# Nutrigenomics and Personalized Diets: What Will They Mean for Food?

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## Abstract

The modern food system feeds six billion people with remarkable diversity, safety, and nutrition. Yet, the current rise in diet-related diseases is compromising health and devaluing many aspects of modern agriculture. Steps to increase the nutritional quality of individual foods will assist in personalizing health and in guiding individuals to achieve superior health. Nutrigenomics is the scientific field of the genetic basis for varying susceptibilities to disease and the diverse responses to foods. Although some of these genetic determinants will be simple and amenable to personal genotyping as the means to predict health, in practice most will not. As a result, genotyping will not be the secret to personalizing diet and health. Human assessment technologies from imaging to proteomics and metabolomics are providing tools to both understand and accurately assess the nutritional phenotype of individuals. The business models are also emerging to bring these assessment capabilities to industrial practice, in which consumers will know more about their personal health and seek personal solutions.

## INTRODUCTION

The human genome initiative provides life science with a blueprint including goals of basic research and opportunities to translate this research to improvements in human health (Collins et al. 2003). Nutrigenomics, as a subset of the broader field of genomics, actively addresses the genetic basis of response to diet and, in parallel, the variations in dietary responsiveness among humans that are assignable to genotype. Much like pharmacogenomics views its logical translation—personalized medicine—the logical translation of nutrigenomics, both in principle and in detail, is the establishment of a more personalized approach to diet and health. However, diet has a much broader mandate than simply curative therapeutics of disease. Diet as a cornerstone of an individual's overall environment has a major influence on health in the widest sense, from the prevention of diseases to performance, enjoyment, and the overall quality of life. Foods will be the carriers of this value once science has related the various aspects of health to diet. Understanding both the role of diet in the varying expression of a genome and the role of genetics in the varying responses to diet are fundamental to understanding human health.

It is known that individuals respond differently to the same dietary intake. For example, it has been known for the past 20 years that dietary cholesterol can cause changes in plasma cholesterol (Miettinen & Kesaniemi 1989), but this is dependant upon the individual (Glatz et al. 1993). In fact, it has been shown that some variation in response to dietary cholesterol is genotype-dependent (Ordovas 2009). Nutrition's greatest opportunity and its most difficult challenge will be in establishing these basic relationships and applying them to improving the health of all individuals, at all ages, with the most obvious goal of actively preventing disease. Nonetheless, nutrigenomics can only provide part of the answer to personalizing diet. Other nongenetic factors are also intimately involved in an individual's phenotype, their health status, and their risks of and trajectories toward different disease states. Understanding the postgenomic and posttranscriptional events from single cells all the way to whole body behaviors will also take part in the scientific underpinning of personalizing diet and health. Once diet and health are understood, foods will need to be the central providers and value generators of this systems approach to personalizing diet and health.

Food research is going to have its hands full in moving to personalized health, yet this is not news. Food, as both a scientific field and a practical venture, has been changing continuously for the past 100 years. The twentieth century experienced a massive transformation in all aspects of the agricultural enterprise. Societies themselves changed from rural, farm-dominated lifestyles to urban, technology-driven lifestyles. Agriculture changed from many small family farms to a few corporate industries. Food as a business went from a commodity-focused model, in which processing was performed mostly by consumers in-house, to a product-focused model employing centralized, in-factory processing. The food marketplace went from a clearing house for raw commodities to a packaged, personal product showcase. The health challenges of diet went from solving nutrient deficiencies caused by inadequate food choices to caloric imbalances caused by inappropriate food choices. In turn, consumers' concerns of food changed from fear of acute safety to fear of long-term health deterioration.

It is fashionable today to view all of these major changes in agriculture and food as being a net failure simply because of the visibility of some of the health problems remaining. It is true that twentieth century agriculture and food did not solve all of life's problems. Nonetheless, the successes are undeniable and the epic challenge of feeding six billion largely urbanized people, most of whom will live to an unprecedented lifespan, is vivid proof of what is achievable. In fact, the knowledge gained during the past century of food research on the composition of commodities and food materials, the structure-function relationships of those biomaterials, and the technologies to disassemble and reformulate complex, stable foods are precisely the capabilities needed to move

adroitly into a more personalized future. As health sciences identify the basis of human diversity and diagnostic sciences commercialize technologies to bring personalizing health assessment to practice, the dexterity available to food manufacturing is ready to develop equally personalized diets as health solutions. The first steps of functional foods, although clumsy, provide evidence of how rapidly, seamlessly, and eventually effectively those solutions will emerge.

The systemic response of metabolism to the combined effects of nutrient status, genetic background, epigenetic changes, lifestyle choices, and environmental fluctuations within an individual at a specific point in time (e.g., metabolic phenotype) is potentially a more sensitive and actionable reflection of nutritional and metabolic status. With such nutritional and metabolic status indicators in place, intelligent interventions, including foods, supplements, and lifestyle modifications, would be recommended to guide an individual's metabolic phenotype in a more beneficial or personally desired direction. Such a vision would bring a fundamentally different perspective to human diet management and empower a much more detailed, interactive, and ultimately valuable industrial engine to delivering health. At this point in time, it is appropriate to ask, where are we in the scientific development of the needed tools and knowledge?

In this review, nutrigenomics is defined as the combination of three complementary areas: (*a*) the direct relationship between nutrients and DNA to modify genetic expression, (*b*) epigenetic interactions in which nutrients modify the structure of DNA (DNA methylation and chromatin remodeling), affecting gene expression, and (*c*) genetic variations within humans that relate to the variations between humans in their response to diet (single nucleotide polymorphisms). The combination of these nutrient-gene mechanisms define an individual's metabolic phenotype—measurable physical and biochemical characteristics, including nutrient status and requirements (German et al. 2003).

## NUTRIGENOMICS AND FOOD

The arrival of genomics is unquestionably altering our view of humans and informing the next generation of disease care. However, for food science as an integrative field of science, genomics will create an even wider range of opportunities. The same tools that probe genetic and metabolic diversity of humans in their health-related responses to food can be used to identify the diversity of personal sensory preferences to foods and sensitivities and intolerances to food materials, as well as apply the same toolsets to probe food materials themselves. Nutrigenomics will inform research into the nutritional requirements and responses of humans and the genetic basis of their diversity across a wide range of traits. Agricultural genomics of food commodities will in turn inform our understanding of the biology, chemistry, and functionality of all the biomaterials that make up food (Sequencing et al. 2009). The genomes of production animals will guide research into everything from the efficiency of absolute production yields to redesigning the composition of edible tissues to their protection from pathogens and toxins (Lemay et al. 2009, Sequencing et al. 2009). One final subset of genomics is becoming increasingly interesting to food: metagenomics or the genomics of microbial ecosystems. The genomes of microorganisms are already redefining all aspects of microbial food safety and are beginning to guide the science of food microbiology and its applications to professional microorganisms from enhanced bioprocessing of foods to the explicit inclusion of live microorganisms for their food health value (Sela et al. 2008).

Genomics is also the centerpiece of systems biology as the science of understanding living organisms and entire living ecosystems. Food is society's most important industrial system, and many of the principles being developed in other fields of systems biology will apply to food. One of the most obvious examples of a systems approach to food is lactation and milk. The Darwinian pressure to supply a complete system of nourishment for offspring has driven the development of

an unparalleled bioreactor in mammals, the mammary gland (Lemay et al. 2009). The structures, functions, and benefits of the components of milk arising through evolution have guided nutrition research for over a century. The arrival of mammalian genomes and the insights into molecular evolution that they provide will drive a new era of research in which the biology of the mammary gland and lactation will guide a much broader view of food research from ingredient functionality to bioprocessing.

## NUTRIGENOMICS: ESSENTIAL AND NONESSENTIAL NUTRIENTS

The task of discovering the essential nutrients for human health is scientifically complete. The public health mandate is now to ensure that everyone in the population chooses a diet replete with these nutrients. The food strategy of ensuring adequacy of all of the essential nutrients in a diverse population is to overdose everyone. This approach is based on an important biological advantage. Because individual humans normally regulate each essential nutrient relatively well across a wide range of intakes, it is possible to resolve the problem of essential nutrients by ostensibly slightly overdosing most of the population. In spite of this, subsets of the population still suffer from deficiencies or suboptimal intakes of essential nutrients. This continuing problem of nutrient deficiency is due to overt poverty, food choices, genetic polymorphisms that increase or modify needs, conditions or medications that alter nutrient utilization or metabolism, or malabsorption syndromes such as celiac disease. In some examples, such as vitamin D, unusual diets and lifestyle choices that minimize alternative sources (e.g., sun exposure) are the basis of isolated inadequacies and even deficiencies. In addition, using a one-size-fits-all model, population-based fortification of one nutrient can lead to detrimental consequences. For example, the fortification of folic acid in the food supply has not only concealed vitamin B12 deficient–anemia, but evidence is emerging that this may result in impaired cognitive functioning in subsets of the population (Refsum & Smith 2008, Winkels et al. 2008).

How will food recommendations deal with the biological reality that some individuals, even following normal dietary guidelines, do not achieve effective nutrient adequacy? The causes in many cases are genetic, and the field of nutrigenomics is actively tracking them down, from the effects of dietary fat composition on plasma lipids (Ferguson et al. 2010, Joffe et al. 2010) and risk for obesity (Joffe et al. 2010) to the effect of epigenetics on the widespread increased rates of food allergy (Allen & Martin 2010) (**Table 1**). The application of this science will almost invariably require a more personalized approach to delivering essential nutrients. Solving the problems of personalizing essential nutrient intakes will be simple because they can be delivered as supplements. Personalizing the overall diet will not be as simple.

Nutritional health depends on more than essential nutrient intake. In fact, the global epidemic of noncommunicative diseases is largely driven by diets in which essential nutrition is adequate, but chronic imbalances of diet in a background of varying lifestyles and genetics are causing metabolic diseases. In addition to the essential nutrients, nonessential nutrients and other environmental factors also interact with the genome and postgenomic products (**Table 2**). Such factors include diet composition, fiber, food structure, and antioxidant capacity (Domínguez et al. 2010, O'Sullivan et al. 2010, Papathanasopoulos & Camilleri 2009, Puchau et al. 2009), as well as environmental and metabolic regulation, including gut microbiota composition (Vijay-Kumar et al. 2010), prebiotics (Cani et al. 2009), metabolic phenotype (Peppa et al. 2010), and activity (Ilanne-Parikka et al. 2010). The goal of personalizing nutrition based on individuals' genotypic and metabolic variations will first require the identification of responders from nonresponders to diet. Individually and in concert, food commodities will be produced to meet the growing health, metabolism, performance, and cognitive demands of the consumer.

## GENOTYPE AND PHENOTYPE

Humans are different in their needs for and responses to the various components of a diet. The active subject of research is exactly how and why. Identifying which of those differences are due to heritable genetic sequence variations is a key area of ongoing nutrigenomics research. The most complete picture emerging to date is the variation around the metabolism of folic acid (Zeisel 2007). The common polymorphism in the methylene tetrahydrofolate reductase (MTHFR) gene is associated with a functional difference in metabolism in carriers. This variation affects both the absolute requirement of individuals for the nutrient folate and has been recognized to be associated with an increasing number of phenotypic outcomes, including heart disease (Gohil et al. 2009) and cancer (Galván-Portillo et al. 2009). Most importantly for the success of applying the genetics to nutrition, evidence is emerging that folate supplementation in those carrying genetic risk due to MTHFR reduces the incidence of various health problems associated with low folic acid status (Galván-Portillo et al. 2009).

Genotyping determines individual (or species) genetic variation, ranging in nucleotide coverage from single allele and genome-wide determination of particular genetic differences [e.g., single nucleotide polymorphisms (SNPs)] to complete genomic sequencing (Venter et al. 2001). The tools used to conduct genotyping experiments include hybridization methods, allele-specific polymerase chain reaction (PCR) [e.g., fluorescence resonance energy transfer (FRET) primers], primer extensions (e.g., pyrosequencing), oligonucleotide ligation (e.g., microarray ligation), rolling circle amplification, and endonuclease cleavage (e.g., restriction site analysis) (Syvänen 2001). By mapping genetic differences among individuals and comparing them to phenotypic data, genome-wide association studies have led to the discovery of hypothesis-generating associations between genetic variation and phenotypes (Hindorff et al. 2009). Complete sequencing and mapping of all genetic variation in association with phenotypes are proceeding with projects like the Human Variome Project (Cotton 2007) and the 1,000 Genomes Project (Zhang & Dolan 2010). Variations in the genome are associated with susceptibility or resistance to disease, and metabolic responses to diet, pharmacology, and environment. Thus, metabolic phenotype is influenced in part by developmental plasticity, by imprinting early in life, and by the interactions of environmental factors over time. Both intrauterine signaling and early childhood environmental exposures influence full genotypic expression and ultimately metabolic phenotype (Montmayeur & le Coutre 2009). For example, a polymorphism in a fatty acid desaturase gene involved in long-chain polyunsaturated fatty acid (PUFA) synthesis is associated with higher IQ associated with breastfeeding, illustrating the crucial effects of early imprinting (Caspi et al. 2007). The epigenetic control of gene expression by dietary and environmental factors in utero determines lifelong health trajectories through DNA methylation (Kim et al. 2009). In addition, nutrigenomic imprinting early in life modulates gene expression during development and maturity, and enables an organism to respond to environmental cues and adjust its phenotypic development to match its environment (Gluckman et al. 2009). Such phenotypic plasticity demonstrates how natural selective pressures influence the metabolic outcomes resulting from the interactions between genetic variation and the environment. The high degree of developmental plasticity (Gluckman et al. 2009) and technology (Omenn 2010) has led to the widespread prevalence of positively selected traits. However, by sharing the same genes and epigenetic regulation but not the environment of our Paleolithic ancestors, contemporary humans are accosted with the epidemics of metabolic diseases (Eaton et al. 2010). The goal of nutrigenomics is not to persuade individuals to consume the diets and adopt the lifestyles of ancient hunter-gatherers, but to identify phenotypic responses in the population caused by the interaction between diet and genomic variation.

**Table 1 Interactions between essential nutrients and gene polymorphisms on clinical outcomes**

| Nutrient | Gene polymorphism | Effects on nutrient status | Clinical manifestations | References |
|---|---|---|---|---|
| Calcium | Calcium sensing receptor (CASR) A986S | Loss of function for calcium, associated with higher serum calcium, and higher urinary calcium excretion | Association with bone mineral density | (Laaksonen et al. 2009) |
| Selenium | Missense mutation in selenium binding protein 2 (SBP2) | Causes defective selenocysteine insertion sequence (SECIS)-driven selenocysteine incorporation, downregulates expression of selenoproteins | Defective thyroid function | (Hesketh 2008) |
| Iron | Human hemochromatosis protein (HFE) 187C>G or 845G>A | Both187C>G or 845G>A associated with iron overload (hemochromatosis) | Iron overload, liver cirrhosis, and cardiomyopathy, especially in diets high in iron | (Hulgan et al. 2008) |
| Folate | 5,10-methylenetetrahydrofolate reductase (MTHFR) 677C>T | Causes a 70% reduction in MTHFR activity, hyperhomocysteinemia and reduced plasma folate concentration | Hyperhomocysteinemia is associated with increased risk of coronary heart disease, neural tube defects, occlusive vascular disease and breast cancer. In carriers, sufficient folate dietary intake decreases risk of colorectal cancer, and deficiencies increase risk of colorectal cancer | (Ericson et al. 2009, Friso & Choi 2002, Hustad et al. 2004, Messika et al. 2010, Simopoulos 2010) |
| Sodium | Angiotensin gene (AGT) nucleotide −6 G>A, | The A substitution in AGT affects the interaction between at least one *trans*-acting nuclear factor and its promoter, resulting in increased gene transcription and increased angiotensin protein levels | Carriers of the A allele respond to low sodium diets with reductions in blood pressure; GG genotype is not salt-sensitive | (Simopoulos 2010) |

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| Vitamin D | Vitamin D binding protein DBP-1 (rs7041, exon 11 T>G) and DBP-2 (rs4588, exon 11C>A) | SNPs for DBP-1 and DBP-2 are inversely related to levels of circulating 25(OH) vit $D_3$ in premenopausal women | Unclear whether carriers would benefit from dietary supplementation or sun exposure | (Sinotte et al. 2009) |
| Vitamin K | Vitamin K epoxide reductase complex subunit 1 (VKORC1)j –+2255T>C | Associated with vitamin K recycling, vitamin K–dependent clotting factors and Warfarin resistance | Increased risk of arterial vascular disease such as stroke, coronary heart disease, and aortic dissection | (Suh et al. 2009) |
| Vitamin A | β-carotene 15,15′-monoxygenase (BCMO1) R267S (rs12934922) and A379V (rs7501331) | Carriers of 267S or 267S + 379V have reduced activity in converting B-carotene to retinal | Increased risk for vitamin A deficiency, when B carotene is the major dietary source | (Leung et al. 2009) |
| Vitamin B12 (cobalamin) | Methionine synthase TCN2 776C>G and 67A>G | Causes hyperhomocysteinemia | Associated with birth defects | (Brouns et al. 2008) |
| Carbohydrates | Beta-2-adrenergic receptors Q27E | Unknown | Higher risk of obesity in female carriers with carbohydrate intake >49% of energy | (Martinez et al. 2003) |
| Omega 3 and 6 fatty acids | Fatty acid desaturase, FADS SNP rs174537 | Lower plasma arachidonic and eicosapentaenoic acids and higher plasma alpha linolenic and linoleic acids in carriers of the minor allele versus noncarriers. | The minor allele homozygotes (TT) have lower plasma total cholesterol and LDL-C compared with noncarriers | (Tanaka et al. 2009) |

**Table 2 Interactions between nonessential nutrients and genomic and postgenomic products**

| Nutrient | Target | Outcome | References |
|---|---|---|---|
| Isothiocyanates | Glutathione S-transferase (GST) subtypes M, T, and P | Deletions in GSTM1 and GSTT1 result in defective enzymatic activities and decreased carcinogen detoxification capacities; high isothiocyanate intake by GSTM1 and T1 carriers had decreased colorectal cancer risk | (Seow et al. 2002) |
| Carotenoids | Manganese superoxide dismutase (MnSOD) Ala16Val | Reduced MnSOD activity and lower response to oxidative stress; dietary carotenoids increase risk of cancer for carriers | (Mikhak et al. 2008) |
| Lipoic acid | Gene expression for B cell receptor, T cell differentiation signaling pathway, and free radical scavengers | Supplementation reduces high fat diet–induced chronic oxidative stress and immuno-suppression in mice jejunum | (Cui et al. 2008) |
| Catechin | Gene expression for adhesion molecules, energy and lipid metabolism, lipid trafficking | Supplementation reduces atherosclerotic lesion development in apo E-deficient mice | (Auclair et al. 2009) |
| | Gene expression for mitochondrial activity | Supplementation with regular exercise ameliorates age-associated decline in physical performance in mice | (Murase et al. 2008) |
| Cholesterol | 7-alpha hydroxylase (CYP7A1) A278C | Larger increase in plasma HDL-C in carriers in response to a cholesterol-rich diet; elevated LDL-C is found in homozygous carriers | (Hofman et al. 2004) |
| Fiber | Adiponectin (ADIPOQ) rs1501299 | Lower plasma ADIPOQ levels in carriers when fiber intake was low; associated with increased risk of childhood obesity | (Ntalla et al. 2009) |
| Saturated fat (SFA) | Scavenger receptor class B type I (SRB-I) gene, −1 G->A | Higher plasma LDL-C in heterozygote carriers in response to an SFA-rich diet; carriers had greater reductions of plasma LDL-C after switching from a high SFA diet to high carbohydrate diet compared with noncarriers; possible increased risk for atherosclerosis when consuming a SFA-rich diet. | (Perez-Martinez et al. 2005) |
| | Apolipoprotein E (ApoE), E2 and E4 alleles | Larger increases in plasma LDL-C in response to SFA intake in E2 and E4 carriers; impact of SFA intake on incidence of myocardial infarction is more evident in the E2 and E4 allele carriers than noncarriers | (Minihane 2010) |

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|---|---|---|---|
| Sesame seed lignans | Gene expression for hepatic genes involved in fatty acid oxidation and fatty acid transport | Unknown | (Puiggros et al. 2009) |
| Grape seed proanthocyanidins | Gene expression for hepatic genes related to lipogenesis and lipoprotein secretion | Normalized plasma triglycerides and LDL-C on a high fat diet | (Quesada et al. 2009) |
| Choline | Epigenetic modification | Reduction in methylation influences on neurogenesis, including increased neural tube closure defects in infants of mothers with choline deficiency; maternal choline intake during early pregnancy is associated with increased hippocampal progenitor cell proliferation, decreased apoptosis, and enhanced visual-spatial and auditory memory in rodents' lifetimes; prevents memory loss during aging | (Mehedint et al. 2010, Zeisel 2009) |
| Soy isoflavones | Gene expression for cell adhesion, apoptosis, autophagy, cell cycle, cell differentiation, DNA associated proteins, mRNA processing and splicing, transport, and inflammatory responses | Protection against oxidative stress and cancer | (Barve et al. 2008) |

## PROBING NUTRIGENOMIC DIVERSITY: THE TOOLS AT HAND

The tools of systems biology are being used to examine the genetic variations in humans that affect metabolic status and health, the variations in microbial pathogens that are threats to food safety, the variations in microbial communities within humans that affect their health, and the diversity of food and food commodities. In addition to identifying genotypic variation, a systems biology approach encompasses the use of highly sensitive, high-throughput and comprehensive postgenomic technologies—transcriptomics, proteomics, and metabolomics—combined with bioinformatics and multivariate statistics all directed to discover how human phenotypes vary in response to diet and how those phenotypes could be improved.

### Gene Expression as an Output: Transcriptomics

Transcriptomics simultaneously measures thousands of transcripts from a tissue or biofluid (Nguyen et al. 2002). DNA microarray technology and quantitative real time PCR have successfully evaluated the interactions between diet and genes measured as changes in genetic expression. Compared with traditional biochemical methods, transcriptomics is a more sensitive and informative tool to assess nutrient status, including minor deficiencies (Harvey & McArdle 2008) and metabolic responses to diet (Fukasawa et al. 2010). For example, the upregulation of transcripts-related adverse changes in skeletal muscle function and structure suggested that the current recommended daily allowance (RDA) for protein is too low. This inadequacy of the RDA was not seen before with typical measurements of protein sufficiency, including nitrogen balance and isotope labeling studies (Thalacker-Mercer et al. 2010). Expression technology can also reveal the interactions between diet and metabolic outcomes. Energy balance (Kallio et al. 2007), dietary structure (Crujeiras et al. 2008, Fukasawa et al. 2010), and composition (Konstantinidou et al. 2010, Wang et al. 2008) have been shown to alter expression of genes involved in insulin sensitivity, lipid metabolism, oxidation, immunity, and inflammation.

The tools of genomics research are being used in identifying functional molecular markers in everything from human and animal health to accelerating crop improvement in efficiency, nutrient quality, disease resistance, and safety (EFSA 2008, Kogel et al. 2010, Polesani et al. 2010). The knowledge gained from identifying the alleles at all loci in a population allow breeders to design a genotype in silico based on the desired phenotype.

### Protein as an Output: Proteomics

Proteomics is dedicated to describing the entire complement of proteins and their modifications of cells, tissues, and organisms (Mischak et al. 2007). Unlike the human genome, which is relatively fixed and steady throughout the human body, the human proteome is far more complex and dynamic, varying over time and among cells. It is the proteins themselves and their modifications that elicit their biochemical, physiological, and structural functions in tissues and cells. Mass spectrometry platforms are used to detect, identify, and quantify thousands of proteins in a sample (Cravatt et al. 2007). Still viewed as the most challenging of the 'omics fields, proteomics has struggled to reach a proof-of-principle success story, in part because scientists are still coming to grips with the analytical challenges posed by the true breadth and extent of protein diversity in biology. The use of proteomics for biomarker identification and validation was imagined to revolutionize clinical diagnostics. However, this most obvious application still faces several challenges ranging from appropriate platforms (Rifai et al. 2006) to study design (Mischak et al. 2007) to regulatory oversight (Regnier et al. 2010). Nonetheless, significant progress has been made, and

diagnostic products based on the simultaneous measurement of multiple proteins are beginning to emerge (Kolberg et al. 2009). Notably, true proteomics is currently used as the means to identify a subset of proteins that are carried forward as diagnostics.

Although consensus has yet to be achieved for the standardization and application of proteomic technologies for use in the clinical setting, this field has revealed cutting-edge breakthroughs for the fields of nutrition and food science. Proteomics is capable of exposing many of the molecular mechanisms resulting from dietary interventions compared with traditional biochemical methods. Parallel proteomic analysis from the livers of grape seed extract–supplemented rats revealed 140 differentially expressed proteins, uncovering effects of grape seed extract on a variety of biochemical processes, including zinc transport, lipogenesis, G-protein signaling, and sulfur metabolism (Baiges et al. 2010).

For the fields of food science, biotechnology, and nutrition, proteomics is strategically positioned for discovering functional foods with metabolic effects. This is especially relevant in the research of plant- and animal-secreted proteins for breeding next generation crop plants (Agrawal et al. 2010), in identifying novel clinical biomarkers (Pavlou & Diamandis 2010), and in discovering therapeutic targets (Katz-Jaffe et al. 2009). The secretome describes the global study of proteins that are secreted by a cell, tissue, or organism at any given time or under certain conditions (Hathout 2007). During cellular posttranslational modification, proteins become chemically modified, which plays a key role in product secretion. Furthermore, posttranslational modification also influences protein biological and physiological functions such as cell signaling, cell recognition, and cell protection. Rather than simply providing amino acid substrates, the complex proteins in milk are secretory, which, as intact or partially digested products, exert bioactive functions (Affolter et al. 2010, Froehlich et al. 2010, Kanwar et al. 2009, Mok et al. 2007). Food science and biotechnology are beginning to exploit the health enhancing effects of bioactive proteins and peptides of milk.



## Metabolism as an Output: Metabolomics

Metabolomics—the measurement of small molecules in biofluids, tissues, and cells using spectroscopic analytical platforms—has been included in the National Institutes of Health (NIH) roadmap as a core technology in the overall initiative to guide the development of diagnostics and assist in delivering the therapeutic solutions to human metabolic diseases (Zerhouni 2003). Metabolomics is more helpful in identifying the complexities of metabolic regulation than measurements of single biomarkers using traditional biochemical methods (Bakker et al. 2010). The metabolome, like the proteome, is not definable in the same sense as the genome. Unlike the genome, which remains static, metabolites change in every cell and body fluid, notably in response to food intake, for example (Zivkovic & German 2009). All of our cells and biofluids contain a finite number of key metabolites, and metabolic homeostasis is generally maintained so that the actual variations in any given metabolite pool are typically minor relative to the abundance of the metabolites. These basic molecules and their fluxes through human metabolism, i.e., those that all humans have in relatively constant amounts (Bernini et al. 2009), include substrates, intermediates, and products of endogenous metabolism (Holmes et al. 2008). Hence, the metabolome will remain a discussable biological construction in which pragmatic clinical utility will require that assumptions, protocols, and reference conditions are standardized. Nonetheless, metabolomics is already proving to be informative in revealing the complex metabolic effects to diet (Vinaixa et al. 2010), in predicting responders to drugs (Winnike et al. 2010) and changes in body composition during energy restriction (Smilowitz et al. 2009), and in identifying metabolic aberrations associated with disease (Yap et al. 2010).

Application of metabolomics specifically to the field of nutrition faces a number of challenges. The ongoing development of analytical platforms is beyond the scope of this review (Büscher et al. 2009, Dettmer et al. 2007, Issaq et al. 2009, Wikoff et al. 2009, Zhang et al. 2009), and the challenges of identification are being addressed in part through increasingly accurate libraries of metabolite spectra (mass, nuclear magnetic resonance, etc.) and chemical properties of diverse biological samples (Forsythe & Wishart 2009). Defining the molecules that constitute this core metabolite pool is an immediate priority. The Human Metabolome Project (Forsythe & Wishart 2009) has established the first draft of this endogenous metabolome. The problem of quantification is more daunting. Whether in early discovery research or in clinical applications, probing an individual's nutritional status will invariably require that the amount of metabolites, not their simple presence or absence, is accurately determined. Studies that take quantitative measures of metabolites are already revealing both the complexity of metabolism and the value of measuring it.

## GENOMICS OF FOOD

The molecular tools used to elucidate the metabolic effects of genetic-nutrient interactions are proving to be valuable across the food and agricultural sciences. The genetic structure and expression of bovine genes identified numerous quantitative trait loci (QTL) affecting nutrient quality and quantity (Naslund et al. 2008, Roy et al. 2006). Additionally, recombinant technology has led to the production of food commodities with bioactive ingredients found in breast milk. Human genes for milk proteins with known bioactive functions expressed in rice (Tang et al. 2010, Zavaleta et al. 2007) are resistant to heat and acid/basic environments, thereby maintaining biological activities identical to their native counterparts (Lönnerdal 2006). Interestingly, molecules found in milk, such as the products of lactoferrin digestion, lactoferricin and lactoferrampin, exert their activities after exposure to physiological processing. Recently, microbial peptide fusion to crystalline proteins produced from genes cipA and cipB of *Photorhabdus luminescens* subsp. *akhurstii* led to high-level expression and purification of these two proteins (Tang et al. 2010). Together, the bioactive properties of milk, guided by natural selection and the applications of biotechnologies to isolate them, are increasingly being viewed as a first generation ingredient list for the production of functional and medical foods that address the targeted health needs of individuals from diarrheal to metabolic diseases.

## COMMODITY GENOMES

Humans are not the only genomes of interest to food. The genomes of commodity plants, animals, yeast, molds, bacteria, and viruses are guiding scientists to understand nutrient contents, stability, processing strategies, and safety.

### Plants

Plant genomes tend to be monstrous due to polyploidy. Hence, the sequencing of entire plant genomes lags somewhat behind other life forms simply because of the scale of the projects. Nonetheless, a variety of agriculturally important genomes are complete or nearing completion, and are forming the basis of a major knowledge resource for food research. From the perspective of production agriculture, these genomes have already shown value. Quantity traits for yield, pest resistance, and water stress are increasingly deliverable as genetic inserts (Cui et al. 2008, Deshmukh et al. 2010, Fu et al. 2010, Zhang et al. 2009). Similarly, there are striking examples of how specific crop plants can be manipulated to improve their basic nutritional value

(Hirschi 2009). However, nutritionists are still struggling with the basic strategies for moving beyond the identification of genes associated with essential nutrients to maximizing their agricultural suitability and nutrient bioavailability. The genome of an organism represents the culmination of its evolutionary history and the ensemble of genes emerging under the Darwinian selection pressures that guided the organism's development. For plants, this pressure was applied, in part, by the need to avoid the ubiquitous pathogens and aggressive predation by the other organisms in their environment. Understanding these predatory influences and the strategies that different plants have developed in the context of their overall genomes will be critical to appreciating the net nutritional value when plants and plant parts are consumed (Lagaert et al. 2009). It is also in this context of composition and protective strategies of plants that we need to understand the ingenuity of the vast array of food processing techniques that humans invented as they first gathered and subsequently grew and harvested plant commodities (Anastasio et al. 2010, Reale et al. 2007, Sieuwerts et al. 2008).

## Animals

The anthropological history of humans is consistent with a carnivorous hunter-predator wed to an omnivorous gatherer. A diet rich in diverse animal products was clearly a part of our evolutionary history (Braun et al. 2010). Humans migrated to and succeeded in a remarkable breadth of environmental ecosystems literally from equator to pole (Wells & Stock 2007). One intriguing additional complexity on human diets and evolution was the tantalizing discovery of the confounding effects of cooking on the quality of diets (Carmody & Wrangham 2009). Unquestionably, whether raw or cooked, the rich nutrient quality of animal products was one of the enabling factors to the apparently healthy Paleolithic diet and the spread of humans around the globe (Jonsson et al. 2009).

The challenges for modern animal products as food is to understand productivity and bioactivity, and to defend their higher production cost using health and other value attributes. The genomes of the major domestic agricultural animals—fish, chicken, swine, beef, lamb, goat—are complete or in the final phases of assembly and annotation. Chicken and bovine emerged as production animals for good reasons, and their genomes encode for both the animals themselves and for the associated nourishing products, eggs and milk. Productivity of the chicken is already a remarkable achievement in feed conversion and egg production, and genomics is accelerating progress in research focused on minimizing disease for production costs and food safety (Cheng 2010).

The bovine genome has only recently been completed but already considerable information is emerging from genomics research on lactation and its various biological and nutritional qualities (Lemay et al. 2009, Sequencing et al. 2009). Companion research is taking advantage of sequence information to assemble the milk proteome (Affolter et al. 2010). Genetic analyses are beginning to describe the natural variability in bovine species, revealing the basis for differences in key nutrients in milk (van Hulzen et al. 2009). Expanding to a systems biology approach, the bioprocess of lactation offers researchers invaluable insight about the structures and functions of safe and effective bioactive ingredients. Expression arrays can monitor the effects of breeding and dietary manipulation (Carriquiry et al. 2009).

## Microorganisms

Microbial fermentation is one of the mainstays of historic food processing (Poutanen et al. 2009), owing benefits to food stability, safety, and bioavailability, as well as myriad advantages to the

organoleptic properties of foods (Gálvez et al. 2010). The concept that living microorganisms or their direct products are valuable constituents of human diets beyond the provision of specific vitamins is not new, yet it remains relatively unexplored both scientifically and technologically.

Variation in the gut microbiota within and between individuals is large (Turnbaugh & Gordon 2009). Modulation of gut microbiota could be a key component of personalized nutrition, as gut microbiota and their byproducts have been shown to alter host metabolome, genome, transcriptome, proteome, and health status (Lewis & Burton-Freeman 2010). The gut microbiome of individuals contributes to the variation in systemic energy balance. Plasma urinary metabolites reflect human gut microflora metabolism and the obesity phenotype (Calvani et al. 2010). The metabolism of indigestible carbohydrates by gut microbiota can alter energy extraction from the diet by the host (O'Keefe 2008). Short chain fatty acids produced by microflora represent 7% of the substrates that enter gluconeogenesis (Ford & Simmons 2008) and 5%–15% of the total human energy requirement (Neish 2009). However, it is unknown how different dietary components enhance the selective growth of one microbial population over another to produce desirable systemic metabolic consequences. The intimate link between gut microbiota composition and health is demonstrated by the prepathogenic state induced by the inoculation of germ-free mice with human bacteria (Martin et al. 2007, Rezzi et al. 2008), the priming of the innate immune system by microbiota-produced peptidoglycans (Clarke et al. 2010), and the association of specific bacterial populations with obesity (Lewis & Burton-Freeman 2010, Turnbaugh et al. 2008, Vrieze et al. 2010).

Diet can alter host microbial composition based on carbohydrate and fiber content, cruciferous vegetable and fat intake (Benus et al. 2010, Carroll et al. 2009, Hildebrandt et al. 2009), and through direct inoculation via fermented or functional foods (Sanders & Marco 2010). Prebiotics have been shown to alter host microbiota (Candela et al. 2010). For example, oligosaccharides in human milk selectively feed the beneficial gut bacteria *Bifidobacterium longum* subsp. *infantis* to the exclusion of other bacteria (Sela et al. 2008), and the prebiotic panose shows in vitro stimulation of *Bifidoba terium* growth and reduction in *Bacteroides* and *Clostridium* growth (Mäkeläinen et al. 2009). Modulation of gut bacteria with prebiotics has been shown to reduce intestinal barrier dysfunction, endotoxemia, and systemic and liver inflammation induced by a high-fat diet (Cani et al. 2009) and improve cholesterol homeostasis (Martinez et al. 2009). It is clear that human gut microbiota have profound effects on human metabolism, gene expression, and health. Identifying these microbial-food interactions has biological potential and holds innovative promise for developing new metabolically targeted foods, which will lead to improved health, metabolism, and protection.

## INTESTINAL FUNCTION: FROM IMMUNITY TO MICROBIOLOGY

Dietary compounds and nutrients have widespread effects on gene expression in all tissues, including the intestine. Their effects can be either direct (e.g., as ligands for nuclear transcription factors) or indirect. The indirect effects of dietary compounds on intestinal function and gene expression can be manifested in a number of ways as whole compounds or as modified, metabolized, or hydrolyzed molecules (e.g., peptides). For example, consumption of human milk oligossaccharides, which are completely indigestible by the developing neonate, are actually consumed by specific strains of bifidobacteria that are posultated to maintain a healthy gut (Zivkovic et al. 2010). Although still in its infancy, the relationship between dietary components and the modulation of gut microflora has recently received a great deal of interest as a result of the Human Microbiome Project (Turnbaugh et al. 2007) as well as in research highlighting the importance of the interaction between diet and the intestinal microbiome as a new dimension of human health.

The modulation of the immune system in the gastrointestinal tract by food compounds is involved in the induction of oral tolerance or the suppression of immune response to food antigens. Food proteins (e.g., antigens) may have direct effects on intestinal immune cells, inducing phenotypic maturation and the secretion of specific cytokine profiles, which in turn have a net effect on T cell activation and immune response (MacDonald et al. 2009). It also appears that the timing of introduction of foods in early childhood can determine the risk of developing food allergies and autoimmune disease (Prescott et al. 2008), and that these effects are mediated in part by the host-microbe interactions.

Dietary compounds also play a key role in the establishment of infant gut microflora. Specific constituents in human milk guide the colonization of the infant gut by selectively promoting the growth of specific microbial populations. *B. longum* subsp. *infantis* found in the intestine of breast-fed infants is the first bacterial strain to be characterized as selectively supported by constituents in human milk (LoCascio et al. 2007). The genomic sequence and metabolic characterization of *B. infantis* revealed multiple genes in four discrete clusters that are required to digest, metabolize, and ferment the oligosaccharides in human milk and thus support its ecological niche in the infant.



## ADIPOSE TISSUE: EFFICIENCY OR DYSFUNCTION?

Adipose tissue is not a new theme of nutrition-related research. The importance of this dynamic tissue to metabolic health and disease has brought adipose to modern celebrity status. The attention is warranted by the dramatic increase in the global prevalence of obesity (Balkau et al. 2007). The variations in the development and consequences of obesity are due in part to the complex interactions of genetic predisposition (Bochukova et al. 2010, Cauchi et al. 2009, Cheung et al. 2010, Walters et al. 2010) and genetic-nutrient interactions (Garaulet et al. 2009, Warodomwichit et al. 2009). The burgeoning field of nutrigenomics has taken on a tremendous feat to discover interactions between genetic variation and diet to produce measurable phenotypes ultimately stratified into subject cohorts as responders and nonresponders to various food-based solutions. For example, carriers of the ADIPOQ −11391 G>A SNP had both lower BMI and risk of obesity when monounsaturated fat (MUFA) was ≥13% of total energy intake. However, the effect of genetic variation on disease risk was not found in −11391A carriers in which MUFA intake was <13% of total energy (Warodomwichit et al. 2009). Intake of MUFA ≥13% of total energy was associated with higher fasting plasma concentrations and HOMA-IR (a measurement of insulin resistance) individuals carrying the major allele rs4850704 CLOCK gene (Garaulet et al. 2009).

As the field of nutrigenomics offers great insight in the interactions between genes and diet, many challenges remain. Research in the field of nutrigenomics does not only require large and long validation studies necessary to identify all of the nutrient-gene interactions and their phenotypic outcomes. The clinical relevance attributed to the genetic causes of obesity is quite small and are not translatable to all individuals in the population (Cauchi et al. 2009, Cheung et al. 2010, Han et al. 2010, Wen et al. 2010). Obesity is a complex multifactorial metabolic disease such that its causes, and approaches for its treatment and prevention, will vary within the population. Nutrigenomics alone cannot identify all of the variation that determines metabolic responses to food. Metabolic regulation is a result of the complex interactions between genomics, metabolic phenotype, and environment—largely diet.

Attempts to elucidate gene-diet interactions have largely focused on composition, yet food structure influences the rate at which dietary composition—substrates and intermediates of metabolic pathways—flux into circulation and influence hormones and enzymes that regulate metabolic pathways. For example, a low- versus high-glycemic index dietary challenge

administered after a bout of exercise increased the gene expression and protein levels of the fatty acid transporter (FAT/CD36) of skeletal muscle (Cheng et al. 2009), partially explaining how low-glycemic meals enhance fatty acid oxidation (Stevenson et al. 2009). Using an integrated 'omics approach, carbohydrate structure alters the serum metabolic profile, involving lysophosphatidylcholine species, and mRNA expression of stress reactions-related and adipose tissue differentiation-related genes in adipose tissue, demonstrating that high glycemic carbohydrates elicit proinflammatory responses involved in adversely altering insulin and glucose metabolism (Lankinen et al. 2010). Manufacturing foods that will target metabolic pathways of interest requires understanding how food composition and structure interact with the dynamic complexity of all metabolic processes.

## SKELETAL MUSCLE: ARE ATHLETES BORN OR MADE?

Epidemiologic data show profound benefits of exercise to health, protection from disease, even longevity (Sun et al. 2010), yet this would seem paradoxical. If you want to increase the longevity of your car, you keep it in the garage. Why does moving your muscles improve the health of not only your muscle but apparently everything else? Skeletal muscle has been studied for its impact on multiple aspects of metabolism, physiology, and immunology. These studies provide interesting roles for skeletal muscle in everything from glucose clearance and diabetes protection to fat oxidation and protection from obesity. However, these are all acute effects. It took studies on organelle-biogenesis to reveal the mechanism behind long-term, systemic protection. The understanding of cellular responses to exercise links genetic regulation of mitochondria biogenesis to tissue protection (Handschin & Spiegelman 2008, Narkar et al. 2008). In effect, stimulation of muscle via exercise signals the transcription coactivator PGC1-α, which simultaneously controls the complete system of mitochondrial biogenesis and a variety of muscle phenotypic features (Calvo et al. 2008). In parallel, PGC1-α stimulates the expression of a wide range of genes that protect against precisely the consequences of mitochondrial activity and reactive oxygen (Handschin & Spiegelman 2008). In turn, the activity of these genes facilitates protection from a wide range of cellular toxins. Demonstrating this molecular mechanism, the single insertion of PGC1-α in a murine genetic model produces the same exercise protection from sarcopenia during aging without the exercise (Wenz et al. 2009).

## NUTRIGENOMICS AND THE LIVER

Probing the liver's status with measures of its metabolic products has been a hallmark of diagnostics for decades (e.g., the measurement of plasma lipoprotein cholesterol as a marker of heart disease risk). How much variation is genuinely genetic, and how much is postgenomic and diet dependent? Several recent articles characterized the general effects of high-fat diets as well as the specific effects of individual fatty acids and plant-derived compounds on hepatic gene expression, particularly those involved in lipid metabolism. Researchers found a multiphasic adaptation response to high-fat feeding in a mouse model of obesity and metabolic syndrome, which was characterized by an inflammatory, lipotoxic early phase and a steatotic, adipogenic late phase (Radonjic et al. 2009). The inflammatory effects associated with the early phase were largely regulated by NFkβ, whereas the steatotic phase was largely mediated by PPARγ, suggesting two distinct transcriptional programs at work in the acute response compared with the chronic response to high-fat feeding in mouse liver. In rats, a long-term, high-fat diet was associated with greater weight gain, a greater increase in adiposity, and increased expression of metabolic genes in adipose tissue and muscle of female rats compared with male rats (Priego et al. 2008). In male rats, the increased expressions of

PPARα and CPT1 in the liver were associated with higher liver triglyceride content and higher blood insulin compared with female rats, suggesting gender-related differences in fuel partitioning between the major metabolic organs in response to high-fat feeding in rats. Researchers also found that longer-chain, more unsaturated fatty acids had much stronger effects on gene expression in mouse liver than did shorter-chain, more saturated fatty acids, which were mostly mediated by PPARα (Sanderson et al. 2008).

A number of recent nutrigenomic studies have revealed important features of metabolic regulation mediated by PPARs. PPARα is known to be responsive to dietary fatty acids, but recent evidence points to its sister transcription factor, PPARβ/δ, as the sensor of plasma-free fatty acids in the liver. Researchers showed that transcriptional activation of PPARβ/δ genes Lpin2, a gene involved in lipid metabolism, followed plasma-free fatty acid concentrations, whereas this was not the case for PPARα (Sanderson et al. 2009). A more recent study by the same group further showed that PPARβ/δ deletion resulted in upregulation of pathways related to innate immunity and inflammation, and downregulation of pathways related to lipoprotein metabolism and glucose utilization, which was correlated with increased plasma glucose and triglycerides (Sanderson et al. 2010).

In contrast to the metabolic response of dietary fats alone, consumption of grape seed proanthocyanidins on the background of a high-fat diet attenuated the increased expression of hepatic genes related to lipogenesis and lipoprotein secretion, and normalized plasma triglycerides and LDL-cholesterol in rats (Quesada et al. 2009). Grape seed flavonoids were also found to regulate the expression of genes involved in oxidative stress (Puiggros et al. 2009). Sesame seed lignans, however, increased the expression of genes involved in fatty acid oxidation in male rats, as well as increasing the expression of other proteins involved in fatty acid transport (Ide et al. 2009).

## PERSONALIZING HEALTH AND NUTRITION

The ultimate goal of personalizing nutrition is to enable each individual to be guided by predictive knowledge of their personal health to diets that prevent disease and maximize health potential. To achieve such a goal, the science needed will extend from new accurate and predictive measures of health based on molecular signatures of metabolites, proteins, transcripts, genes, and microbiota (Panagiotou & Nielsen 2009). The need for personalized nutrition is derived from the recognition that people are metabolically, physiologically, and genetically different and therefore have different responses to food compounds (Panagiotou & Nielsen 2009). These differences are not just genetic but also extend to age, current lifestyle, and prior lifestyle (Zivkovic et al. 2009). For example, it is clear that the diet of an elderly person should be different than the diet of an elite athlete, as these two groups have unique needs and requirements. The differences between individuals are not simply a reflection of acute needs for fuel and protection.

The increasing incidence of diet-related metabolic disorders such as obesity, being overweight, hypertension, and diabetes in Western populations, although considered epidemic, are affecting the population differently and indeed some populations appear unaffected (Alberti 2001, Watzke & German 2009). Hence, the health and economic cost of noncontagious disease has made the need for a more personalized approach to nutrition particularly apparent. Personalization of aspects of diet as simple as total caloric intake are needed, as research shows that for many, their diets today are unbalanced simply in terms of calories and macronutrients (Popkin 2006, Watzke & German 2009). Despite the visible effects of an unbalanced diet and individual awareness of the problem, people continue to struggle with changing their health trajectories (Petrovici & Ritson 2006, Watzke & German 2009). The question for the entire agriculture and health sector, however,

from consumers to industries, from health regulators to educators, is how do you personalize this massive global enterprise?

## THE COMMERCIALIZATION OF PERSONALIZED DIETS

Achieving personal health will require that entire diets are personal not just occasional foods. This means that at the most basic level nutritional needs are integrated in some way with all foods consumed in a day. Entire diet plans that deliver all foods in a day to each individual match this nutritional need, but such approaches destroy the traditional joy of the diversity in the open food marketplace and are unlikely to be sustainable for this reason alone. Knowledge-based foods systems that combine the ability to formulate dietary needs for each individual and yet allow for personal choices are needed. Once basic nutritional needs are met, opportunities to providing for the more personal aspirations for health will invariably arrive. Developing diets based on individual metabolic, performance, and even cognitive needs are first steps, and food products and devices are already reaching the marketplace. The substantial research accomplishments in genetic diversity of humans will be valuable, but likely only for a subset of consumers for whom genotype is particularly predictive. Food companies have created diets for such individuals based on genetic analysis of up to 30 gene polymorphisms (McCabe-Sellers et al. 2009). This technology allows individuals to make meal choices and produce this meal from basic ingredients.

Sensation is food's greatest asset. Food is critical to one's quality of life, and the freedom to choose foods that we each find delicious is synonymous with success at every socioeconomic level. The food marketplace is driven by personal choice. And, from a nutrition perspective, sensation drives compliance. Individuals, whose diets are imbalanced, still find that foods that make up the diet are attractive. How can these disparate forces be reconciled? How can the foods that are most personally healthy be most personally delicious? Is it even possible? From a biological perspective, only the sensation of taste is innate (Chandrashekar et al. 2006). That is, we are born liking the tastes of sweet, salty, and umami and born disliking bitter and sour. These taste preferences are thought to be the logical drivers of nutrition (essential fuel, salt, amino acids, and toxicity), secondary plant metabolites, and spoilage (Hevezi et al. 2009, Liman 2006). The balance of sensory preferences—olfaction, texture, and sound—are almost completely learned (Beauchamp & Mennella 2009). That is, however delightful or repulsive you find a particular aroma, you have personally acquired that preference within your lifetime. Scientific research is rapidly building a detailed mechanistic understanding of these innate and learned processes and how they differ and how different commodities interact with these sensations (Crowhurst et al. 2008). Understanding the sensation of foods and the variation in human responses is providing clues to how particular individuals self-select inappropriate diets (Garcia-Bailo et al. 2009). An obvious next step is to simultaneously match genetic health needs with sensory preferences into organoleptic-based, personalized foods.

## CONCLUSION

The nutritional status of humans remains a major challenge for public health agencies, clinical practices, and the food industry, as people around the world are suffering diet-related illness due to inappropriate food choices and lifestyles. Routine assessment could provide the means to recognize individual variations in nutritional status, but a merging of scientific knowledge and commercial innovation will be needed to bring such assessment to practice. Technologies of assessment from genotyping to metabolomics and imaging to activity measurement are bringing diagnostic sciences to health practice. Engineering innovations are actively developing analytical platforms capable

of providing these measures fast and cheap in accessible biological fluids. In parallel, the scientific community is beginning to apply these tools to annotating how these genetic, metabolic, and physiological profiles differ in individuals according to their health. Electronic databases are being designed to house the results of this initiative as public knowledge resources. The first generations of these innovations are likely to be in more acute health problems. For example, the dysregulations in hepatic lipid metabolism are at the center of a new diet-disease paradigm (metabolic syndrome, type 2 diabetes, obesity) and are amenable to a first generation of personalizing health through metabolic assessment. The first proofs of principle building the knowledge to bring actionable diagnostics to food and diet practice are now appearing. In time, personalizing diets to enable each individual to achieve their own aspirations for health will realize a major change in the human condition. We will look back and ask what took so long?

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## LITERATURE CITED

Affolter M, Grass L, Vanrobaeys F, Casado B, Kussmann M. 2010. Qualitative and quantitative profiling of the bovine milk fat globule membrane proteome. *J. Proteomics* 73:1079–88

Agrawal GK, Jwa N-S, Lebrun M-H, Job D, Rakwal R. 2010. Plant secretome: unlocking secrets of the secreted proteins. *Proteomics* 10:799–827

Alberti G. 2001. Noncommunicable diseases: tomorrow's pandemics. *Bull. WHO* 79:907

Allen KJ, Martin PE. 2010. Clinical aspects of pediatric food allergy and failed oral immune tolerance. *J. Clin. Gastroenterol.* 44:391–401

Anastasio M, Pepe O, Cirillo T, Palomba S, Blaiotta G, Villani F. 2010. Selection and use of phytate-degrading LAB to improve cereal-based products by mineral solubilization during dough fermentation. *J. Food Sci.* 75:M28–35

Auclair S, Milenkovic D, Besson C, Chauvet S, Gueux E, et al. 2009. Catechin reduces atherosclerotic lesion development in apo E-deficient mice: a transcriptomic study. *Atherosclerosis* 204(2):e21–27

Baiges I, Palmfeldt J, Bladé C, Gregersen N, Arola L. 2010. Lipogenesis is decreased by grape seed proanthocyanidins according to liver proteomics of rats fed a high fat diet. *Mol. Cell. Proteomics* 9:1499–513

Bakker G, van Erk M, Pellis L, Wopereis S, Rubingh C, et al. 2010. An antiinflammatory dietary mix modulates inflammation and oxidative and metabolic stress in overweight men: a nutrigenomics approach. *Am. J. Clin. Nutr.* 91:1044–59

Balkau B, Deanfield JE, Després J-P, Bassand J-P, Fox KA, et al. 2007. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation* 116:1942–51

Barve A, Khor T, Nair S, Lin W, Yu S, et al. 2008. Pharmacogenomic profile of soy isoflavone concentrate in the prostate of Nrf2 deficient and wild-type mice. *J. Pharm. Sci.* 97:4528–45

Beauchamp GK, Mennella JA. 2009. Early flavor learning and its impact on later feeding behavior. *J. Pediatr. Gastroenterol. Nutr.* 48(Suppl. 1):S25–30

Benus RFJ, van der Werf TS, Welling GW, Judd PA, Taylor MA, et al. 2010. Association between *Faecalibacterium prausnitzii* and dietary fibre in colonic fermentation in healthy human subjects. *Br. J. Nutr.* 29:1–8

Bernini P, Bertini I, Luchinat C, Nepi S, Saccenti E, et al. 2009. Individual human phenotypes in metabolic space and time. *J. Proteome Res* 8:4264–71

Bochukova EG, Huang N, Keogh J, Henning E, Purmann C, et al. 2010. Large, rare chromosomal deletions associated with severe early-onset obesity. *Nature* 463:666–70

Bovine Genome Seq. Anal. Consort., Elsik CG, Tellam RL, Worley KC, Gibbs RA, Muzny DM, et al. 2009. The genome sequence of taurine cattle: a window to ruminant biology and evolution. *Science* 324:522–28

Braun DR, Harris JWK, Levin NE, McCoy JT, Herries AIR, et al. 2010. Early hominin diet included diverse terrestrial and aquatic animals 1.95 Ma in East Turkana, Kenya. *Proc. Natl. Acad. Sci. USA* 107:10002–7

Brouns R, Ursem N, Lindemans J, Hop W, Pluijm S, et al. 2008. Polymorphisms in genes related to folate and cobalamin metabolism and the associations with complex birth defects. *Prenat. Diagn.* 28:485–93

Burdge G. 2004. α-Linolenic acid metabolism in men and women: nutritional and biological implications. *Curr. Opin. Clin. Nutr. Metab. Care* 7:137–44

Büscher J, Czernik D, Ewald J, Sauer U, Zamboni N. 2009. Cross-platform comparison of methods for quantitative metabolomics of primary metabolism. *Anal. Chem.* 81:2135–43

Calvani R, Miccheli A, Capuani G, Tomassini Miccheli A, Puccetti C, et al. 2010. Gut microbiome-derived metabolites characterize a peculiar obese urinary metabotype. *Int. J. Obes.* 34:1095–98

Calvo JA, Daniels TG, Wang X, Paul A, Lin J, et al. 2008. Muscle-specific expression of PPARγ coactivator-1 α improves exercise performance and increases peak oxygen uptake. *J. Appl. Physiol.* 104(5):1304–12

Candela M, Maccaferri S, Turroni S, Carnevali P, Brigidi P. 2010. Functional intestinal microbiome, new frontiers in prebiotic design. *Int. J. Food Microbiol.* 140:93–101

Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, et al. 2009. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am. J. Clin. Nutr.* 90:1236–43

Carmody RN, Wrangham RW. 2009. Cooking and the human commitment to a high-quality diet. *Cold Spring Harb. Symp. Quant. Biol.* 74:427–34

Carriquiry M, Weber WJ, Fahrenkrug SC, Crooker BA. 2009. Hepatic gene expression in multiparous Holstein cows treated with bovine somatotropin and fed n-3 fatty acids in early lactation. *J. Dairy Sci.* 92:4889–900

Carroll IM, Threadgill DW, Threadgill DS. 2009. The gastrointestinal microbiome: a malleable, third genome of mammals. *Mamm. Genome* 20:395–403

Caspi A, Williams B, Kim-Cohen J, Craig IW, Milne BJ, et al. 2007. Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proc. Natl. Acad. Sci. USA* 104:18860–65

Cauchi S, Stutzmann F, Cavalcanti-Proença C, Durand E, Pouta A, et al. 2009. Combined effects of MC4R and FTO common genetic variants on obesity in European general populations. *J. Mol. Med.* 87:537–46

Chandrashekar J, Hoon MA, Ryba NJP, Zuker CS. 2006. The receptors and cells for mammalian taste. *Nature* 444:288–94

Cheng H-W. 2010. Breeding of tomorrow's chickens to improve well-being. *Poult. Sci.* 89:805–13

Cheng IS, Liao SF, Liu KL, Liu HY, Wu CL, et al. 2009. Effect of dietary glycemic index on substrate transporter gene expression in human skeletal muscle after exercise. *Eur. J. Clin. Nutr.* 63:1404–10

Cheung CY, Tso AW, Cheung BM, Xu A, Ong KL, et al. 2010. Obesity susceptibility genetic variants identified from recent genome-wide association studies: implications in a Chinese population. *J. Clin. Endocrinol. Metab.* 95:1395–403

Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. 2010. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nat. Med.* 16:228–31

Collins FS, Green ED, Guttmacher AE, Guyer MS. 2003. A vision for the future of genomics research. *Nature* 422:835–47

Cotton RGH. 2007. Recommendations of the 2006 Human Variome Project meeting. *Nat. Genet.* 39:433–36

Cravatt BF, Simon GM, Yates JR 3rd. 2007. The biological impact of mass-spectrometry-based proteomics. *Nature* 450:991–1000

Crowhurst RN, Gleave AP, MacRae EA, Ampomah-Dwamena C, Atkinson RG, et al. 2008. Analysis of expressed sequence tags from Actinidia: applications of a cross species EST database for gene discovery in the areas of flavor, health, color and ripening. *BMC Genomics* 9:351

Crujeiras AB, Parra D, Milagro FI, Goyenechea E, Larrarte E, et al. 2008. Differential expression of oxidative stress and inflammation related genes in peripheral blood mononuclear cells in response to a low-calorie diet: a nutrigenomics study. *OMICS: J. Integr. Biol.* 12:251–61

Cui K, Huang J, Xing Y, Yu S, Xu C, Peng S. 2008. Mapping QTLs for seedling characteristics under different water supply conditions in rice (*Oryza sativa*). *Physiol. Plant.* 132:53–68

Deshmukh R, Singh A, Jain N, Anand S, Gacche R, et al. 2010. Identification of candidate genes for grain number in rice (*Oryza sativa* L.). *Funct. Integr. Genomics* 10:339–47

Dettmer K, Aronov PA, Hammock BD. 2007. Mass spectrometry-based metabolomics. *Mass Spectrom. Rev.* 26:51–78

Domínguez C, Cabrera L, Rodríguez P, Borges Á, Carrillo F, et al. 2010. Association between glycemic index, glycemic load, and fructose with insulin resistance: the CDC of the Canary Islands study. *Eur. J. Nutr.* Online First: 1–8

Eaton SB, Konner MJ, Cordain L. 2010. Diet-dependent acid load, Paleolithic nutrition, and evolutionary health promotion. *Am. J. Clin. Nutr.* 91:295–97

EFSA (Eur. Food Saf. Auth.). 2008. Panel Working Group on Animal Feeding Trials (2008) Safety and nutritional assessment of GM plants and derived food and feed: the role of animal feeding trials. *Food Chem. Toxicol.* 46:2–70

Ericson UC, Ivarsson MI, Sonestedt E, Gullberg B, Carlson J, et al. 2009. Increased breast cancer risk at high plasma folate concentrations among women with the MTHFR 677T allele. *Am. J. Clin. Nutr.* 90:1380–89

Ferguson JF, Phillips CM, McMonagle J, Pérez-Martínez P, Shaw DI, et al. 2010. NOS3 gene polymorphisms are associated with risk markers of cardiovascular disease, and interact with omega-3 polyunsaturated fatty acids. *Atherosclerosis* 211:539–44

Ford E, Simmons H. 2008. Gluconeogenesis from caecal propionate in the horse. *Br. J. Nutr.* 53:55–60

Forsythe IJ, Wishart DS. 2009. Exploring human metabolites using the human metabolome database. *Curr. Protocols Bioinforma.* 25:14.8-1–45

Friso S, Choi SW. 2002. Gene-nutrient interactions and DNA methylation. *J. Nutr.* 132(Suppl. 8):S2382–87

Froehlich JW, Dodds EE, Barboza M, McJimpsey EL, Seipert RR, et al. 2010. Glycoprotein expression in human milk during lactation. *J. Agric. Food Chem.* 58:6440–48

Fu Q, Zhang P, Tan L, Zhu Z, Ma D, et al. 2010. Analysis of QTLs for yield-related traits in Yuanjiang common wild rice (*Oryza rufipogon Griff.*). *J. Genet. Genomics* 37:147–57

Fukasawa T, Kamei A, Watanabe Y, Koga J, Abe K. 2010. Short-chain fructooligosaccharide regulates hepatic peroxisome proliferator-activated receptor $\alpha$ and farnesoid X receptor target gene expression in rats. *J. Agric. Food Chem.* 58:7007–12

Galván-Portillo M, Oñate-Ocaña LF, Pérez-Pérez GI, Chen J, Herrera-Goepfert R, et al. 2009. Dietary folate and vitamin B12 intake before diagnosis decreases gastric cancer mortality risk among susceptible MTHFR 677TT carriers. *Nutrition* 26:201–8

Gálvez A, Abriouel H, Benomar N, Lucas R. 2010. Microbial antagonists to food-borne pathogens and biocontrol. *Curr. Opin. Biotechnol.* 21:142–48

Garaulet M, Lee YC, Shen J, Parnell LD, Arnett DK, et al. 2009. CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. *Am. J. Clin. Nutr.* 90:1466–75

Garcia-Bailo B, Toguri C, Eny KM, El-Sohemy A. 2009. Genetic variation in taste and its influence on food selection. *OMICS: J. Integr. Biol.* 13:69–80

German JB, Roberts MA, Watkins SM. 2003. Personal metabolomics as a next generation nutritional assessment. *J. Nutr.* 133:4260–66

Glatz JF, Turner PR, Katan MB, Stalenhoef AF, Lewis B. 1993. Hypo- and hyperresponse of serum cholesterol level and low density lipoprotein production and degradation to dietary cholesterol in man. *Ann. N.Y. Acad. Sci.* 676:163–79

Gluckman P, Hanson M, Buklijas T, Low F, Beedle A. 2009. Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat. Rev. Endocrinol.* 5:401–8

Gohil R, Peck G, Sharma P. 2009. The genetics of venous thromboembolism. A meta-analysis involving ~120,000 cases and 180,000 controls. *Thromb. Haemost.* 102:360–70

Han X, Luo Y, Ren Q, Zhang X, Wang F, et al. 2010. Implication of genetic variants near SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, FTO, TCF2, KCNQ1, and WFS1 in type 2 diabetes in a Chinese population. *BMC Med. Genet.* 11:81

Handschin C, Spiegelman B. 2008. The role of exercise and PGC1 in inflammation and chronic disease. *Nature* 454:463–69

Harvey L, McArdle H. 2008. Biomarkers of copper status: a brief update. *Br. J. Nutr.* 99:10–13

Hathout Y. 2007. Approaches to the study of the cell secretome. *Expert Rev. Proteomics* 4:239–48

Hesketh J. 2008. Nutrigenomics and selenium: gene expression patterns, physiological targets, and genetics. *Annu. Rev. Nutr.* 28:157–77

Hevezi P, Moyer BD, Lu M, Gao N, White E, et al. 2009. Genome-wide analysis of gene expression in primate taste buds reveals links to diverse processes. *PLoS One* 4:e6395

Hildebrandt M, Hoffmann C, Sherrill-Mix S, Keilbaugh S, Hamady M, et al. 2009. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* 137:1716–24

Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, et al. 2009. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc. Natl. Acad. Sci. USA* 106:9362–67

Hofman MK, Weggemans RM, Zock PL, Schouten EG, Katan MB, Princen HM. 2004. CYP7A1 A-278C polymorphism affects the response of plasma lipids after dietary cholesterol or cafestol interventions in humans. *J. Nutr.* 134:2200–4

Holmes E, Wilson ID, Nicholson JK. 2008. Metabolic phenotyping in health and disease. *Cell* 134:714–17

Hulgan T, Tebas P, Canter J, Mulligan K, Haas D, et al. 2008. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy. *J. Infect. Dis.* 197:858–66

Hustad S, Nedrebø BG, Ueland PM, Schneede J, Vollset SE, et al. 2004. Phenotypic expression of the methylenetetrahydrofolate reductase 677C- > T polymorphism and flavin cofactor availability in thyroid dysfunction. *Am. J. Clin. Nutr.* 80:1050–57

Ide T, Nakashima Y, Iida H, Yasumoto S, Katsuta M. 2009. Lipid metabolism and nutrigenomics–impact of sesame lignans on gene expression profiles and fatty acid oxidation in rat liver. *Forum Nutr.* 61:10–24

Ilanne-Parikka P, Laaksonen DE, Eriksson JG, Lakka TA, Lindström J, et al. 2010. Leisure-time physical activity and the metabolic syndrome in the Finnish diabetes prevention study. *Diabetes Care* 33:1610–17

Issaq HJ, Van QN, Waybright TJ, Muschik GM, Veenstra TD. 2009. Analytical and statistical approaches to metabolomics research. *J. Sep. Sci.* 32:2183–99

Joffe Y, van der Merwe L, Carstens M, Collins M, Jennings C, et al. 2010. Tumor necrosis factor-alpha gene-308 G/A polymorphism modulates the relationship between dietary fat intake, serum lipids, and obesity risk in black South African women. *J. Nutr.* 140:901–7

Jönsson T, Granfeldt Y, Ahrén B, Branell U-C, Pålsson G, et al. 2009. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. *Cardiovasc. Diabetol.* 8:35

Kallio P, Kolehmainen M, Laaksonen DE, Kekäläinen J, Salopuro T, 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.* 85:1417–27

Kanwar J, Kanwar R, Sun X, Punj V, Matta H, et al. 2009. Molecular and biotechnological advances in milk proteins in relation to human health. *Curr. Protein Pept. Sci.* 10:308–38

Katz-Jaffe MG, McReynolds S, Gardner DK, Schoolcraft WB. 2009. The role of proteomics in defining the human embryonic secretome. *Mol. Hum. Reprod.* 15:271–77

Kim KC, Friso S, Choi SW. 2009. DNA methylation, an epigenetic mechanism connecting folate to healthy embryonic development and aging. *J. Nutr. Biochem.* 20:917–26

Kogel KH, Voll LM, Schäfer P, Jansen C, Wu Y, et al. 2010. Transcriptome and metabolome profiling of field-grown transgenic barley lack induced differences but show cultivar-specific variances. *Proc. Natl. Acad. Sci. USA* 107:6198–203

Kolberg JA, Jørgensen T, Gerwien RW, Hamren S, McKenna MP, et al. 2009. Development of a type 2 diabetes risk model from a panel of serum biomarkers from the Inter99 cohort. *Diabetes Care* 32:1207–12

Konstantinidou V, Covas MI, Muñoz-Aguayo D, Khymenets O, de la Torre R, et al. 2010. In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: a randomized controlled trial. *FASEB J.* 24:2546–57

Laaksonen MM, Outila TA, Kärkkäinen MU, Kemi VE, Rita HJ, et al. 2009. Associations of vitamin D receptor, calcium-sensing receptor and parathyroid hormone gene polymorphisms with calcium homeostasis and peripheral bone density in adult Finns. *J. Nutrigenet. Nutrigenomics* 2:55–63

Lagaert S, Beliën T, Volckaert G. 2009. Plant cell walls: protecting the barrier from degradation by microbial enzymes. *Semin. Cell Dev. Biol.* 20:1064–73

Lankinen M, Schwab U, Gopalacharyulu PV, Seppänen-Laakso T, Yetukuri L, et al. 2010. Dietary carbohydrate modification alters serum metabolic profiles in individuals with the metabolic syndrome. *Nutr. Metab. Cardiovasc. Dis.* 20:249–57

Lemay D, Lynn D, Martin W, Neville M, Casey T, et al. 2009. The bovine lactation genome: insights into the evolution of mammalian milk. *Genome Biol.* 10:R43

Leung WC, Hessel S, Meplan C, Flint J, Oberhauser V, et al. 2009. Two common single nucleotide polymorphisms in the gene encoding beta-carotene 15,15′-monoxygenase alter {beta}-carotene metabolism in female volunteers. *FASEB J.* 23:1041–53

Lewis KD, Burton-Freeman BM. 2010. The role of innovation and technology in meeting individual nutritional needs. *J. Nutr.* 140:S26–36

Liman ER. 2006. Use it or lose it: molecular evolution of sensory signaling in primates. *Pflügers Arch. Eur. J. Physiol.* 453:125–31

LoCascio RG, Ninonuevo MR, Freeman SL, Sela DA, Grimm R, et al. 2007. Glycoprofiling of bifidobacterial consumption of human milk oligosaccharides demonstrates strain specific, preferential consumption of small chain glycans secreted in early human lactation. *J. Agric. Food Chem.* 55:8914–19

Lönnerdal B. 2006. Recombinant human milk proteins. *Nestlé Nutr. Workshop Ser. Pediatr. Program* 58:207–15

MacDonald T, Voessenkamper A, Di Sabatino A. 2009. Antigen presenting cells and T cell interactions in the gastrointestinal tract. *Mol. Nutr. Food Res.* 53:947–51

Mäkeläinen H, Hasselwander O, Rautonen N, Ouwehand A. 2009. Panose, a new prebiotic candidate. *Lett. Appl. Microbiol.* 49:666–72

Martin FP, Dumas ME, Wang Y, Legido-Quigley C, Yap IK, et al. 2007. A top-down systems biology view of microbiome-mammalian metabolic interactions in a mouse model. *Mol. Syst. Biol.* 3:112

Martinez I, Wallace G, Zhang C, Legge R, Benson AK, et al. 2009. Diet-induced metabolic improvements in a hamster model of hypercholesterolemia are strongly linked to alterations of the gut microbiota. *Appl. Environ. Microbiol.* 75:4175–84

Martinez JA, Corbalán MS, Sánchez-Villegas A, Forga L, Marti A, Martínez-González MA. 2003. Obesity risk is associated with carbohydrate intake in women carrying the Gln27Glu beta2-adrenoceptor polymorphism. *J. Nutr.* 133:2549–54

McCabe-Sellers B, Chenard C, Lovera D, Champagne C, Bogle M, Kaput J. 2009. Readiness of food composition databases and food component analysis systems for nutrigenomics. *J. Food Compos. Anal.* 22:S57–62

Mehedint MG, Niculescu MD, Craciunescu CN, Zeisel SH. 2010. Choline deficiency alters global histone methylation and epigenetic marking at the Re1 site of the calbindin 1 gene. *FASEB J.* 24:184–95

Messika A, Kaluski D, Lev E, Iakobishvili Z, Shohat M, et al. 2010. Nutrigenetic impact of daily folate intake on plasma homocysteine and folate levels in patients with different methylenetetrahydrofolate reductase genotypes. *Eur. J. Cardiovasc. Prev. Rehabil.* Published Ahead of Print: 10.1097/HJR.1090b1013e32833a32831cb32835

Miettinen TA, Kesäniemi Y. 1989. Cholesterol absorption: regulation of cholesterol synthesis and elimination and within-population variations of serum cholesterol levels. *Am. J. Clin. Nutr.* 49:629–35

Mikhak B, Hunter D, Spiegelman D, Platz E, Wu K, et al. 2008. Manganese superoxide dismutase (MnSOD) gene polymorphism, interactions with carotenoid levels and prostate cancer risk. *Carcinogenesis* 29:2335–40

Minihane AM. 2010. Fatty acid–genotype interactions and cardiovascular risk. *Prostaglandins Leukot. Essent. Fat. Acids* 82:259–64

Mischak H, Apweiler R, Banks RE, Conaway M, Coon J, et al. 2007. Clinical proteomics: a need to define the field and to begin to set adequate standards. *Proteomics Clin. Appl.* 1:148–56

Mok K, Pettersson J, Orrenius S, Svanborg C. 2007. HAMLET, protein folding, and tumor cell death. *Biochem. Biophys. Res. Commun.* 354:1–7

Montmayeur J-P, le Coutre J, eds. 2009. *Fat Detection: Taste, Texture, and Post Ingestive Effects*. Boca Raton, FL: CRC

Murase T, Haramizu S, Ota N, Hase T. 2008. Tea catechin ingestion combined with habitual exercise suppresses the aging-associated decline in physical performance in senescence-accelerated mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 295:R281

Narkar VA, Downes M, Yu RT, Embler E, Wang YX, et al. 2008. AMPK and PPARdelta agonists are exercise mimetics. *Cell* 134:405–15

Näslund J, Fikse WF, Pielberg GR, Lundén A. 2008. Frequency and effect of the bovine acyl-CoA: diacylglycerol acyltransferase 1 (DGAT1) K232A polymorphism in Swedish dairy cattle. *J. Dairy Sci.* 91:2127–34

Navarro-Allende A, Khataan N, El-Sohemy A. 2008. Impact of genetic and environmental determinants of taste with food preferences in older adults. *J. Nutrit. Elder.* 27:267–76

Neish AS. 2009. Microbes in gastrointestinal health and disease. *Gastroenterology* 136:65–80

Nguyen D, Arpat A, Wang N, Carroll R. 2002. DNA microarray experiments: biological and technological aspects. *Biometrics* 58:701–17

Ntalla I, Dedoussis G, Yannakoulia M, Smart M, Louizou E, et al. 2009. ADIPOQ gene polymorphism rs1501299 interacts with fibre intake to affect adiponectin concentration in children: the GENe–Diet Attica Investigation on childhood obesity. *Eur. J. Nutr.* 48:493–97

O'Keefe SJ. 2008. Nutrition and colonic health: the critical role of the microbiota. *Curr. Opin. Gastroenterol.* 24:51–58

Omenn GS. 2010. Evolution in health and medicine Sackler colloquium: evolution and public health. *Proc. Natl. Acad. Sci. USA* 107(Suppl. 1):1702–9

Ordovas JM. 2009. Genetic influences on blood lipids and cardiovascular disease risk: tools for primary prevention. *Am. J. Clin. Nutr.* 89:S1509–17

O'Sullivan TA, Bremner AP, O'Neill S, Lyons-Wall P. 2010. Comparison of multiple and novel measures of dietary glycemic carbohydrate with insulin resistant status in older women. *Nutr. Metab.* 7:25

Panagiotou G, Nielsen J. 2009. Nutritional systems biology: definitions and approaches. *Annu. Rev. Nutr.* 29:329–39

Papathanasopoulos A, Camilleri M. 2009. Dietary fiber supplements: effects in obesity and metabolic syndrome and relationship to gastrointestinal functions. *Gastroenterology* 138:65–72

Pavlou M, Diamandis E. 2010. The cancer cell secretome: A good source for discovering biomarkers? *J. Proteomics* 73(10):1896–1906

Peppa M, Koliaki C, Nikolopoulos P, Raptis SA. 2010. Skeletal muscle insulin resistance in endocrine disease. *J. Biomed. Biotechnol.* 2010:527850

Pérez-Martínez P, Pérez-Jiménez F, Bellido C, Ordovas JM, Moreno JA, et al. 2005. A polymorphism exon 1 variant at the locus of the scavenger receptor class B type I (SCARB1) gene is associated with differences in insulin sensitivity in healthy people during the consumption of an olive oil-rich diet. *J. Clin. Endocrinol. Metab.* 90:2297–300

Petrovici D, Ritson C. 2006. Factors influencing consumer dietary health preventative behaviours. *BMC Public Health* 6:222

Polesani M, Bortesi L, Ferrarini A, Zamboni A, Fasoli M, et al. 2010. General and species-specific transcriptional responses to downy mildew infection in a susceptible (*Vitis vinifera*) and a resistant (*V. riparia*) grapevine species. *BMC Genomics* 11:117

Popkin BM. 2006. Global nutrition dynamics: The world is shifting rapidly toward a diet linked with noncommunicable diseases. *Am. J. Clin. Nutr.* 84:289–98

Poutanen K, Flander L, Katina K. 2009. Sourdough and cereal fermentation in a nutritional perspective. *Food Microbiol.* 26:693–99

Prescott S, Smith P, Tang M, Palmer D, Sinn J, et al. 2008. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. *Pediatr. Allergy Immunol.* 19:375–80

Priego T, Sánchez J, Picó C, Palou A. 2008. Sex-differential expression of metabolism-related genes in response to a high-fat diet. *Obesity* 16:819–26

Puchau B, Zulet MA, de Echávarri AG, Hermsdorff HH, Martinez JA. 2009. Dietary total antioxidant capacity: a novel indicator of diet quality in healthy young adults. *J. Am. Coll. Nutr.* 28:648–56

Puiggros F, Sala E, Vaqué M, Ardévol A, Blay M, et al. 2009. In vivo, in vitro, and in silico studies of Cu/Zn-superoxide dismutase regulation by molecules in grape seed procyanidin extract. *J. Agric. Food Chem.* 57:3934–42

Quesada H, Del Bas J, Pajuelo D, Díaz S, Fernandez-Larrea J, et al. 2009. Grape seed proanthocyanidins correct dyslipidemia associated with a high-fat diet in rats and repress genes controlling lipogenesis and VLDL assembling in liver. *Int. J. Obes.* 33:1007–12

Radonjic M, de Haan JR, van Erk MJ, van Dijk KW, van den Berg SA, et al. 2009. Genome-wide mRNA expression analysis of hepatic adaptation to high-fat diets reveals switch from an inflammatory to steatotic transcriptional program. *PLoS One* 4:e6646

Reale A, Konietzny U, Coppola R, Sorrentino E, Greiner R. 2007. The importance of lactic acid bacteria for phytate degradation during cereal dough fermentation. *J. Agric. Food Chem.* 55:2993–97

Refsum H, Smith AD. 2008. Are we ready for mandatory fortification with vitamin B-12? *Am. J. Clin. Nutr.* 88:253–54

Regnier FE, Skates SJ, Mesri M, Rodriguez H, Tezak Z, et al. 2010. Protein-based multiplex assays: mock presubmissions to the U.S. Food and Drug Administration. *Clin. Chem.* 56:165–71

Rezzi S, Martin FP, Kochhar S. 2008. Defining personal nutrition and metabolic health through metabonomics. *Ernst Schering Found. Symp. Proc.* 4:251–64

Rifai N, Gillette M, Carr S. 2006. Protein biomarker discovery and validation: the long and uncertain path to clinical utility. *Nat. Biotechnol.* 24:971–83

Roy R, Ordovas L, Zaragoza P, Romero A, Moreno C, et al. 2006. Association of polymorphisms in the bovine FASN gene with milk-fat content. *Anim. Genet.* 37:215–18

Sanders ME, Marco ML. 2010. Food formats for effective delivery of probiotics. *Annu. Rev. Food Sci. Technol.* 1:65–85

Sanderson LM, Degenhardt T, Koppen A, Kalkhoven E, Desvergne B, et al. 2009. Peroxisome proliferator-activated receptor beta/delta (PPAR beta/delta) but not PPARalpha serves as a plasma free fatty acid sensor in liver. *Mol. Cell. Biol.* 29:6257–67

Sanderson LM, de Groot PJ, Hooiveld GJ, Koppen A, Kalkhoven E, et al. 2008. Effect of synthetic dietary triglycerides: a novel research paradigm for nutrigenomics. *PLoS One* 3:e1681

Sela DA, Chapman J, Adeuya A, Kim JH, Chen F, et al. 2008. The genome sequence of *Bifidobacterium longum* subsp. *infantis* reveals adaptations for milk utilization within the infant microbiome. *Proc. Natl. Acad. Sci. USA* 105:18964–69

Seow A, Yuan JM, Sun CL, Van Den Berg D, Lee HP, Yu MC. 2002. Dietary isothiocyanates, glutathione S-transferase polymorphisms and colorectal cancer risk in the Singapore Chinese Health Study. *Carcinogenesis* 23:2055–61

Sieuwerts S, de Bok FA, Hugenholtz J, van Hylckama Vlieg JE. 2008. Unraveling microbial interactions in food fermentations: from classical to genomics approaches. *Appl. Environ. Microbiol.* 74:4997–5007

Simopoulos A. 2010. Nutrigenetics/nutrigenomics. *Annu. Rev. Public Health* 31:53–68

Sinotte M, Diorio C, Bérubé S, Pollak M, Brisson J. 2009. Genetic polymorphisms of the vitamin D binding protein and plasma concentrations of 25-hydroxyvitamin D in premenopausal women. *Am. J. Clin. Nutr.* 89:634–40

Smilowitz JT, Wiest MM, Watkins SM, Teegarden D, Zemel MB, et al. 2009. Lipid metabolism predicts changes in body composition during energy restriction in overweight humans. *J. Nutr.* 139:222–29

Stevenson EJ, Astbury NM, Simpson EJ, Taylor MA, Macdonald IA. 2009. Fat oxidation during exercise and satiety during recovery are increased following a low-glycemic index breakfast in sedentary women. *J. Nutr.* 139:890–97

Suh JW, Baek SH, Park JS, Kang HJ, Chae IH, et al. 2009. Vitamin K epoxide reductase complex subunit 1 gene polymorphism is associated with atherothrombotic complication after drug-eluting stent implantation: 2-center prospective cohort study. *Am. Heart J.* 157:908–12

Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F. 2010. Physical activity at midlife in relation to successful survival in women at age 70 years or older. *Arch. Intern. Med.* 170:194–201

Syvänen A. 2001. Accessing genetic variation: genotyping single nucleotide polymorphisms. *Nat. Rev. Genet.* 2:930–42

Tanaka T, Shen J, Abecasis GR, Kisialiou A, Ordovas JM, et al. 2009. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. *PLoS Genet.* 5:e1000338

Tang L, Wu JJ, Ma Q, Cui T, Andreopoulos FM, et al. 2010. Human lactoferrin stimulates skin keratinocyte function and wound re-epithelialization. *Br. J. Dermatol.* 163:38–47

Tang Z, Zhang Y, Stewart AF, Geng M, Tang X, et al. 2010. High-level expression, purification and antibacterial activity of bovine lactoferricin and lactoferrampin in *Photorhabdus luminescens*. *Protein Expr. Purif.* 73:132–39

Thalacker-Mercer AE, Fleet JC, Craig BA, Campbell WW. 2010. The skeletal muscle transcript profile reflects accommodative responses to inadequate protein intake in younger and older males. *J. Nutr. Biochem.* Epub ahead of print

Turnbaugh PJ, Gordon JI. 2009. The core gut microbiome, energy balance and obesity. *J. Physiol.* 587:4153–58

Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, et al. 2008. A core gut microbiome in obese and lean twins. *Nature* 457:480–84

Turnbaugh PJ, Ley R, Hamady M, Fraser-Liggett C, Knight R, Gordon J. 2007. The human microbiome project. *Nature* 449:804–10

van Hulzen KJE, Sprong RC, Van Der Meer R, van Arendonk JAM. 2009. Genetic and nongenetic variation in concentration of selenium, calcium, potassium, zinc, magnesium, and phosphorus in milk of Dutch Holstein-Friesian cows. *J. Dairy Sci.* 92:5754–59

Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, et al. 2001. The sequence of the human genome. *Science* 291:1304–51

Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, et al. 2010. Metabolic syndrome and altered gut microbiota in mice lacking toll-like receptor 5. *Science* 328:228–31

Vinaixa M, Rodríguez M, Rull A, Beltrán R, Bladé C, et al. 2010. Metabolomic assessment of the effect of dietary cholesterol in the progressive development of fatty liver disease. *J. Proteome Res.* 9:2527–38

Vrieze A, Holleman F, Zoetendal E, de Vos WM, Hoekstra JB, Nieuwdorp M. 2010. The environment within: how gut microbiota may influence metabolism and body composition. *Diabetologia* 53:606–13

Walters R, Jacquemont S, Valsesia A, de Smith A, Martinet D, et al. 2010. A new highly penetrant form of obesity due to deletions on chromosome 16p11. 2. *Nature* 463:671–75

Wang J, Chen L, Li P, Li X, Zhou H, et al. 2008. Gene expression is altered in piglet small intestine by weaning and dietary glutamine supplementation. *J. Nutr.* 138:1025–32

Warodomwichit D, Shen J, Arnett DK, Tsai MY, Kabagambe EK, et al. 2009. ADIPOQ polymorphisms, monounsaturated fatty acids, and obesity risk: the GOLDN study. *Obesity* 17:510–17

Watzke HJ, German JB. 2009. Personalizing foods. In *An Integrated Approach to New Food Product Development*, ed. HR Moskowitz, S Saguy, T Straus, Chapter 9, pp. 133–73. Boca Raton, FL: CRC

Wells JCK, Stock JT. 2007. The biology of the colonizing ape. *Yearb. Phys. Anthropol.* 50:191–222

Wen J, Rönn T, Olsson A, Yang Z, Lu B, et al. 2010. Investigation of type 2 diabetes risk alleles support *CDKN2A/B*, *CDKAL1*, and *TCF7L2* as susceptibility genes in a Han Chinese cohort. *PLoS One* 5(2):e9153

Wenz T, Rossi SG, Rotundo RL, Spiegelman BM, Moraes CT. 2009. Increased muscle PGC-1α expression protects from sarcopenia and metabolic disease during aging. *Proc. Natl. Acad. Sci. USA* 106:20405–10

Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, et al. 2009. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc. Natl. Acad. Sci. USA* 106:3698–703

Winkels RM, Brouwer IA, Clarke R, Katan MB, Verhoef P. 2008. Bread cofortified with folic acid and vitamin B-12 improves the folate and vitamin B-12 status of healthy older people: a randomized controlled trial. *Am. J. Clin. Nutr.* 88:348–55

Winnike JH, Li Z, Wright FA, Macdonald JM, O'Connell TM, Watkins PB. 2010. Use of pharmacometabonomics for early prediction of acetaminophen-induced hepatotoxicity in humans. *Clin. Pharmacol. Ther.* 88:45–51

Yap IKS, Angley M, Veselkov KA, Holmes E, Lindon JC, Nicholson JK. 2010. Urinary metabolic phenotyping differentiates children with autism from their unaffected siblings and age-matched controls. *J. Proteome Res.* 9:2996–3004

Zavaleta N, Figueroa D, Rivera J, Sánchez J, Alfaro S, Lönnerdal B. 2007. Efficacy of rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme in Peruvian children with acute diarrhea. *J. Pediatr. Gastroenterol. Nutr.* 44:258–64

Zeisel SH. 2007. Nutrigenomics and metabolomics will change clinical nutrition and public health practice: insights from studies on dietary requirements for choline. *Am. J. Clin. Nutr.* 86:542–48

Zeisel SH. 2009. Epigenetic mechanisms for nutrition determinants of later health outcomes. *Am. J. Clin. Nutr.* 89:S1488–93

Zerhouni E. 2003. The NIH roadmap. *Science* 302:63–72

Zhang G, Gu C, Wang D. 2009. Molecular mapping of soybean aphid resistance genes in PI 567541B. *Theor. Appl. Genet.* 118:473–82

Zhang N, Yu S, Tiller P, Yeh S, Mahan E, Emary W. 2009. Quantitation of small molecules using high-resolution accurate mass spectrometers-a different approach for analysis of biological samples. *Rapid Commun. Mass Spectrom.* 23:1085–94

Zhang W, Dolan M. 2010. Impact of the 1000 Genomes Project on the next wave of pharmacogenomic discovery. *Pharmacogenomics* 11:249–56

Zivkovic AM, German JB. 2009. Metabolomics for assessment of nutritional status. *Curr. Opin. Clin. Nutr. Metab. Care* 12:501–7

Zivkovic AM, German JB, Lebrilla CB, Mills DA. 2010. Human milk glycobiome and its impact on the infant gastrointestinal microbiota. *Proc. Natl. Acad. Sci. USA* Epub ahead of print

Zivkovic AM, Wiest MM, Nguyen U, Nording ML, Watkins SM, German JB. 2009. Assessing individual metabolic responsiveness to a lipid challenge using a targeted metabolomic approach. *Metabolomics* 5:209–18

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**Errata**

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