a low-fat diet saw greater improvement in glucose homeostasis than *CC* individuals (737 overweight men and women)
Wang et al. 2009	Age-related macular degeneration	Fish	CFH rs1061170	AMD risk increases with each additional *C* allele, so *CT* and *CC* individuals are at greater risk, especially if they smoke. Increased fish consumption reduces AMD risk in *CC* homozygotes but not in *CT* or *TT* individuals. (1881 middle aged cases and controls)
Tikkanen et al. 2009	Committing violent acts	Alcohol	MAOA-LPR	Carriers of the high activity allele are more at risk for committing violent acts as alcohol intake increases, but this risk decreases with age. Noncarriers do not follow these trends (174 Finnish alcoholic offenders)
Mazzotti et al. 2011	Sleep inefficiency	Caffeine	ADA G22A	*AA* and *AG* individuals who consumed caffeine the day before a polysomnography study had higher sleep efficiency and more REM sleep than GG homozygotes. There were no differences in sleep efficiency between genotypes in those that did not consume caffeine (958 participants)
Lacasaña et al. 2012	Anencephaly	Folate	MTFHR C677T	The risk of anencephaly decreased 18% for each 1 ng/mL increase in serum folate for mothers with the *677TT* genotype. Increasing folate levels did not protect against anencephaly in mothers with the *677CC* and *677CT* genotypes. (151 Mexican mothers)

Note: LIBCSP, Long Island Breast Cancer Study Project; MCS, Multiethnic Cohort Study; NCS, Netherlands Cohort Study; ARIC, Atherosclerosis Risk in Communities Study; RISCK, Reading Imperial Surrey Cambridge King's Study; SNPHS, Second Northwick Park Heart Study; EPIC, European Prospective Investigation in Cancer and nutrition; DESIR, Data from an Epidemiological Study on the Insulin Resistance syndrome; FHS, Framingham Heart Study; GENESIS, Growth Exercise and Nutrition Epidemiological Study in preSchoolers; NUGENOB, NUtrient–GENe interactions in human Obesity; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SFA, saturated fatty acids; FMD, flow-mediated dilatation; CVD, cardiovascular disease; CHD, coronary heart disease; MUFA, mono-unsaturated fatty acids; BMI, body mass index; AMD, age-related macular degeneration.

proving nutritional bioinformatics are well documented in the literature, but the field seems to have stalled between conjecture and implementation. Lemay et al. (2007) put forth a model for enabling bioinformatics in nutrition research that encompassed roles for researchers, IT experts, and nutrition journals. Their plan was multifaceted and has been enriched by other authors (Table 2).

Strides are being made to better share data and several recent papers have shown the use of computational genomics for detecting nutrient-sensitive genes (Lemay and Hwang 2006; Wise and Kaput 2009). Currently the Food and Drug Administration maintains SNP and quantitative trait loci (QTL) databases that they have recently integrated into the ArrayTrack database. The goal of these types of databases is to link all Omics data so that simple searches can yield gene–function relationships (Xu et al. 2010). These databases are growing rapidly, but there is still concern regarding the standards to which the available data have been generated, and therefore the possibility of meaningful comparisons. Further improvements will require a strong commitment, financial and otherwise, from journals and funding agencies.

Nutrigenomics outside the laboratory

For a nutrigenomics study to claim success, it must provide clinically relevant information that can be passed on to patients or consumers. The idea of linking researchers and end-users is termed knowledge translation (KT) and has become a focus of regulatory bodies and research institutes. The Canadian Institutes of Health Research have defined KT as "the dynamic and iterative process that includes synthesis, dissemination, exchange, and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products, and strengthen the health care system" (CIHR 2009).

Currently, one major barrier to bringing nutrigenomics to the masses is that the theory behind this science overwhelms most consumers. Comprehension of the role of SNPs in enzyme and protein function, the role of those proteins in disease state, and the role of specific nutrients in health status will be limited for most consumers. When Ronteltap et al. (2008) used Group Support System technology to run interactive discussions with stakeholder groups linked to nutrigenomics, including academia, policy makers, and health-care professionals, they found several contradictions between consumers' expectations and stakeholders' predictions for how nutrigenomics will develop. Two of the findings were (*i*) consumers will want nutrigenomic products that experts agree are safe and beneficial, but currently consensus is limited, and (*ii*) consumers will want nutrigenomic products that are easy to implement, but currently research is focused on specific, sometimes obscure nutrients rather than mainstream foods that could either be avoided or consumed more often. The same group has also recently outlined the current limitations in developing a business model for commercializing nutrigenomics (Ronteltap et al. 2012). Further studies linking the various stakeholders in this field will be crucial for KT to materialize.

Table 2. Improvements towards nutritional data-sharing.

Improvement	Likely consequence
Major nutrition journals should mandate raw data disclosure as a requisite for publication (Rocca-Serra and Elliott 2006)	Data from GWAS and microarray studies will be recycled for other searches Data will be pooled for biomarker discovery
Journals and funding agencies should introduce standards for nutrition studies.	Meta-analysis will be possible and results will carry more weight
Nutrition ontologies and databases should be developed (Castro et al. 2006)	Reported data will be made machine-readable for easier data-sharing. Ontologies will allow meaningful searches of available data
Methods for measuring nutrient intake should be improved and incorporate metabolomics assessments (Stumbo et al. 2010)	Nutrient–gene interactions will be clearer and conclusions will be more precise

Note: GWAS, genome-wide association studies.

KT derived from nutrigenomic studies is also currently limited because a priori knowledge of the patient or consumer's genotype is required. However, more and more companies are offering nutrigenetic tests in the form of either home kits or genetic counseling as part of a nutritional program. A review of these companies and their marketing strategies and scientific literature is provided by Saukko et al. (2010). As an example, for a brief time in 2005, Salugen, Inc. (USA) marketed a product called Genotrim. They offered to analyze polymorphisms in 5 genes that are linked to weight, including the genes for the serotonin receptor, PPARγ, leptin, MTHFR, and the dopamine D2 receptor, and to design a "DNA-based nutraceutical" formulated for a client's specific genotype. They did not provide the formulation for proprietary reasons, but every supplement contained *Garcinia cambogia* and *Passiflora incarnate*, 2 plant extracts commonly used to aid weight loss (Blum et al. 2007). Under pressure from consumer watch groups, the company stopped manufacturing Genotrim shortly after it was released.

There is considerable controversy over the sale and use of these tests, vocalized by medical and scientific professionals and consumer watch groups like GeneWatch (UK) and the Council for Responsible Genetics (USA). Some of the concerns raised are summarized here:

(*i*) There is currently no adequate regulatory system for the sale and use of direct-to-consumer nutrigenetic tests. Consumers may fall victim to false or misleading advertising (Ries and Castle 2008).
(*ii*) The science of nutrigenetics is in its infancy so "personalized" nutrition advice generated by these tests is often very general or unproven (Hogarth et al. 2008).
(*iii*) Most health care practitioners are currently not well educated on the use of nutrigenetic testing for diagnostic or counseling purposes (Morin 2009).
(*iv*) "Medicalizing" the diet may cause normal healthy foods to be overlooked. Many companies use genetic testing results to advise clients to purchase specially designed, and often expensive, supplements (Goddard et al. 2007).
(*v*) The legal status of genetic material and information, as well as bioethical considerations surrounding genetic testing, are still heavily debated (Bergmann et al. 2008).
(*vi*) Little is known about the psychological ramifications of revealing to patients their genetic propensities to lifestyle-related diseases.

As clinical research and regulatory bodies catch up with the demand for personalized health care and nutrition, it is likely that many of these limitations will be overcome. Until the science of nutrigenomics matures, however, eager consumers and entrepreneurs may be left to philosophize on the future of health care. Alison Harvey offers the following revelation of the post-genomic age:

> *With the advent of technologies such as nutrigenomics, wellness becomes an enhancement of our corporeality at the molecular level, our genetic functioning. Knowledge of the specific weaknesses in one's genome (provided by a nutrigenomic test) allows one to be more proactive in taking steps to counter that weakness, providing one's genome with the best possible environment to maximize its functioning (by following a personalized diet), so attaining a new state of health specific to one's genomic individuality. The quest for health is more than an individual responsibility; it is a route to self-realization.* [Harvey 2009]

At a time when our enthusiasm for nutrigenomics is matched only by our uncertainty of its consequences, we are faced with a long list of obstacles in making personalized nutrition and health a reality. The onus is not only on the researchers to continue churning out evidence of gene–nutrient interactions, but on the governing bodies who must navigate the uncharted waters of elective genetic testing and nutrigenomic marketing, and the social scientists and consumer watch groups tasked with monitoring the individual and societal responses to each new development. Many observers have suggested that debate should be encouraged, but that the "*most appropriate development may for some governance bodies be nondevelopment*" (Cutter 2007), akin to the moratorium on human cloning, despite that this science is being so fervently pursued by the media, consumers, and manufacturers. The responsibilities on the quest to realize the full capacity of nutrigenomics are numerous and shared.

As **consumers,** we are obligated to:

- Educate ourselves and participate actively in the debate surrounding nutrigenomic research.
- Seek ways to incorporate preventative medicine into our daily lives and maintain our health to the best of our abilities.
- Support scientific research that benefits the health of our society as a whole.
- Apply pressure on the appropriate authorities to secure our welfare in the face of misguiding marketing, unfounded claims, unethical practices, and faulty technologies.

As **researchers,** we are obligated to:

- Use available funds for research that is translatable to the general public. Focus on knowledge translation throughout the study process.
- Be cautious in our claims so as not to cause unwarranted use of the knowledge we generate.
- Incorporate the psychological, behavioral, and social sciences into nutrition research so as to provide a more complete picture of the impact of nutrigenomics.

As **regulators,** we are obligated to:

- Be involved in the debate at hand. Even though the route to appropriate governance may be convoluted or uncomfortable, nongovernance in this case puts consumer and patient safety at risk. Bergmann et al. (2008), Hogarth et al. (2008), Morin (2008) and Korthals and Komduur (2010), provide thoughtful commentaries on the regulation of nutrigenomics.
- Focus resources on research that is relevant to the majority of consumers.

- Encourage continuing education for both lawmakers and health-care providers so that involvement in the field of nutrigenomics is possible.

As **health care providers,** we are obligated to:

- Remain current on new nutritional and medical developments. "*If the doctors of today do not become the nutritionists of tomorrow, then the nutritionists of today will become the doctors of tomorrow*" Rockefeller Institute of Medicine.
- Recognize the psychological ramifications of genetic counseling.
- Make nutrition and lifestyle changes a priority in all treatments. "*He who takes medicine and neglects diet wastes the skills of the physician*" Chinese proverb.

We are on the brink of a new age of personalized medicine and nutrition, but the efficiency with which we enter the post-genomic era is in our hands. We cannot remain ambivalent about our health. So, whether we are consumers, scientists, lawmakers, health-care providers, or dissenters, we must be active and conscientious in our obligations to further the health and welfare of everyone.

Acknowledgements

Cara Isaak is supported by the estate of Margurite Germaine Jerome (deceased).

References

Affymetrix. 2012. Product Page. **03/21**. Available from http://www.affymetrix.com/support/technical/datasheets/genomewide_snp6_datasheet.pdf.

Ahn, J., Gammon, M.D., Santella, R.M., Gaudet, M.M., Britton, J.A., Teitelbaum, S.L., et al. 2004. Myeloperoxidase genotype, fruit and vegetable consumption, and breast cancer risk. Cancer Res. **64**(20): 7634–7639. doi:10.1158/0008-5472.CAN-04-1843. PMID:15492293.

Ahn, J., Gammon, M.D., Santella, R.M., Gaudet, M.M., Britton, J.A., Teitelbaum, S.L., et al. 2005. Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use. Am. J. Epidemiol. **162**(10): 943–952. doi:10.1093/aje/kwi306. PMID:16192345.

Ahn, J., Yu, K., Stolzenberg-Solomon, R., Simon, K.C., McCullough, M.L., Gallicchio, L., et al. 2010. Genome-wide association study of circulating vitamin D levels. Hum. Mol. Genet. **19**(13): 2739–2745. doi:10.1093/hmg/ddq155. PMID:20418485.

AlSaleh, A., Sanders, T.A.B., and O'Dell, S.D. 2012. Effect of interaction between *PPARG*, *PPARA* and *ADIPOQ* gene variants and dietary fatty acids on plasma lipid profile and adiponectin concentration in a large intervention study. Proc. Nutr. Soc. **71**(1): 141–153. doi:10.1017/S0029665111003181. PMID:22040870.

Bergmann, M.M., Görman, U., and Mathers, J.C. 2008. Bioethical considerations forhumannutrigenomics.Annu.Rev.Nutr.**28**(1):447–467.doi:10.1146/annurev.nutr.28.061807.155344. PMID:18439132.

Blum, S., Blum, K., Chen, T.J.H., Meshkin, B., Downs, B.W., Gordon, C.A., et al. 2007. Genotrim™, a DNA-customized nutrigenomic product, targets genetic factors of obesity: hypothesizing a dopamine–glucose correlation demonstrating reward deficiency syndrome (RDS). Med. Hypotheses, **68**(4): 844–852. doi:10.1016/j.mehy.2006.08.041. PMID:17071010.

Bowman, R., Joosen, A.M.C.P., Welch, A.A., Luben, R.N., Khaw, K., Wareham, N.J., and Bingham, S.A. 2009. Factor VII, blood lipids and fat intake: gene-nutrient interaction and risk of coronary heart disease with the factor VII polymorphism. Eur. J. Clin. Nutr. **63**(6): 771–777. doi:10.1038/ejcn.2008.28. PMID:18398422.

Canadian Institutes of Health Research. 2009. About knowledge translation. 03/23. Available from http://www.cihr-irsc.gc.ca/e/29418.html.

Castro, A.G., Rocca-Serra, P., Stevens, R., Taylor, C., Nashar, K., Ragan, M.A., and Sansone, S. 2006. The use of concept maps during knowledge elicitation in ontology development processes — the nutrigenomics use case. BMC Bioinformatics, **7**(1): 267–267. doi:10.1186/1471-2105-7-267. PMID:16725019.

Christensen, B. 2010. Increase power and data quality with advanced genotyping and imputation methods. Available from blog.goldenhelix.com/?p=178.

Corella, D., Gonzalez, J.I., Bullo, M., Portoles, O., Diez-Espino, J., Covas, M.I., et al. 2009. Polymorphisms cyclooxygenase-2 –765G>C and interleukin-6 –174G>C are associated with serum inflammation markers in a high cardiovascular risk population and do not modify the response to a Mediterranean diet supplemented with virgin olive oil or nuts. J. Nutr. **139**(1): 128–134. doi:10.3945/jn.108.093054. PMID:19056642.

Cornelis, M.C., El-Sohemy, A., and Campos, H. 2007. GSTT1 genotype modifies the association between cruciferous vegetable intake and the risk of myocardial infarction. Am. J. Clin. Nutr. **86**(3): 752. PMID:17823442.

Corvin, A., Craddock, N., and Sullivan, P.F. 2010. Genome-wide association studies: a primer. Psychol. Med. **40**(7): 1063–1077. doi:10.1017/S0033291709991723. PMID:19895722.

Cutter, A.M. 2007. We are what we eat? Some thoughts on the governance of nutrigenomics and personalised nutrition. Genes Nutr. **2**(1): 63–66. doi:10.1007/s12263-007-0008-7. PMID:18850143.

D'Angelo, A., Coppola, A., Madonna, P., Fermo, I., Pagano, A., Mazzola, G., et al. 2000. The role of vitamin B12 in fasting hyperhomocysteinemia and its interaction with the homozygous C677T mutation of the methylenetetrahydrofolate reductase (*MTHFR*) gene. A case-control study of patients with early-onset thrombotic events. Thromb. Haemost. **83**(4): 563–570. PMID:10780318.

de Luis, A.D., Sagrado, M.G., Aller, R., Conde, R., Izaola, O., de la Fuente, B., and Primo, D. 2012. Role of G1359A polymorphism of the cannabinoid receptor gene on weight loss and adipocytokines levels after two different hypocaloric diets. J. Nutr. Biochem. **23**(3): 287–291. doi:10.1016/j.jnutbio.2010.12.006. PMID:21543209.

de Vogel, S., Wouters, K.A.D., Gottschalk, R.W.H., van Schooten, F.J., de Goeij, A.F.P.M., de Bruïne, A.P., et al. 2011. Dietary methyl donors, methyl metabolizing enzymes, and epigenetic regulators: diet–gene interactions and promoter CpG island hypermethylation in colorectal cancer. Cancer Causes Control, **22**(1): 1–12. doi:10.1007/s10552-010-9659-6. PMID:20960050.

Dedoussis, G., Panagiotakos, D.B., Pitsavos, C., Chrysohoou, C., and Stefanadis, C. 2007. The interaction between adherence to the Mediterranean diet and methylenetetrahydrofolate reductase C677T mutation on homocysteine concentrations. Atherosclerosis, **8**(1): 43–44. doi:10.1016/S1567-5688(07)71117-0.

Dedoussis, G.V., Manios, Y., Kourlaba, G., Kanoni, S., Lagou, V., Butler, J., et al. 2011. An age-dependent diet-modified effect of the PPARγ Pro12Ala polymorphism in children. Metab. Clin. Exp. **60**(4): 467–473. doi:10.1016/j.metabol.2010.04.007. PMID:20580778.

Fisher, E., Boeing, H., Fritsche, A., Doering, F., Joost, H., and Schulze, M.B. 2009. Whole-grain consumption and transcription factor-7-like 2 (TCF7L2) rs7903146: gene–diet interaction in modulating type 2 diabetes risk. Br. J. Nutr. **101**(4): 478–481. PMID:19149908.

Fisher, E., Schreiber, S., Joost, H., Boeing, H., and Döring, F. 2011. A Two-step association study identifies CAV2 rs2270188 single nucleotide polymorphism interaction with fat intake in type 2 diabetes risk. J. Nutr. **141**(2): 177–181. doi:10.3945/jn.110.124206. PMID:21178094.

Fradet, V., Cheng, I., Casey, G., and Witte, J.S. 2008. Dietary long-chain omega-3 fatty acids, *COX2* gene polymorphism, and aggressive prostate cancer. J. Urol. **179**(4): 149–149. doi:10.1016/S0022-5347(08)60427-9.

Freitas, R.N., Khaw, K., Wu, K., Bowman, R., Jeffery, H., Luben, R., et al. 2009. A HMGCR polymorphism is associated with relations between blood pressure and urinary sodium and potassium ratio in the Epic-Norfolk Study. J. Am. Soc. Hypertens. **3**(4): 238–244. doi:10.1016/j.jash.2009.05.001. PMID:20409966.

Glessner, J.T., and Hakonarson, H. 2011. Genome-wide association: from confounded to confident. Neuroscientist, **17**(2): 174–184. doi:10.1177/1073858410381533. PMID:21252379.

Goddard, K.A.B., Moore, C., Ottman, D., Szegda, K.L., Bradley, L., and Khoury, M.J. 2007. Awareness and use of direct-to-consumer nutrigenomic tests, United States, 2006. Genet. Med. **9**(8): 510–517. doi:10.1097/GIM.0b013e31812e6ac3. PMID:17700389.

Harvey, A. 2009. From genetic risk to post-genomic uncertainties: nutrigenomics and the birth of the "genetic entrepreneur". New Genet. Soc. **28**(2): 119–137. doi:10.1080/14636770902901447.

Hedelin, M., Chang, E.T., Wiklund, F., Bellocco, R., Klint, A., Adolfsson, J., et al. 2006. Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX2 polymorphism. Int. J. Cancer, **120**: 398–405. PMID:17066444.

Hogarth, S., Javitt, G., and Melzer, D. 2008. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annu. Rev. Genom. Hum. Genet. **9**(1): 161–182. doi:10.1146/annurev.genom.9.081307.164319. PMID:18767961.

Illumina. 2012. Product Page. **03/21**. Available from http://www.illumina.com/products/humanomni5-quad_beadchip_kit.ilmn.

International HapMap Consortium. 2005. A haplotype map of the human genome. Nature, **437**(7063): 1299–1320. doi:10.1038/nature04226. PMID:16255080.

International Human Genome Sequencing Consortium. 2001. Initial sequencing and analysis of the human genome. Nature, **409**(6822): 860–921. doi:10.1038/35057062. PMID:11237011.

Ioannidis, J.P.A. 2010. Can lessons learned from genome-wide research be applied to nutrition-wide and exposure-wide evidence? Crit. Rev. Food Sci. Nutr. **50**(Suppl. 1): 31–32. doi:10.1080/10408398.2010.526878.

Jung, A.Y., Poole, E.M., Bigler, J., Whitton, J., Potter, J.D., and Ulrich, C.M. 2008. DNA methyltransferase and alcohol dehydrogenase: gene–nutrient interactions in relation to risk of colorectal polyps. Cancer Epidem. Biomar. **17**(2): 330–338. doi:10.1158/1055-9965.EPI-07-2608. PMID:18268116.

Kallio, P., Kolehmainen, M., Laaksonen, D.E., Kekäläinen, J., Salopuro, T., Sivenius, K., et al. 2007. Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT study. Am. J. Clin. Nutr. **85**(5): 1417–1427. PMID:17490981.

Korthals, M., and Komduur, R. 2010. Uncertainties of nutrigenomics and their

ethical meaning. J. Agr. Environ. Ethics, **23**(5): 435–454. doi:10.1007/s10806-009-9223-0.

Kourlaba, G., Pitsiladis, Y.P., Lagou, V., Grammatikaki, E., Moran, C.N., Kondaki, K., et al. 2008. Interaction effects between total energy and macronutrient intakes and angiotensin-converting enzyme 1 (*ACE*) I/D polymorphism on adiposity-related phenotypes in toddlers and preschoolers: the Growth, Exercise and Nutrition Epidemiological Study in preSchoolers (GENESIS). Br. J. Nutr. **100**(6): 1333–1340. doi:10.1017/S0007114508988759.

Kourlaba, G., Pitsiladis, Y.P., Lagou, V., Grammatikaki, A., Moran, C.N., Kondaki, K., et al. 2009. Interaction effects between total energy and macronutrient intakes and angiotensin-converting enzyme 1 (*ACE*) I/D polymorphism on adiposity-related phenotypes in toddlers and preschoolers: the Growth, Exercise and Nutrition Epidemiological Study in preSchoolers (GENESIS) – CORRIGENDUM. Br. J. Nutr. **101**(5): 774. doi:10.1017/S0007114508030766.

Kussmann, M. 2009. Role of proteomics in nutrigenomics and nutrigenetics. Expert. Rev. Proteomic, **6**(5): 453–456. doi:10.1586/epr.09.62. PMID:19811066.

Kussmann, M., Raymond, F., and Affolter, M. 2006. OMICS-driven biomarker discovery in nutrition and health. J. Biotechnol. **124**(4): 758–787. doi:10.1016/j.jbiotec.2006.02.014. PMID:16600411.

Lacasaña, M., Blanco-Muñoz, J., Borja-Aburto, V.H., Aguilar-Garduño, C., Rodríguez-Barranco, M., Sierra-Ramirez, J.A., et al. 2012. Effect on risk of anencephaly of gene–nutrient interactions between methylenetetrahydrofolate reductase C677T polymorphism and maternal folate, vitamin B12 and homocysteine profile. Public Health Nutr. **15**(8): 1–10. doi:10.1017/S1368980011003144. PMID:23294865.

Lamri, A., AbiKhalil, C., Jaziri, R., Velho, G., Lantieri, O., Vol, S., et al. 2012. Dietary fat intake and polymorphisms at the *PPARG* locus modulate BMI and type 2 diabetes risk in the D.E.S.I.R. prospective study. Int. J. Obes. **36**(2): 218–224. doi:10.1038/ijo.2011.91. PMID:21540831.

LeMarchand, L., Haiman, C.A., Wilkens, L.R., Kolonel, L.N., and Henderson, B.E. 2004. MTHFR Polymorphisms, diet, hrt, and breast cancer risk: The Multiethnic Cohort Study. Cancer Epidem. Biomarkers Prev. **13**(12): 2071–2077. PMID:15598763.

Lee, S., Lee, K., Yoo, K., Noh, D., Ahn, S., and Kang, D. 2012. Combined effects of antioxidant vitamin and *NOS3* genetic polymorphisms on breast cancer risk in women. Clin. Nutr. **31**(1): 93–98. doi:10.1016/j.clnu.2011.08.005. PMID:21872972.

Leeson, C.P.M., Hingorani, A.D., Mullen, M.J., Jeerooburkhan, N., Kattenhorn, M., Cole, T.J., et al. 2002. Glu298Asp endothelial nitric oxide synthase gene polymorphism interacts with environmental and dietary factors to influence endothelial function. Circ. Res. **90**(11): 1153–1158. doi:10.1161/01.RES.0000020562.07492.D4. PMID:12065317.

Lemay, D.G., and Hwang, D.H. 2006. Genome-wide identification of peroxisome proliferator response elements using integrated computational genomics. J. Lipid Res. **47**(7): 1583–1587. doi:10.1194/jlr.M500504-JLR200. PMID:16585784.

Lemay, D.G., Zivkovic, A.M., and German, J.B. 2007. Building the bridges to bioinformatics in nutrition research. Am. J. Clin. Nutr. **86**(5): 1261–1269. PMID:17991634.

London, S.J., Yuan, J.M., Chung, F.L., Gao, Y.T., Coetzee, G.A., Ross, R.K., and Yu, M.C. 2000. Isothiocyanates, glutathione *S*-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. Lancet, **356**(9231): 724–729. doi:10.1016/S0140-6736(00)02631-3. PMID:11085692.

Luan, J., Browne, P.O., Harding, A.-., Halsall, D.J., O'Rahilly, S., Chatterjee, V.K.K., and Wareham, N.J. 2001. Evidence for gene–nutrient interaction at the *PPAR* locus. Diabetes, **50**(3): 686–689. doi:10.2337/diabetes.50.3.686. PMID:11246892.

Masotti, A., Da Sacco, L., Bottazzo, G.F., and Alisi, A. 2010. Microarray technology: a promising tool in nutrigenomics. Crit. Rev. Food Sci. Nutr. **50**(7): 693–698. doi:10.1080/10408390903044156. PMID:20694930.

Mazzotti, D.R., Guindalini, C., Pellegrino, R., Barrueco, K.F., Santos-Silva, R., Bittencourt, L.R.A., and Tufik, S. 2011. Effects of the adenosine deaminase polymorphism and caffeine intake on sleep parameters in a large population sample. Sleep, **34**(3): 399–402. PMID:21359089.

McNiven, E.M.S., German, J.B., and Slupsky, C.M. 2011. Analytical metabolomics: nutritional opportunities for personalized health. J. Nutr. Biochem. **22**(11): 995–1002. doi:10.1016/j.jnutbio.2011.05.016. PMID:21999844.

Moleres, A., Ochoa, M.C., Rendo-Urteaga, T., Martínez-González, M.A., Azcona San Julián, M.C., Martínez, J.A., and Marti, A.; GENOI. 2012. Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case-control study of children. Br. J. Nutr. **107**(4): 533–536. doi:10.1017/S0007114511003424. PMID:21798115.

Morin, K. 2008. Canadian legal oversight of pharmacogenomics and nutrigenomics. Health Law Rev. **16**(3): 21–31.

Morin, K. 2009. Knowledge and attitudes of Canadian consumers and health care professionals regarding nutritional genomics. Omics, **13**(1): 37–41. doi:10.1089/omi.2008.0047. PMID:19290810.

Mutch, D.M., Wahli, W., and Williamson, G. 2005. Nutrigenomics and nutrigenetics: the emerging faces of nutrition. FASEB J. **19**(12): 1602–1616. doi:10.1096/fj.05-3911rev. PMID:16195369.

National Center for Biotechnology Information. 2011. GEO and MIAME. 03/21. Available from http://www.ncbi.nlm.nih.gov/geo/info/MIAME.html.

Nettleton, J.A., Volcik, K.A., Hoogeveen, R.C., and Boerwinkle, E. 2009. Carbohydrate intake modifies associations between *ANGPTL4*[*E40K*] genotype and HDL-cholesterol concentrations in White men from the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis, **203**(1): 214–220. doi:10.1016/j.atherosclerosis.2008.05.037. PMID:18599063.

Norat, T., Bowman, R., Luben, R., Welch, A., Khaw, K.T., Wareham, N., and Bingham, S. 2008. Blood pressure and interactions between the angiotensin polymorphism AGT M235T and sodium intake: a cross-sectional population study. Am. J. Clin. Nutr. **88**(2): 392. PMID:18689375.

Okada, Y., Kubo, M., Ohmiya, H., Takahashi, A., Kumasaka, N., Hosono, N., et al.; GIANT Consortium. 2012. Common variants at *CDKAL1* and *KLF9* are associated with body mass index in east Asian populations. Nat. Genet. **44**(3): 302–308. doi:10.1038/ng.1086. PMID:22344221.

Ordovas, J.M., and Mooser, V. 2004. Nutrigenomics and nutrigenetics. Curr. Opin. Lipidol. **15**(2): 101–108. doi:10.1097/00041433-200404000-00002. PMID:15017352.

Pérez-Martínez, P., Adarraga-Cansino, M.D., Fernández de la Puebla, R.A., Blanco-Molina, A., Delgado-Lista, J., Marín, C., et al. 2008*a*. The -675 4G/5G polymorphism at the plasminogen activator inhibitor 1 (PAI-1) gene modulates plasma plasminogen activator inhibitor 1 concentrations in response to dietary fat consumption. Br. J. Nutr. **99**(4): 699–702. doi:10.1017/S0007114507831710. PMID:17903340.

Pérez-Martínez, P., Ordovás, J.M., López-Miranda, J., Cruz-Teno, C., Delgado-Lista, J., Jiménez-Gómez, Y., et al. 2008*b*. Adiponectin gene variants are associated with insulin sensitivity in response to dietary fat consumption in Caucasian men. J. Nutr. **138**(9): 1609–1614. PMID:18716158.

Phillips, C.M., Goumidi, L., Bertrais, S., Field, M.R., Cupples, L.A., Ordovas, J.M., et al. 2010. *ACC2* gene polymorphisms, metabolic syndrome, and gene-nutrient interactions with dietary fat. J. Lipid Res. **51**(12): 3500–3507. doi:10.1194/jlr.M008474. PMID:20855566.

Qi, Q., Bray, G.A., Hu, F.B., Sacks, F.M., and Qi, L. 2012. Weight-loss diets modify glucose-dependent insulinotropic polypeptide receptor *rs2287019* genotype effects on changes in body weight, fasting glucose, and insulin resistance: the Preventing Overweight Using Novel Dietary Strategies trial. Am. J. Clin. Nutr. **95**(2): 506–513. doi:10.3945/ajcn.111.025270. PMID:22237064.

Ries, N.M., and Castle, D. 2008. Nutrigenomics and ethics interface: direct-to-consumer services and commercial aspects. Omics, **12**(4): 245–250. doi:10.1089/omi.2008.0049. PMID:19040371.

Rocca-Serra, P., and Elliott, R.M. 2006. Data storage: bringing us a step closer to data sharing? Br. J. Nutr. **95**(6): 1237–1239. doi:10.1079/BJN20061747. PMID:16768851.

Ronteltap, A., van Trijp, J.C.M., and Renes, R.J. 2008. Making nutrigenomics work — Integrating expert stakeholder opinions and consumer preferences. Trends Food Sci. Technol. **19**(7): 390–398. doi:10.1016/j.tifs.2008.01.012.

Ronteltap, A., Trijp, J.C.M., van, Berezowska, A., and Goossens, J. 2012. Nutrigenomics-based personalised nutritional advice: in search of a business model? (Online first). Genes Nutr. In press. doi:10.1007/s12263-012-0308-4. PMID:22903899.

Rontu, R., Lehtimki, T., Ilveskoski, E., Mikkelsson, J., Kajander, O., Goebeler, S., et al. 2004. Association of paraoxonase-1 M55L genotype and alcohol consumption with coronary atherosclerosis. Pharmacogenetics, **14**(8): 479–485. doi:10.1097/01.fpc.0000114746.08559.00. PMID:15284530.

Rubin, D., Darabaneanu, S., Ruether, A., Schrezenmeir, J., Herrmann, J., et al. 2012. Influence of different CLA isomers on insulin resistance and adipocytokines in pre-diabetic, middle-aged men with PPARγ2 Pro12Ala polymorphism. Genes Nutr. **7**(4): 499–509. doi:10.1007/s12263-012-0289-3. PMID:22399314.

Saito, K., Arai, S., and Kato, H. 2005. A nutrigenomics database — integrated repository for publications and associated microarray data in nutrigenomics research. Br. J. Nutr. **94**(4): 493–495. doi:10.1079/BJN20051536. PMID:16197571.

Santos, J.L., De la Cruz, R., Holst, C., Grau, K., Naranjo, C., Maiz, A., et al.; NUGENOB Consortium. 2011. Allelic variants of melanocortin 3 receptor gene (*MC3R*) and weight loss in obesity: a randomised trial of hypo-energetic high- versus low-fat diets. PloS One, **6**(6): e19934. doi:10.1371/journal.pone.0019934. PMID:21695122.

Saukko, P.M., Reed, M., Britten, N., and Hogarth, S. 2010. Negotiating the boundary between medicine and consumer culture: Online marketing of nutrigenetic tests. Soc. Sci. Med. **70**(5): 744–753. doi:10.1016/j.socscimed.2009.10.066. PMID:20022680.

Schena, M., Shalon, D., Davis, R.W., and Brown, P.O. 1995. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science, **270**(5235): 467–470. doi:10.1126/science.270.5235.467. PMID:7569999.

Seidel, M., and Niessner, R. 2008. Automated analytical microarrays: a critical review. Anal. Bioanal. Chem. **391**(5): 1521–1544. doi:10.1007/s00216-008-2039-3. PMID:18504563.

Simopoulos, A.P. 2010. Nutrigenetics/nutrigenomics. Annu. Rev. Public Health, **31**(1): 53–68. doi:10.1146/annurev.publhealth.031809.130844. PMID:20070200.

Smith, C.E., Arnett, D.K., Corella, D., Tsai, M.Y., Lai, C.Q., Parnell, L.D., et al. 2012. Perilipin polymorphism interacts with saturated fat and carbohydrates to modulate insulin resistance. Nutr. Met. Cardiovasc. Dis. **22**(5): 449–455. doi:10.1016/j.numecd.2010.09.003. PMID:21193293.

Strandhagen, E., Zetterberg, H., Aires, N., Palmér, M., Rymo, L., Blennow, K., et al. 2004. The methylenetetrahydrofolate reductase C677T polymorphism

is a major determinant of coffee-induced increase of plasma homocysteine: a randomized placebo controlled study. Int. J. Mol. Med. **13**(6): 811–815. PMID: 15138617.

Stumbo, P.J., Weiss, R., Newman, W., Pennington, J.A., Tucker, K.L., Wiesenfeld, P.L., et al. 2010. Web-enabled and improved software tools and data are needed to measure nutrient intakes and physical activity for personalized health research. J. Nutr. **140**(12): 2104–2115. doi:10.3945/jn.110.128371. PMID:20980656.

Tai, E.S., Corella, D., Demissie, S., Cupples, L.A., Coltell, O., Schaefer, E.J., et al.; Framingham Heart Study. 2005. Polyunsaturated fatty acids interact with the PPARA-L162V polymorphism to affect plasma triglyceride and apolipoprotein C-III concentrations in the Framingham Heart Study. J. Nutr. **135**(3): 397–403. PMID:15735069.

Tikkanen, R., Sjöberg, R.L., Ducci, F., Goldman, D., Holi, M., Tiihonen, J., and Virkkunen, M. 2009. Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet,centrumbildningar mm, Medicinska och farmaceutiska vetenskapsområdet, and Centrum för klinisk forskning, V. Effects of MAOA-genotype, alcohol consumption, and aging on violent behavior. Alcohol. Clin. Exp. Res. **33**(3): 428–428. doi:10.1111/j.1530-0277.2008.00853.x. PMID: 19120058.

van der Werf, M.J., Schuren, F.H.J., Bijlsma, S., Tas, A.C., and van Ommen, B. 2001. Nutrigenomics: Applications of genomics technologies in nutritional sciences and food technology. J. Food Sci. **66**(6): 772–780. doi:10.1111/j.1365-2621.2001.tb15171.x.

Visscher, P.M., Brown, M.A., McCarthy, M.I., and Yang, J. 2012. Five years of GWAS discovery. Am. J. Hum. Genet. **90**(1): 7–24. doi:10.1016/j.ajhg.2011.11.029. PMID:22243964.

Volcik, K.A., Nettleton, J.A., Ballantyne, C.M., and Boerwinkle, E. 2008. Peroxisome proliferator-activated receptor α genetic variation interacts with n-6 and long-chain n-3 fatty acid intake to affect total cholesterol and LDL-cholesterol concentrations in the Atherosclerosis Risk in Communities Study. Am. J. Clin. Nutr. **87**(6): 1926–1931. PMID:18541586.

Wang, J.J., Rochtchina, E., Smith, W., Klein, R., Klein, B.E.K., Joshi, T., et al. 2009. Combined effects of complement factor H genotypes, fish consumption, and inflammatory markers on long-term risk for age-related macular degeneration in a cohort. Am. J. Epidemiol. **169**(5): 633–641. doi:10.1093/aje/kwn358. PMID:19074778.

Wellcome Trust Case Control Consortium. 2007. Genomewide association study of 14,000 cases of seven common diseases and 3,000 shared controls, supplementary information. Nature, **447**: 661–678. doi:10.1038/nature05911. PMID: 17554300.

Wise, C., and Kaput, J. 2009. A strategy for analyzing gene-nutrient interactions in type 2 diabetes. J. Diabetes Sci. Technol. **3**(4): 710–721. PMID:20144318.

Xu, J., Wise, C., Varma, V., Fang, H., Ning, B., Hong, H., et al. 2010. Two new ArrayTrack libraries for personalized biomedical research. BMC Bioinformatics **11**(Suppl. 6): S6. doi:10.1186/1471-2105-11-S6-S6. PMID:20946617.

Younis, J., Cooper, J.A., Miller, G.J., Humphries, S.E., and Talmud, P.J. 2005. Genetic variation in alcohol dehydrogenase 1C and the beneficial effect of alcohol intake on coronary heart disease risk in the Second Northwick Park Heart Study. Atherosclerosis, **180**(2): 225–232. doi:10.1016/j.atherosclerosis.2004.12.010. PMID:15910847.

Yu, S., Ryu, H.K., Park, H.J., Choi, C.H., Huh, K.B., and Kim, W.Y. 2007. Adiponectin gene SNP 276G → T, nutrient intakes, and cardiovascular disease risk in Korean type 2 DM patients. Nutr. Res. Pract. **1**(4): 363–370. doi:10.4162/nrp.2007.1.4.363. PMID:20368963.

Zee, R.Y.L., Mora, S., Cheng, S., Erlich, H.A., Lindpaintner, K., Rifai, N., et al. 2007. Homocysteine, 5,10-methylenetetrahydrofolate reductase 677C>T polymorphism, nutrient intake, and incident cardiovascular disease in 24 968 initially healthy women. Clin. Chem. **53**(5): 845–851. doi:10.1373/clinchem.2006.083881. PMID:17332146.

Zhang, L., Miyaki, K., Araki, J., Song, Y., Kimura, T., Omae, K., and Muramatsu, M. 2006. Interaction of angiotensin i-converting enzyme insertion–deletion polymorphism and daily salt intake influences hypertension in japanese men. Hypertens. Res. **29**(10): 751–758. doi:10.1291/hypres.29.751. PMID: 17283861.