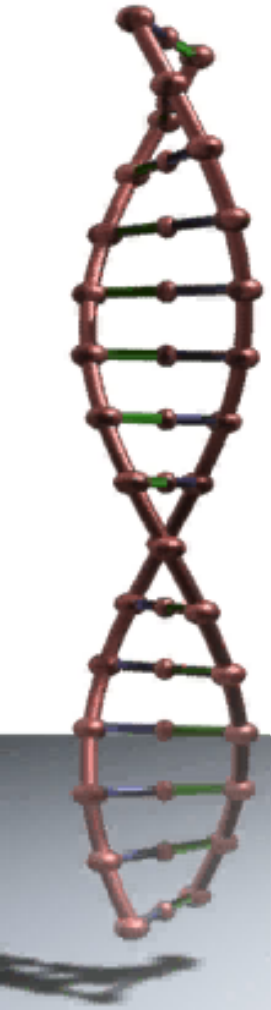

Epigenetics, Genomics and Nutrigenomics:

A Nutrition Perspective

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Food & Spirit™
Fellow and Board Member, American College of Nutrition
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Faculty Disclosure

Commercial Interest	Nature of Relevant Financial Relationship (Include all those that apply)	
	What was received	**For what role**
• Genova Diagnostics	• Honoraria	• Consultant

Presentation Learning Objectives

After participating in this presentation, learners should be better able to:

- Understand the scientific concepts that define nutrigenomics
- Identify how these concepts may be applied in clinical practice

Overview

- Nutrition in the 21st Century
- The Science of Nutrigenomics
- Epigenomics
- Foodomics
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Nutrition is complex with many variables

- 200 decisions every day about food/eating
- We eat ~1.5 kg food & drink ~2 L liquid/day;
- About 40 essential nutrients are known;
- 10,000+ phytonutrients
- Thousands of unknown/known compounds in foods without known biological functions;
- About 10^{13} cells in the body & about 10^{14} bacteria in the GI tract;
- Mostly unknown and complicated interplay between diet and the microbiome;
- Many organs & some hundreds of cell types are found in the body;
- About 25,000 genes in human cells;
- Human genome includes 3 billion base pairs;
- Some millions single nucleotide polymorphisms (SNPs);
- A large epigenetic variation between individuals due to environmental factors;
- About 100,000 transcripts (mRNA);
- About 100,000 proteins;
- About 1000 lipids & thousands of water-soluble metabolites.

Nutrients. 2012 Dec; 4(12): 1898–1944.

21st Century Overhauls in Scientific Thinking

Forecasting Nutrition Research in 2020

1. Global food security
2. Microbiome/microflora
3. **Gene expression**
4. Energy metabolism
5. Cancer
6. Inflammation
7. Aging
8. Bioengineering
9. Nutrition education
10. Interdisciplinary and cross-discipline collaboration

Commentary

Forecasting Nutrition Research in 2020

Robert M. Hackman, PhD, Bharat B. Aggarwal, PhD, Rhona S. Applebaum, PhD, Ralph W. deVere White, MD, Michael A. Dubick, PhD, David Heber, MD, PhD, Toshinori Ito, MD, PhD, Guy H. Johnson, PhD, Carl L. Keen, PhD, Barbara L. Winters, PhD, Sidney J. Stohs, PhD

Department of Nutrition (R.M.H., C.L.K.), and Department of Internal Medicine, University of California, Davis, California (C.L.K.); Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas (B.B.A.); The Coca-Cola Co., Atlanta, Georgia (R.S.A.); Department of Urology and UC Davis Comprehensive Cancer Center, Sacramento, California (R.W.dV.W.); Institute for Surgical Research, U.S. Army, San Antonio, Texas (M.A.D.); Department of Medicine and Department of Public Health, University of California, Los Angeles, California (D.H.); Department of Complementary and Alternative Medicine, Osaka University Graduate School of Medicine, Osaka, JAPAN (T.I.); Nutrition Solutions, Inc., Minneapolis, Minnesota (G.H.J.); Campbell Soup Co., Camden, New Jersey (B.L.W.); School of Pharmacy and Health Professions, Creighton University, Omaha, Nebraska (S.J.S.)

Keywords: clinical nutrition, obesity, microbiome, gene expression, nutrition education, public health

Advances in nutrition during the past century have helped untold numbers of people around the world enjoy healthier and longer lives and be more productive members of society. These advances include the identification of numerous essential nutrients, the identification of common disease states that can arise as a consequence of deficiencies of these essential nutrients, the use of food fortification to correct common deficiencies in the diet, and improvements in agricultural practices and food processing that have resulted in marked advances in food safety and quality. However, many challenges still remain. To a significant extent, these challenges reflect expectations of what constitutes a good diet and what the result of following food guidelines will produce. Moving forward in time in an era of limited economic resources and expanding populations, a critical focus is required to direct attention to the most pressing challenges with the greatest need and opportunity for return on investment. Balancing the desire for quick and effective solutions with the slow, steady, and incremental nature of nutrition research is a struggle confronting academia, industry, and government.

To address these challenges, a group of distinguished nutrition scientists gathered for a panel symposium in celebration of the 10th anniversary of the Kosuna Distinguished Lecture in Nutrition at the University of California, Davis. Eight of the panelists were previous Kosuna Distinguished Lecturers. The symposium discussion revolved around 2 questions that were posed to the panel members prior to the meeting: (1) What will be the "hottest" areas of nutrition research in 2020 and (2) If one were just starting a career in nutrition, what would be a reasonable focus for one's work? A distillation of the discussion follows, organized from the most global to the most individual topics, with some concluding thoughts on the nature of nutrition research.

WHAT WILL BE THE "HOTTEST" AREAS OF NUTRITION RESEARCH IN 2020?

Global Food Security

Collectively, global food security, food safety, and sustainability warrant urgent action and will be among the most pressing topics in nutrition research in 2020. Global concerns regarding ways to safely feed more than 8 billion people on Earth in 2020 in the face of global climate change will likely overshadow the microcosm of issues on a local or national level [1]. Sufficient food may be available to feed everyone on Earth in 2020, but economic and political issues will likely hinder appropriate distribution [2]. Water is an essential nutrient, and access to clean water is also among the most pressing global health challenges.

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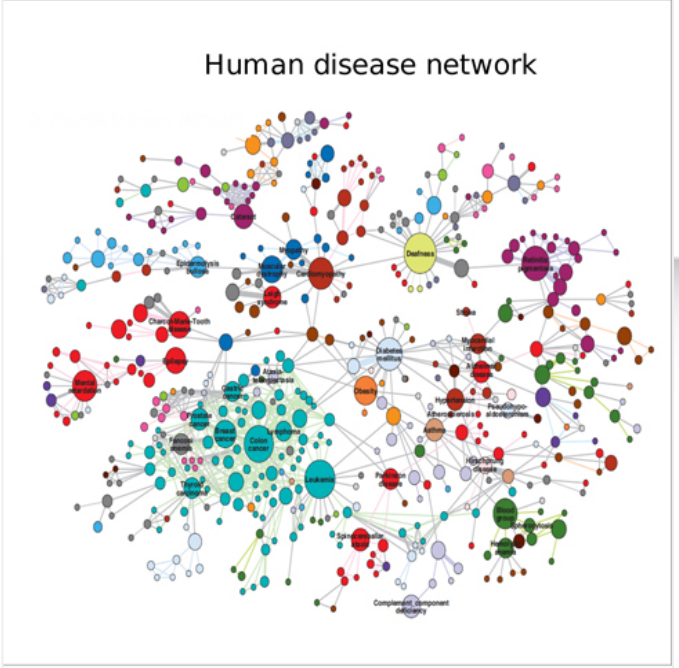
Journal of the American College of Nutrition, Vol. 33, No. 4, 340–346 (2014)
Published with license by Taylor & Francis Group, LLC

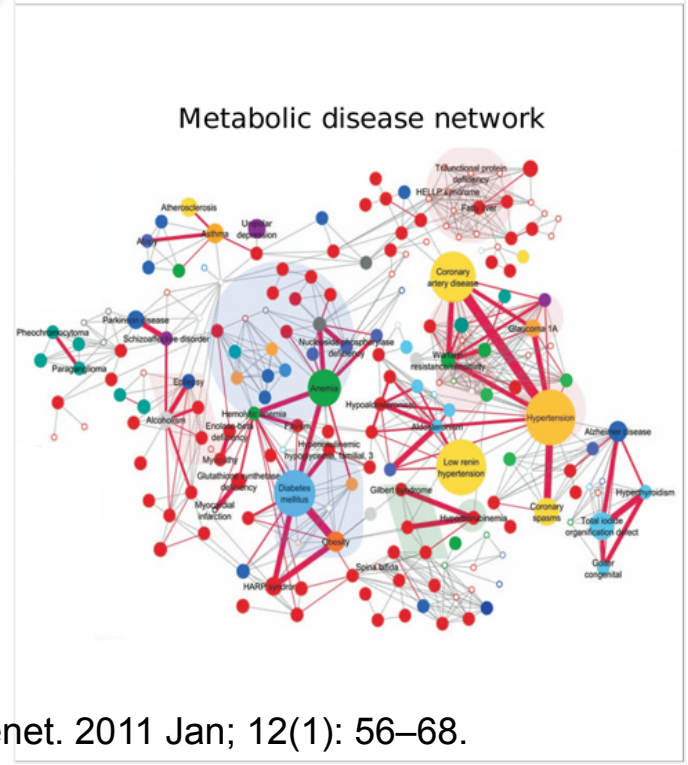
J Am Coll Nutr. 2014;33(4):340-6. doi: 10.1080/07315724.2014.943113. Epub 2014 Aug 21.

Forecasting Nutrition Research in 2020

Gene Expression

- Human genome
- Microflora microbiome
- Nutrient influences (phytochemicals)
- Transgenerational effects





The Human Disease Network

Systems Biology Network Medicine

Nat Rev Genet. 2011 Jan; 12(1): 56–68.

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Food Is…

- Medicine
- Connection
- Information

Nutrition in Clinical Practice 20:75-87, February 2005

Food and Eating Communicate to Genes

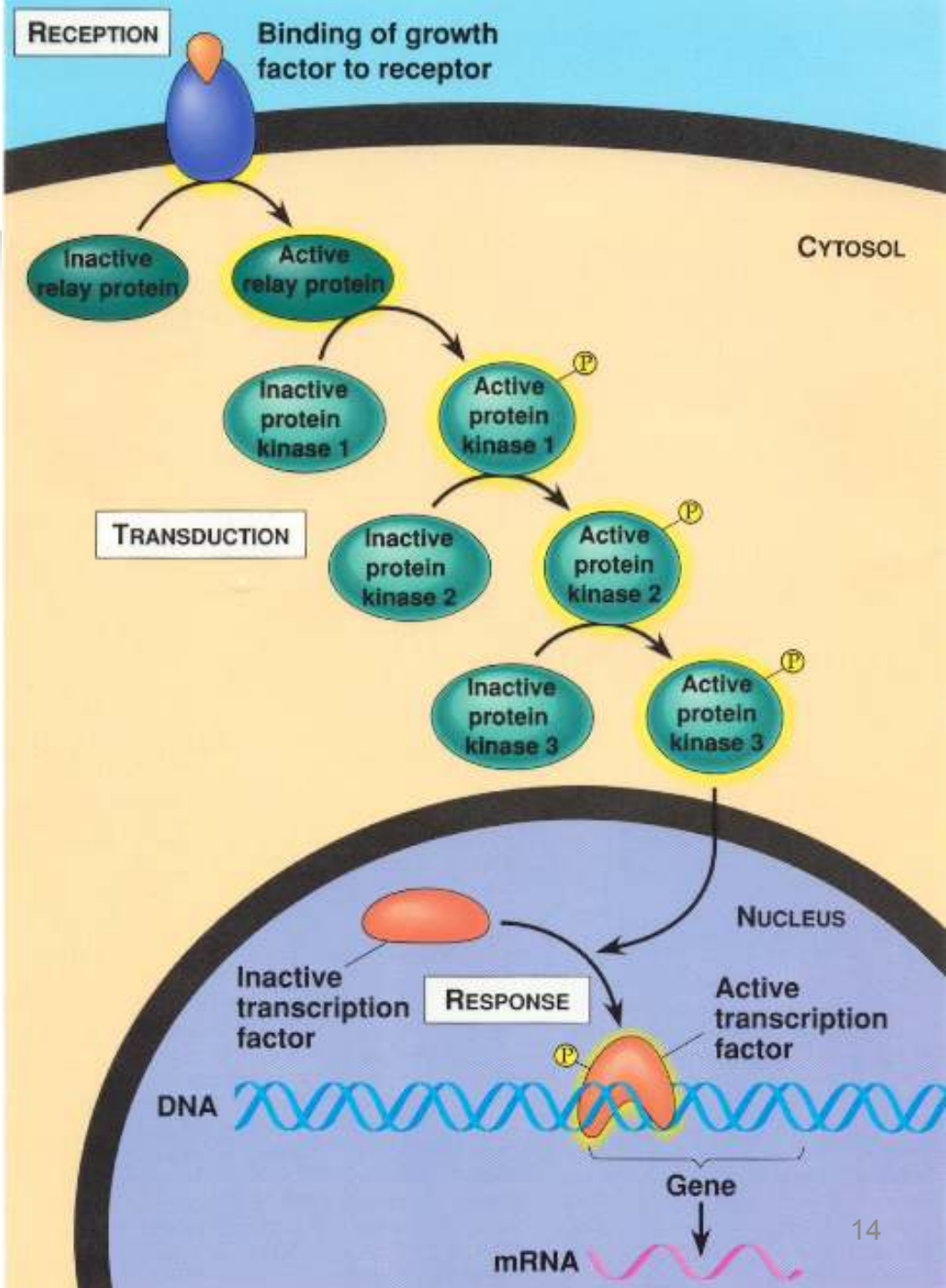
"…we are witnessing food being redefined as **"information"** that alters cellular function in the post-prandial state…The message is translated to the cell through a **complex web of enzymes called kinases**, which, through their **activation or inhibition**, alter genetic expression of a cell and change its function in response to the message."

Bland, J. What role has nutrition been playing in our health? The xenohormesis connection. *Integrative Medicine* 6(3); Jun/Jul 2007.

Graphic: Environ Health Perspect. 2007 December; 115(12): A582–A589.

Cell Signaling Cascade

Food sends signals to genes



http://www.uic.edu/classes/bios/bios100/mike/spring2003/lect07.htm

Nutrigenomics = Food is Information

- Gene expression or DNA is modified by the action of nutrients and bioactive food components.
- Modification can occur directly or indirectly.
- Chronic disease onset, incidence, progression, and/or severity influenced by diet-regulated genes and their common variants.

Nutrition in Clinical Practice 20:75-87, February 2005

The Many Layers of Food and Informational Signals

- SAD vs. Mediterranean Diet
  - Organically grown or conventional?
  - GMO or non-GMO?
  - Combinations of food
  - Eating circumstances

Nutrition in Clinical Practice 20:75-87, February 2005

Nutrigenomics allows us to question current dogma

- Food is more than calories.
- A calorie is a calorie.
- Bad foods give you disease unless you have genes to intervene and protect you.

New concepts to ‘digest’

- Food is full of informational signals.
- A calorie is to be judged upon the context it comes from.
- We are continually interacting with dietary signals, in which certain foods enhance a beneficial, neutral or negative effect on genes.

All carbohydrates are not created equal.

- Study with subjects on two different diets of exactly the same number of calories and grams of CHO
- Different types of CHO
  - Rye
  - Oat, wheat and potato
- Needle biopsy of adipose tissue revealed an upregulation of inflammatory and stress genes in the high glycemic (o/w/p group)
- “Dietary carbohydrate modification with rye vs. oat, wheat and potato differentially modulates the gene expression profile in abdominal subcutaneous adipose tissue, even the absence of weight loss.”

Am J Clin Nutr. 2007 May;85(5):1417-27.

The power of non-nutritive phytonutrients

- Acute dietary study
- 2-day standard phytochemical diet
- 2-day low-phytochemical diet
- No significant differences were found between the 3 diets for total energy, protein, carbohydrate, or fat intakes.
- “The results indicate that a varying phytochemical consumption can contribute to differences in urinary metabolic profiles.”

Am J Clin Nutr. 2007 Dec;86(6):1687-93.

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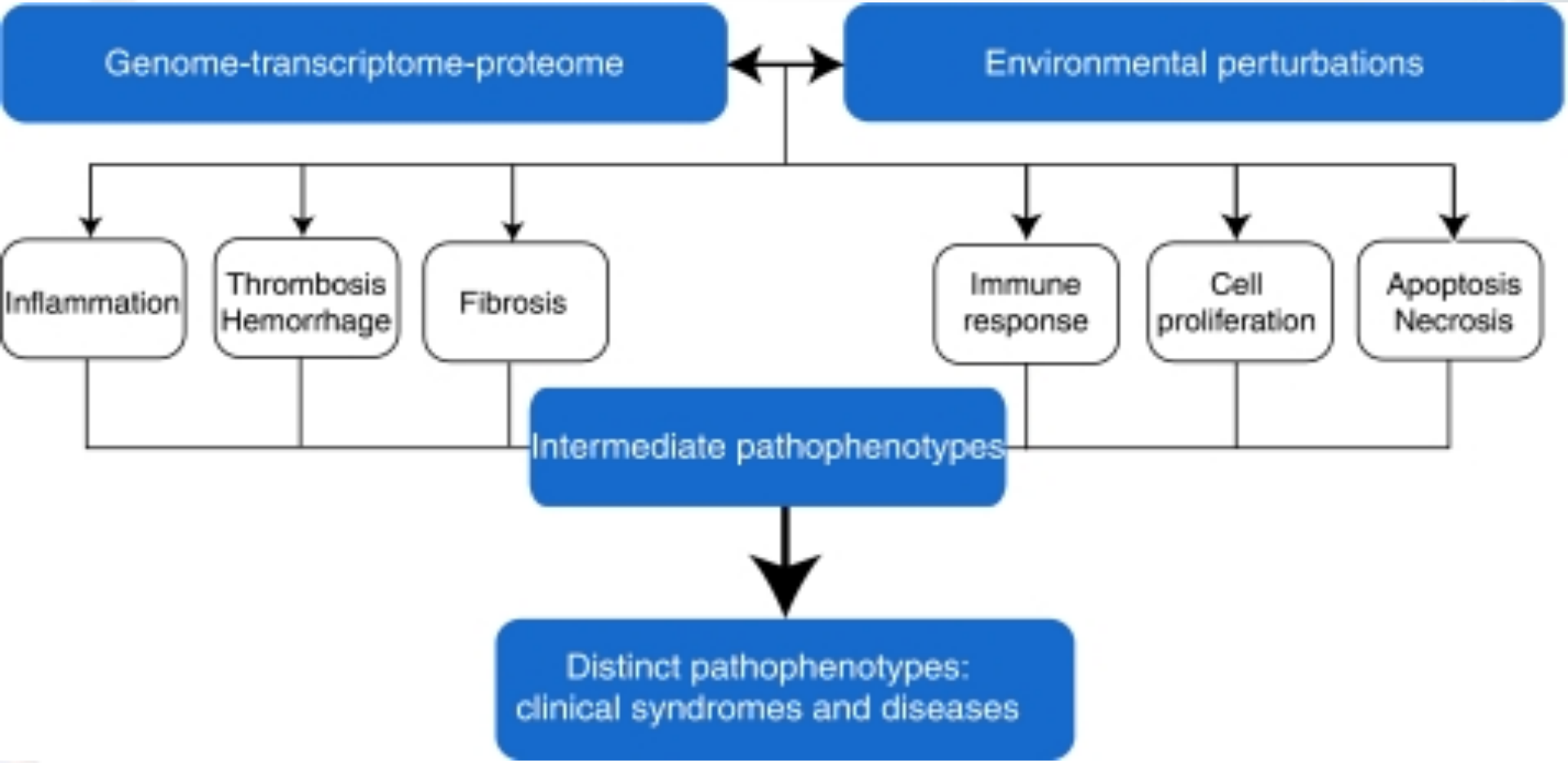
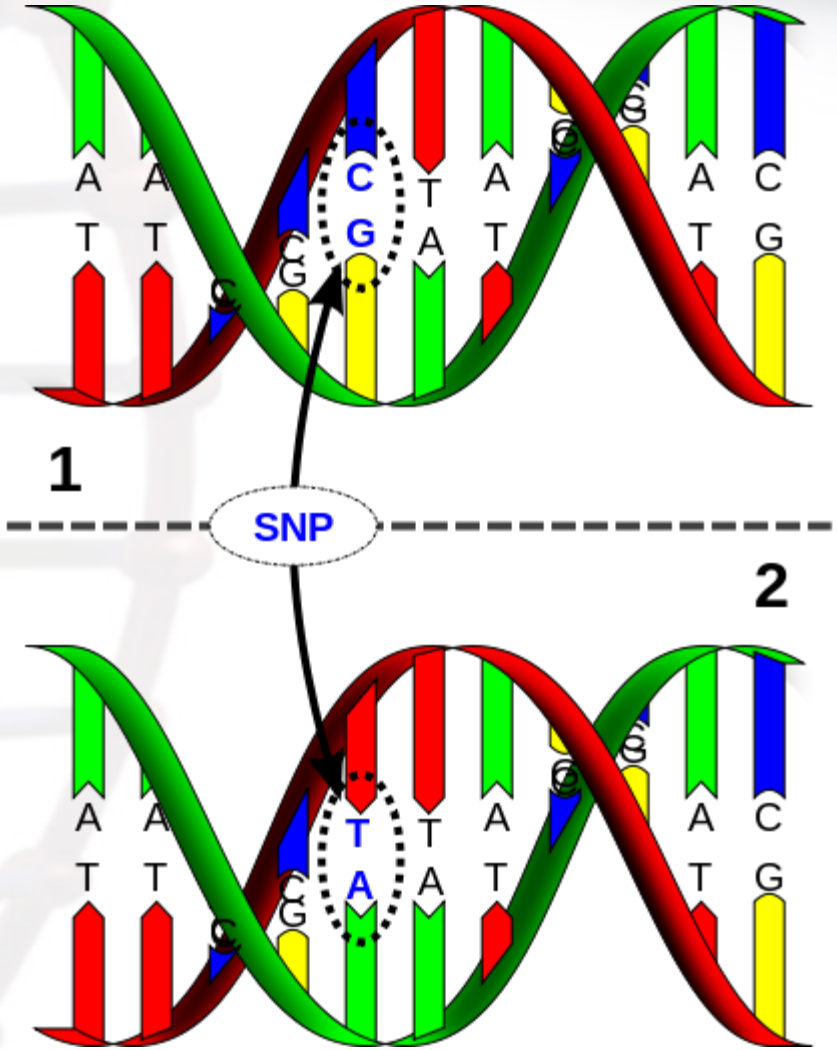
But, we know that we are more than our genes…

The Gene-Environment Dynamic



Mol Syst Biol. 2007; 3: 124.

An Essential Nexus for Clinical Nutrigenomics: SNPs



- 30,000 genes in human chromosomes
- 50% of genome – repetitive sequence
- About 1 SNP (“gene variant”) for every 1000 genes
- Influence drug response and disease risk (multi-genetic influence)
- May lead to different nutrient requirements due to the different function and metabolism

Ayu. 2011 Apr;32(2):141-6. doi: 10.4103/0974-8520.92539. Prakriti-based medicine: A step towards personalized medicine. Chatterjee B, Pancholi J

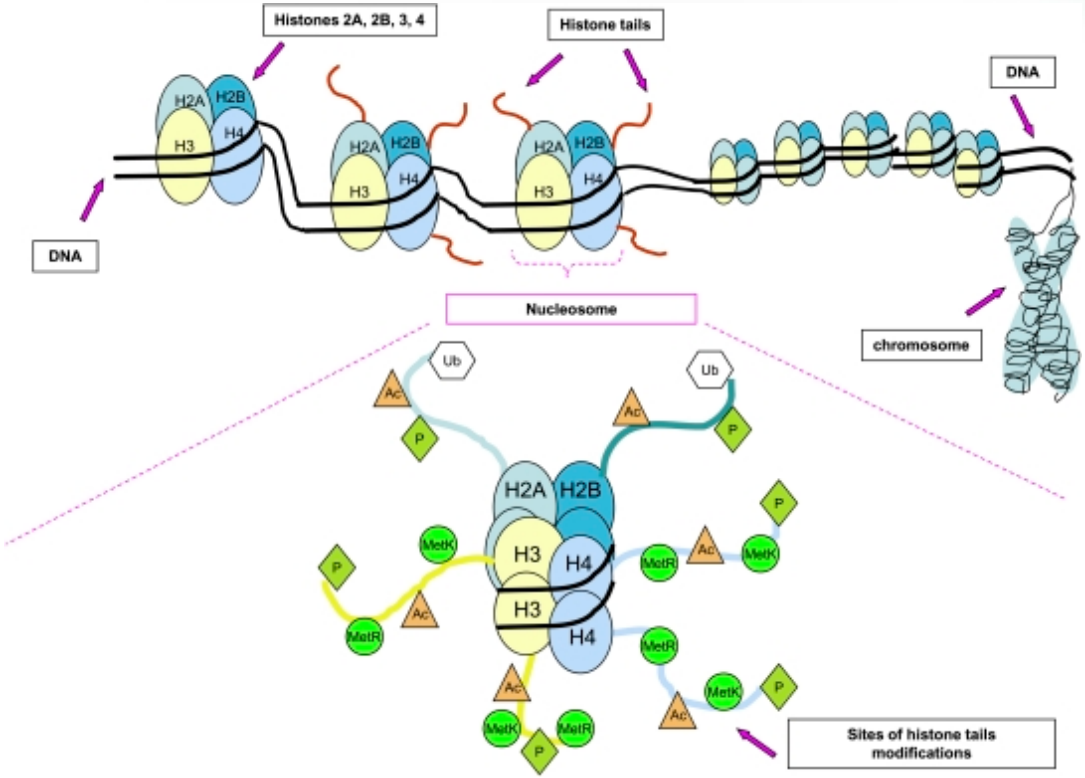
SNPs and High-Dose Nutrients

- SNP-regulated enzymes exhibit reduced functionality due to reduced cofactor or coenzyme binding
- About 30% of the 1000 disease phenotypes related to SNP polymorphisms exhibit reduced enzyme binding
- At least 50 diseases shown to respond to high-dose nutrient supplements
- “Our analysis of metabolic disease that affects cofactor binding, particularly as a result of polymorphic mutations, may present a novel rationale for high dose vitamin therapy, perhaps hundreds of times the normal dietary reference intake in some cases.”

Ames et al., AJCN. 2002; 75:616-658

Epigenetics: The Wild Card

- Heritable changes that do not impact gene sequence.
- Modification to gene sites or histone proteins
  - Methylation
  - Phosphorylation
  - Acetylation
  - Ubiquinylation



Nutrition in Clinical Practice 20:75-87, February 2005

General examples of the gene-environment interaction

- Warrior genes in environmental excess
- Pima Indians in the Southwest get type 2 diabetes at eight times the rate of white Americans.
- Individuals have widely varying responses to high- or low-fat diets, wine, salt, even exercise.
- Adverse reactions to drugs and drug/nutrient interactions
- Famine and transgenerational fetal programming
- Stressed signals from foods translating into inflammation

Sodium Restriction & HTN

- Varying degrees of salt sensitivity exist
- Is it universally beneficial?
- Lack of assessments and genotypic analyses
- Population-specific effects
- Specific gene variants identified, clinical application lacking
  - Bradykinin receptor B2 gene
  - Endothelin converting enzyme 1 gene
- Could be influenced by environmental factors such as degree of physical activity

Personalized lifestyle medicine: relevance for nutrition and **lifestyle** recommendations. Minich DM, Bland JS. ScientificWorldJournal. 2013 Jun 26;2013:129841. doi: 10.1155/2013/129841. Print 2013.

Dietary Cholesterol and Hypercholesterolemia

- Dietary limitation of 300 mg cholesterol daily for Americans
- Current epidemiological evidence does not support the correlation between dietary cholesterol and increased CHD risk
- About ¼ of population is sensitive to dietary cholesterol and responds with increased plasma LDL, but with a compensatory rise in HDL
- Dietary cholesterol may help to reduce small dense LDL particles
- Egg consumption variability between diabetics and non-diabetics

Personalized lifestyle medicine: relevance for nutrition and **lifestyle** recommendations. Minich DM, Bland JS. ScientificWorldJournal. 2013 Jun 26;2013:129841. doi: 10.1155/2013/129841. Print 2013.

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‘FOODOMICS’

Foodomics is the comprehensive, high-throughput approach for the exploitation of food science in the light of an improvement of human nutrition.

Foodomics is a new approach to food and nutrition that studies the food domain as a whole with the nutrition domain to reach the main objective, the optimization of human health and well-being.

Genes Nutr. 2013 Jan;8(1):1-4. doi: 10.1007/s12263-012-0310-x. Epub 2012 Aug 30.

Food synergy

Reducing dietary recommendations to individual nutrients without considering the whole food and its multitude of constituents, including phytonutrients, may not be accounting for “food synergy”.

Phytoprofiling

The role of phytochemical modulation of cellular physiology and propose phytochemical profiling, or phytoprofiling, to assist in the facilitation of determining phytonutrient requirements with more effective interventions with plant-derived compounds.

J Proteome Res. 2013 Mar 4. [Epub ahead of print]
Toward Personalized Nutrition: Comprehensive Phytoprofiling and Metabotyping. Xie G, Li X, Li H, Jia W.

Phytoprofiling: The Role of Color

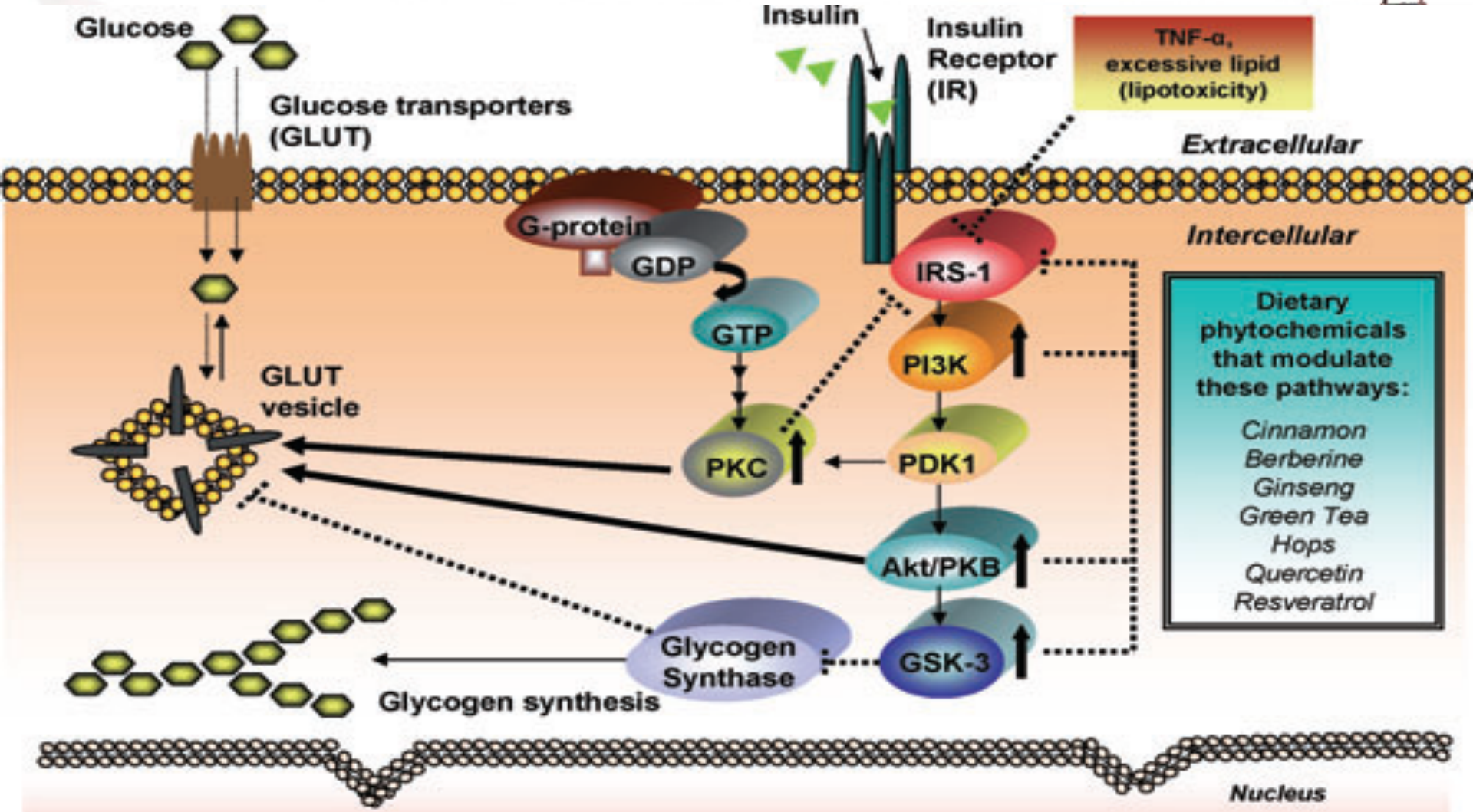
- Associations of colors of fruits and vegetable subgroups and cardiometabolic risk factors
- 3-year changes of cardiometabolic risk factors in adults
- Higher intake of red/purple FV may be related to lower weight and abdominal fat gain
- Yellow, green and white FV may be related to lipid parameters.

Eur J Clin Nutr. 2015 Apr 8. doi: 10.1038/ejcn.2015.49. [Epub ahead of print]

The New Frontier for Nutrigenomics:

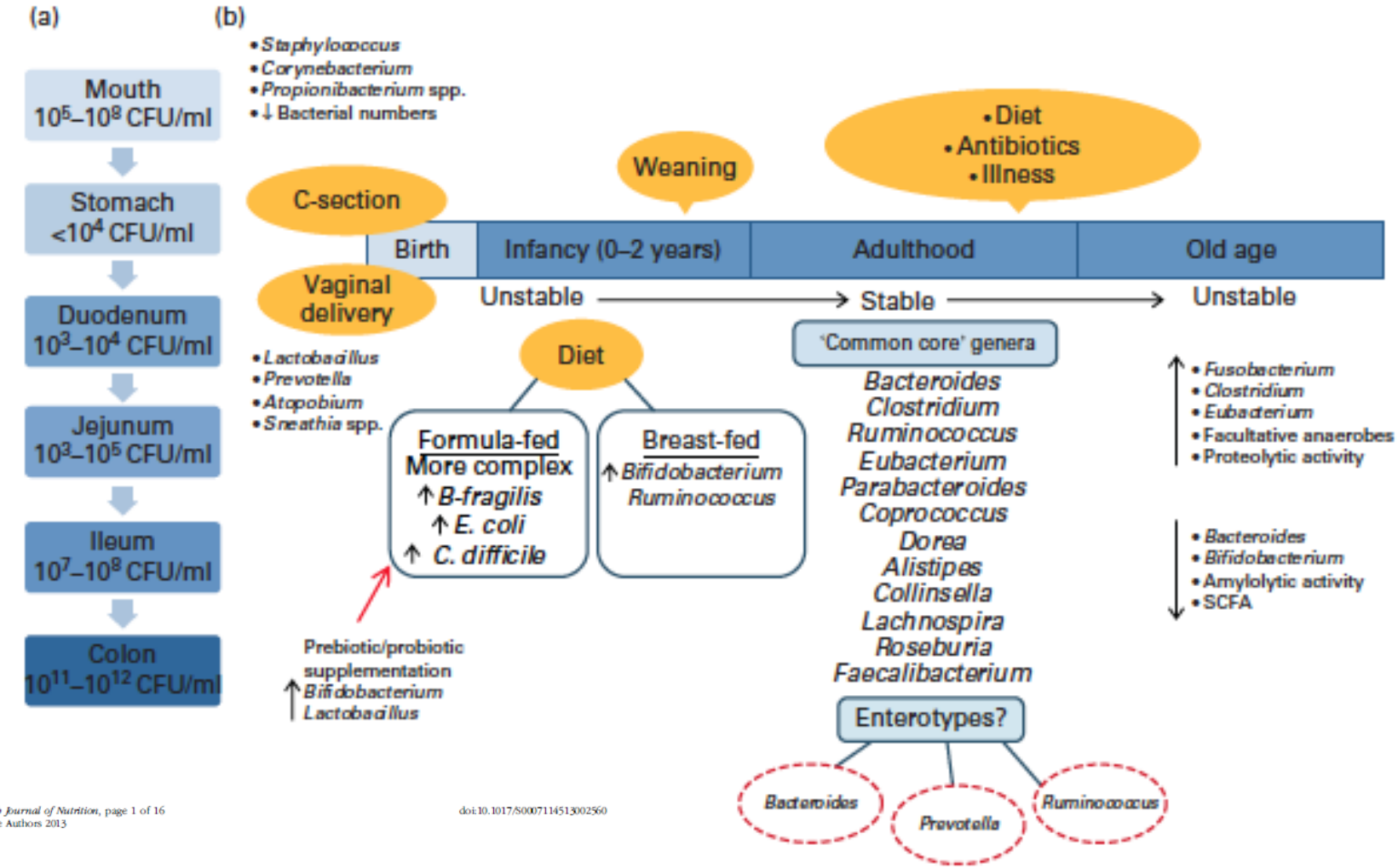
Phytonutrients to Modulate Cellular Signaling

Targeted Supplemental Nutrients to Overcome Dysfunctional Cell Signaling



Minich and Bland, Nutrition Reviews 2008 66(8):429-444.

Perhaps phytonutrients are only as good as our gut microbiome



British Journal of Nutrition, page 1 of 16

doi:10.1017/S0007114513002560

Fig. 1. (a) Variations in microbial numbers across the length of the gastrointestinal tract. (b) Selected features affecting the establishment and maintenance of the microbiota and factors influencing the composition of the microbiota. Micro-organisms are listed where their abundance is related to a particular environmental factor[6–8,13,16,25,26,45,173]. C-section, Caesarean section; CFU, colony-forming units; *B. fragilis*, *Bacteroides fragilis*; *E. coli*, *Escherichia coli*; *C. difficile*, *Clostridium difficile*.

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Now that we have broken ground on nutrigenomics, where is the clinical translation?

Can we truly tailor food and dietary supplements in a personalized gene and epigenetic approach?

One-size-fits-all eating

USDA and US Department of Health and Human Services lifestyle recommendations:

(1) Prevent overweight and obesity

(2) Control calorie intake to manage body weight

(3) Increase physical activity and reduce time spent in sedentary behaviors

Personalized lifestyle medicine: relevance for nutrition and **lifestyle** recommendations. Minich DM, Bland JS. ScientificWorldJournal. 2013 Jun 26;2013:129841. doi: 10.1155/2013/129841. Print 2013.

One-size-fits-all eating

(1) Reduce **daily sodium intake** to less than 2300 mg; further reduce intake to 1500 mg for those 51 yrs+

(2) Consume less than 10% of calories from **saturated fat, replace with mono- and poly-unsaturated fat**

(3) Consume less than 300 mg of **dietary cholesterol**

(4) Keep **trans fat** as low as possible

(5) Reduce intake of calories from **solid fats and added sugars**

(6) Limit consumption of foods that contain **refined grains**

(7) Consume **alcohol** in moderation – one drink daily for women; two for men.

Personalized lifestyle medicine: relevance for nutrition and **lifestyle** recommendations. Minich DM, Bland JS. ScientificWorldJournal. 2013 Jun 26;2013:129841. doi: 10.1155/2013/129841. Print 2013.

Similar Dietary Recommendations

(1) American Heart Association for CVD risk reduction

(2) American Cancer Society

(3) American Diabetes Association

Personalized lifestyle medicine: relevance for nutrition and **lifestyle** recommendations. Minich DM, Bland JS. ScientificWorldJournal. 2013 Jun 26;2013:129841. doi: 10.1155/2013/129841. Print 2013.

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The Scientific World Journal
Volume 2013, Article ID 129841, 14 pages
http://dx.doi.org/10.1155/2013/129841

Hindawi

Review Article

Personalized Lifestyle Medicine: Relevance for Nutrition and Lifestyle Recommendations

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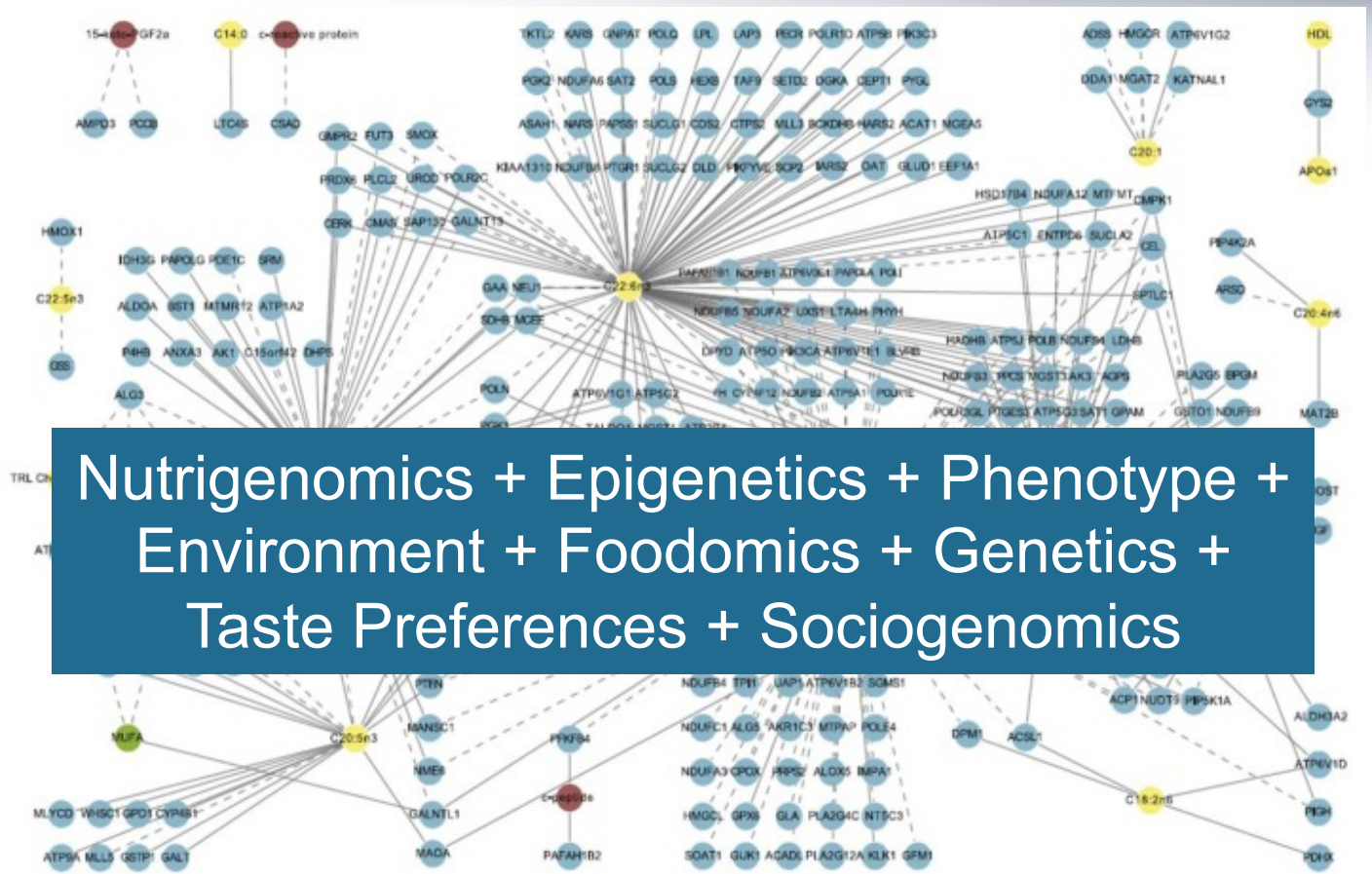
"Nutritionism" slowly phasing out and being replaced with personalized, nutrigenomics-based lifestyle approaches to health in the 21st century.

lifestyle-induced, preventable diseases. Therefore, due to the exorbitant cost and lack of resources to deal with the rising tide of illness, the importance of lifestyle factors in the origin and progression of disease can no longer be ignored. In fact, Dysinger [2] documented that in 2012, the American Medical Association issued a call to action for physicians to "acquire and apply the 15 clinical competencies of lifestyle medicine, and offer evidence-based lifestyle medicine interventions as the first and primary mode of preventing and, when appropriate, treating chronic disease within clinical medicine."

like Harvard, Stanford, and Yale have implemented the inclusion of lifestyle medicine into their curriculum, ranging from postgraduate courses to the development of separate institutes devoted to the cause. Additionally, the *American Journal of Lifestyle Medicine* is a peer-reviewed journal that was launched in 2007 for the purpose of educating practitioners on how to incorporate lifestyle medicine into clinical practice.

Lifestyle medicine is not a new or alternative medical discipline. The value of food as medicine was acknowledged several centuries ago by Hippocrates. Despite the fact that

Systems and Systems Nutrition



Network of associations between dietary intake, adipose gene expression, and phenotypic markers. Green nodes: nutrients; yellow: lipid, fatty acid, and apolipoprotein variables in blood; red: inflammatory and oxidative stress markers in blood; blue: gene expression (enzyme) in adipose tissue. Solid line: positive correlation/covariance; dashed line: negative correlation/covariance.

Nutrients. 2012 December; 4(12): 1898–1944.

Diet for your DNA

People are ready, but is technology?

"Nutrigenomics has the potential to be the next big thing in our fight against lifestyle-linked diseases…"

– Dr. Lynn Frewer

OPEN ACCESS Freely available online

PLOS ONE

Psychological Determinants of Consumer Acceptance of Personalised Nutrition in 9 European Countries

Rui Poínhos[1], Ivo A. van der Lans[2], Audrey Rankin[3], Arnout R. H. Fischer[2], Brendan Bunting[4], Sharron Kuznesof[5], Barbara Stewart-Knox[6], Lynn J. Frewer[5]*

1 Faculty of Nutrition and Food Sciences, University of Porto, Porto, Portugal, 2 Marketing and Consumer Behaviour Group, Wageningen University, Wageningen, The Netherlands, 3 Northern Ireland Centre for Food and Health, University of Ulster, Coleraine, United Kingdom, 4 School of Psychology, University of Ulster, Londonderry, United Kingdom, 5 Food and Society Group, SAFRD, Newcastle University, Newcastle Upon Tyne, United Kingdom, 6 Division of Psychology, University of Bradford, Bradford, United Kingdom

Abstract

Objective: To develop a model of the psychological factors which predict people's intention to adopt personalised nutrition. Potential determinants of adoption included perceived risk and benefit, perceived self-efficacy, internal locus of control and health commitment.

Methods: A questionnaire, developed from exploratory study data and the existing theoretical literature, and including validated psychological scales was administered to N = 9381 participants from 9 European countries (Germany, Greece, Ireland, Poland, Portugal, Spain, the Netherlands, the UK, and Norway).

Results: Structural equation modelling indicated that the greater participants' perceived benefits to be associated with personalised nutrition, the more positive their attitudes were towards personalised nutrition, and the greater their intention to adopt it. Higher levels of nutrition self-efficacy were related to more positive attitudes towards, and a greater expressed intention to adopt, personalised nutrition. Other constructs positively impacting attitudes towards personalised nutrition included more positive perceptions of the efficacy of regulatory control to protect consumers (e.g. in relation to personal data protection), higher self-reported internal health locus of control, and health commitment. Although higher perceived risk had a negative relationship with attitude and an inverse relationship with perceived benefit, its effects on attitude and intention to adopt personalised nutrition was less influential than perceived benefit. The model was stable across the different European countries, suggesting that psychological factors determining adoption of personalised nutrition have generic applicability across different European countries.

Conclusion: The results suggest that transparent provision of information about potential benefits, and protection of consumers' personal data is important for adoption, delivery of public health benefits, and commercialisation of personalised nutrition.

Citation: Poínhos R, van der Lans IA, Rankin A, Fischer ARH, Bunting B, et al. (2014) Psychological Determinants of Consumer Acceptance of Personalised Nutrition in 9 European Countries. PLoS ONE 9(10): e110614. doi:10.1371/journal.pone.0110614

Editor: Fabio Lucidi, University of Rome, Italy

Received June 17, 2014; **Accepted** September 15, 2014; **Published** October 21, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Funding: This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 265494 (http://cordis.europa.eu/fp7/home_en.html). Food4Me is the acronym of the project "Personalised nutrition: an integrated analysis of opportunities and challenges" (http://www.food4me.org/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Poor nutrition contributes to the incidence of many diseases, see *inter alia*, [1–5]. It has been estimated that approximately 80% of cases of cardiac disease, stroke, type 2 diabetes, and 40% of cancers could be avoided through improved lifestyle, including those related to diet [6]. However, there may be substantial *genetically determined* variation *between* individuals in what constitutes an optimal diet with regard to health protection [7]. *Nutrigenomics* is the study of the effects of foods and food constituents on gene expression and health. Personalised nutrition, or personalised dietary advice, which can also be based on an individual's genotype, can be translated into personalised dietary recommendations [8–9]. The advantage of nutrigenomics-based nutrition advice over and above that based on age, sex, body mass index (BMI), diet, physical activity and health status, is that genetic differences between individuals, which may interact with phenotype and co-determine health impacts of dietary choices, are explicitly taken into account [10]. Various (primarily internet based) personalised nutrition and nutrigenomics based personalised dietary advice services are currently, and increasingly, available commercially [11], although consumer acceptance of

Citation: Poínhos R, van der Lans IA, Rankin A, Fischer ARH, Bunting B, et al. (2014) Psychological Determinants of Consumer Acceptance of Personalised Nutrition in 9 European Countries. PLoS ONE 9(10): e110614. doi:10.1371/journal.pone.0110614

The future direction of personalized nutrition: my diet, my phenotype, my genes

Personalized nutrition currently exists at three levels:

- Internet-delivered services
- Personalized dietary advice using phenotypic information to get a "metabotype" (anthropometry, physical activity, clinical parameters, biochemical markers)
- Genomic data - Epigenomic?

Proc Nutr Soc. 2013 May;72(2):219-25. doi: 10.1017/S0029665112003436. Epub 2013 Jan 30.

Examples of nutrigenomic approaches

- Iron need and iron transport polymorphisms
- Zinc need and polymorphisms
- Vitamin D requirement for diabetics with polymorphisms in the vitamin D receptor
- The influence of polymorphisms on coenzyme Q10 (CoQ10) need for energy production and its role in cerebellar ataxia
- Folate, MTHFR polymorphisms and depression
- B vitamin gene variants and risk to smoking induced lung cancer
- Antioxidants and polymorphisms in glutathione S-transferases (GST)
- Bitter tasting and body composition differences

J Proteome Res. 2013 Mar 4. [Epub ahead of print] **Toward Personalized Nutrition: Comprehensive Phytoprofiling and Metabotyping.** Xie G, Li X, Li H, Jia W.

Food modulates genetic variants that relate to changes in apoA-V and triglyceride concentrations

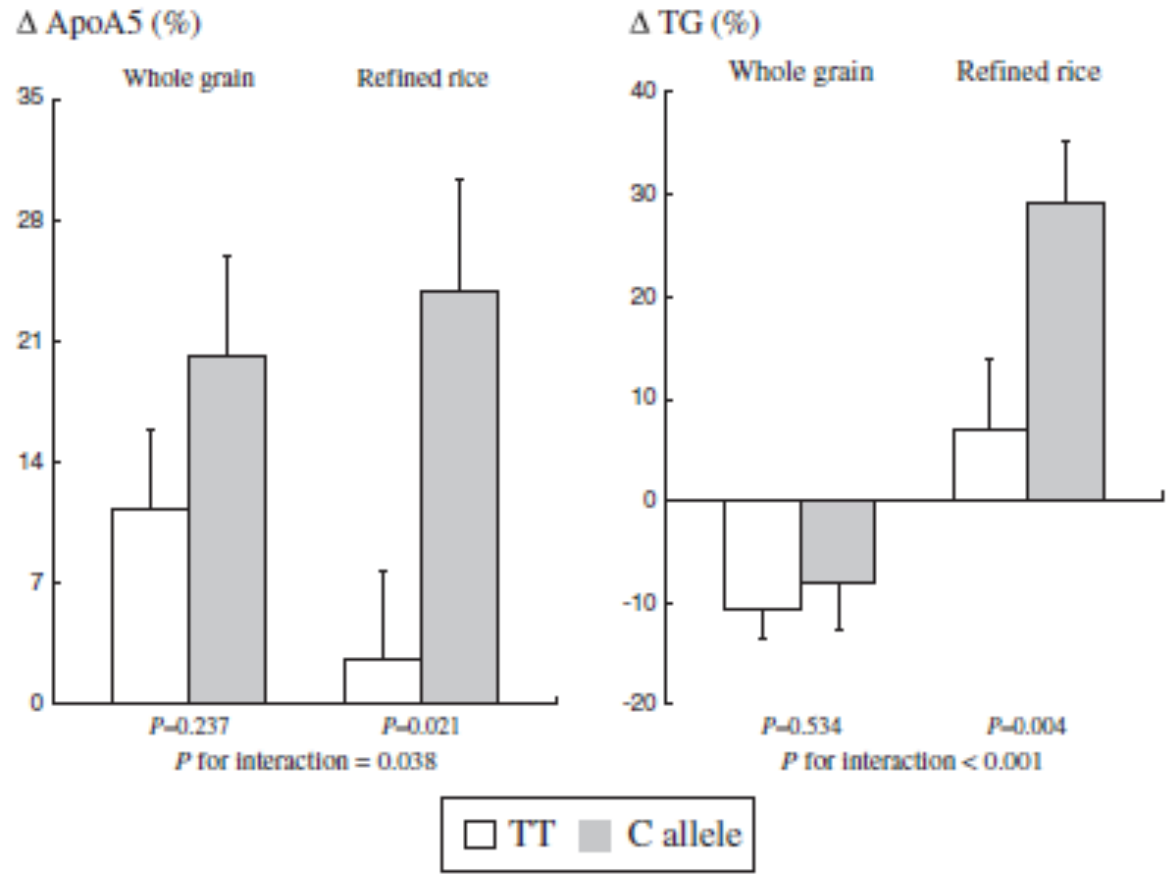

Figure 1 Genotype effect of *APOA5* -1131 T>C on mean percent changes in fasting apolipoprotein A-V and triglyceride by whole grains and legumes and refined rice groups at 12 weeks. Means ± SE. *P*-values derived from an independent *t*-test after adjusting for change in HOMA-IR. HOMA-IR, homeostatic model assessment; TG, triglyceride.

Trials. 2014 Apr 1;15:100. doi: 10.1186/1745-6215-15-100.

Nutrition Journal

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Research

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Improved weight management using genetic information to personalize a calorie controlled diet

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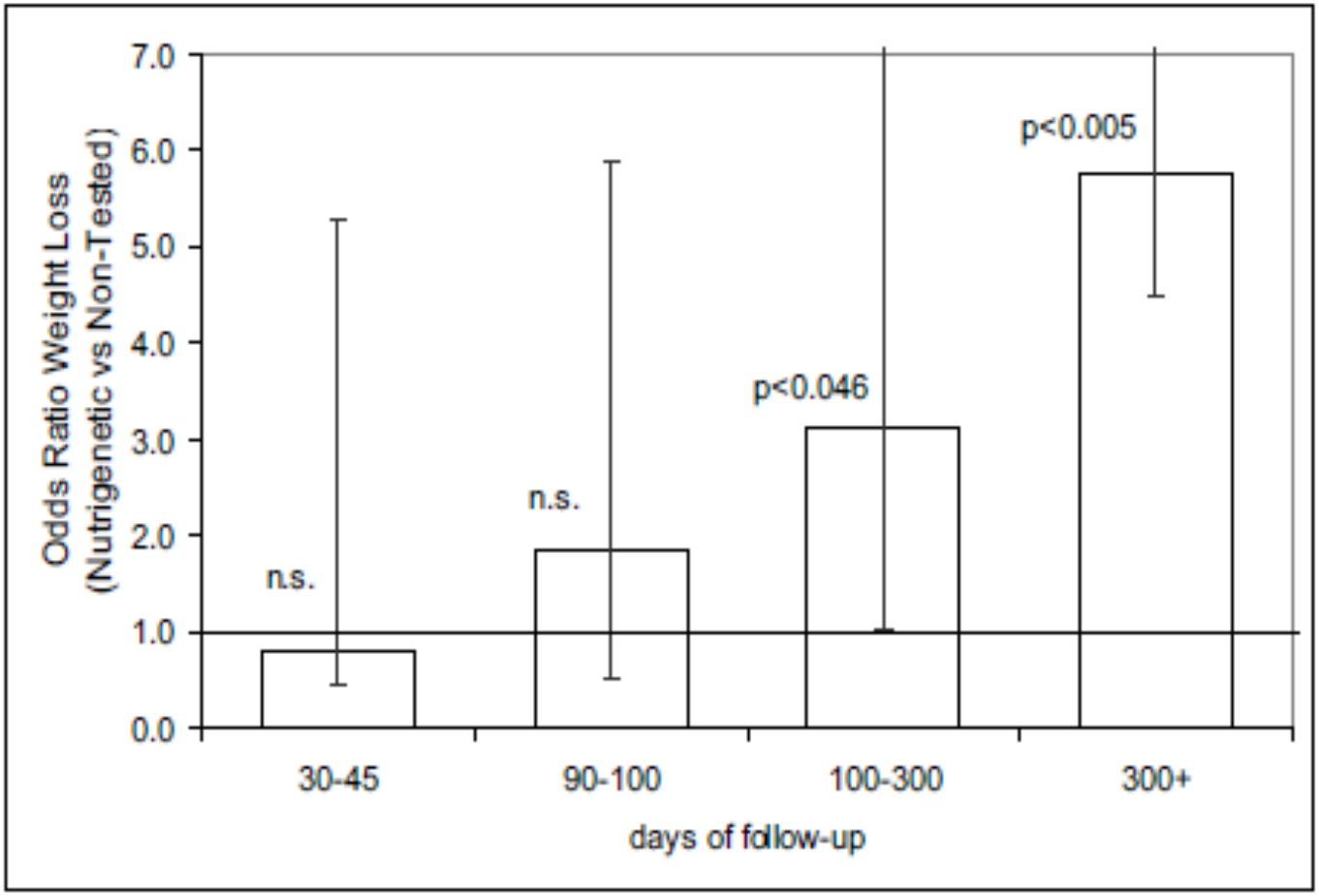
Gene	Gene symbol
Angiotensin I converting enzyme	*ACE*
Apolipoprotein C-III	*APOC3*
Cystathionine-beta-synthase	*CBS*
Cholesteryl ester transfer protein	*CETP*
Collagen, type I, alpha 1	*COL1A1*
Glutathione S-transferase M1	*GSTM1*
Glutathione S-transferase pi	*GSTP1*
Glutathione S-transferase theta 1	*GSTT1*
Interleukin 6	*IL6*
Lipoprotein lipase	*LPL*
5-methyltetrahydrofolate-homocysteine methyltransferase reductase	*MTRR*
5,10-methylenetetrahydrofolate reductase	*MTHFR*
5-methyltetrahydrofolate-homocysteine methyltransferase	*MTR*
Nitric oxide synthase 3 (endothelial cell)	*NOS3*
Peroxisome proliferator-activated receptor gamma	*PPARG*
Superoxide dismutase 2, mitochondrial	*SOD2*
Superoxide dismutase 3, extracellular	*SOD3*
Tumor necrosis factor	*TNFα*
Vitamin D receptor	*VDR*

- **Can including genetic information to personalize a patient's diet (nutrigenetics) improve long-term weight management?**
- **N=50 patients in genetic group; N=43 patients in control group**
- **Standard Mediterranean diet, modified for nutrigenetic group**

Nutrition Journal 2007, 6:29 doi:10.1186/1475-2891-6-29



After 300 days of follow-up individuals in the nutrigenetic group were more likely to have maintained some weight loss (73%) than those in the comparison group (32%).

Nutrition Journal 2007, **6**:29 doi:10.1186/1475-2891-6-29

Overview

- Nutrition in the 21st Century
- The Science of Nutrigenomics
- Epigenomics
- Foodomics
- Dietary Recommendations Based on Nutrigenomics
- Clinical Applications of Nutrigenomics

Personalized Approaches to Nutrition & Dietary Supplements

MTHFR Polymorphisms

Conditions associated with folate metabolism

- Alzheimer's Disease
- Anxiety
- Cancer
- Cognitive Decline
- Depression
- Heart Disease and Stroke
- Obsessive Compulsive Disorder
- Spina Bifida and NTDs

The Modern Day Genetic Variant

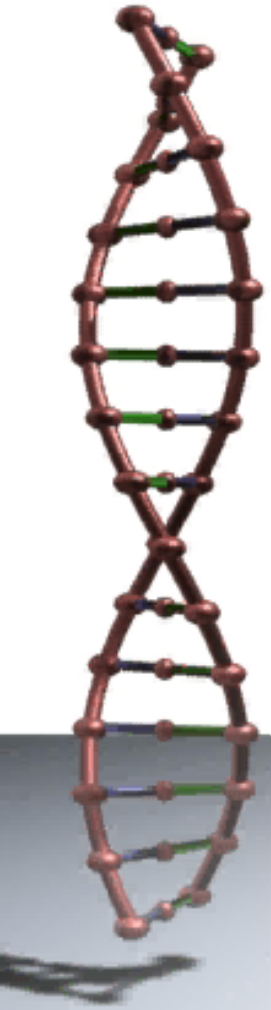
- MTHFR 677 C->T polymorphism
- Homogyzous expression of 677 TT (~33%)
  - Small-scale intervention studies to support the hypothesis that these individuals may have higher folate requirements.
  - Risk for vascular and neoplastic diseases, neural tube defects
  - TT could have a protective effect such as in the Physicians Health Study with men showing 55% lower risk for colorectal cancer, but protective effect lost when folate status impaired.

Nutrition in Clinical Practice 20:75-87, February 2005

Clinical Practice Experience with MTHFR Polymorphisms and Methylfolate

- 30 patients, 8 physicians
- Patients reported improvements in physical (60%) and mental/behavioral symptoms (36%) following treatment.
- A minority of participants reported side effects, but they occurred in almost every body system and ranged in severity. Doctors relied on trial and error to determine treatment doses, frequency and components.
- However, patients report largely positive experience.
- MTHFR testing results in variable clinical processes in domains related to delivery of diagnosis and prognosis, and therapeutic options.
- Clinicians and patients would benefit from therapeutic algorithms based on rigorous research.

J Nutrigenet Nutrigenomics. 2015;8(3):137-50. doi: 10.1159/000440700. Epub 2015 Oct 21.



Bitter Taste Receptor Polymorphisms

The Metabolic Benefits of Bitter Bio-Actives

Humans are capable of sensing five basic tastes: sweet, sour, salt, umami and bitter.

Bitter taste is sensed by bitter taste receptors (T2Rs) that belong to the G-protein coupled receptors (GPCRs) superfamily.

Humans have T2Rs that are expressed in the oral cavity, gastrointestinal (GI) neuroendocrine cells and airway cells.

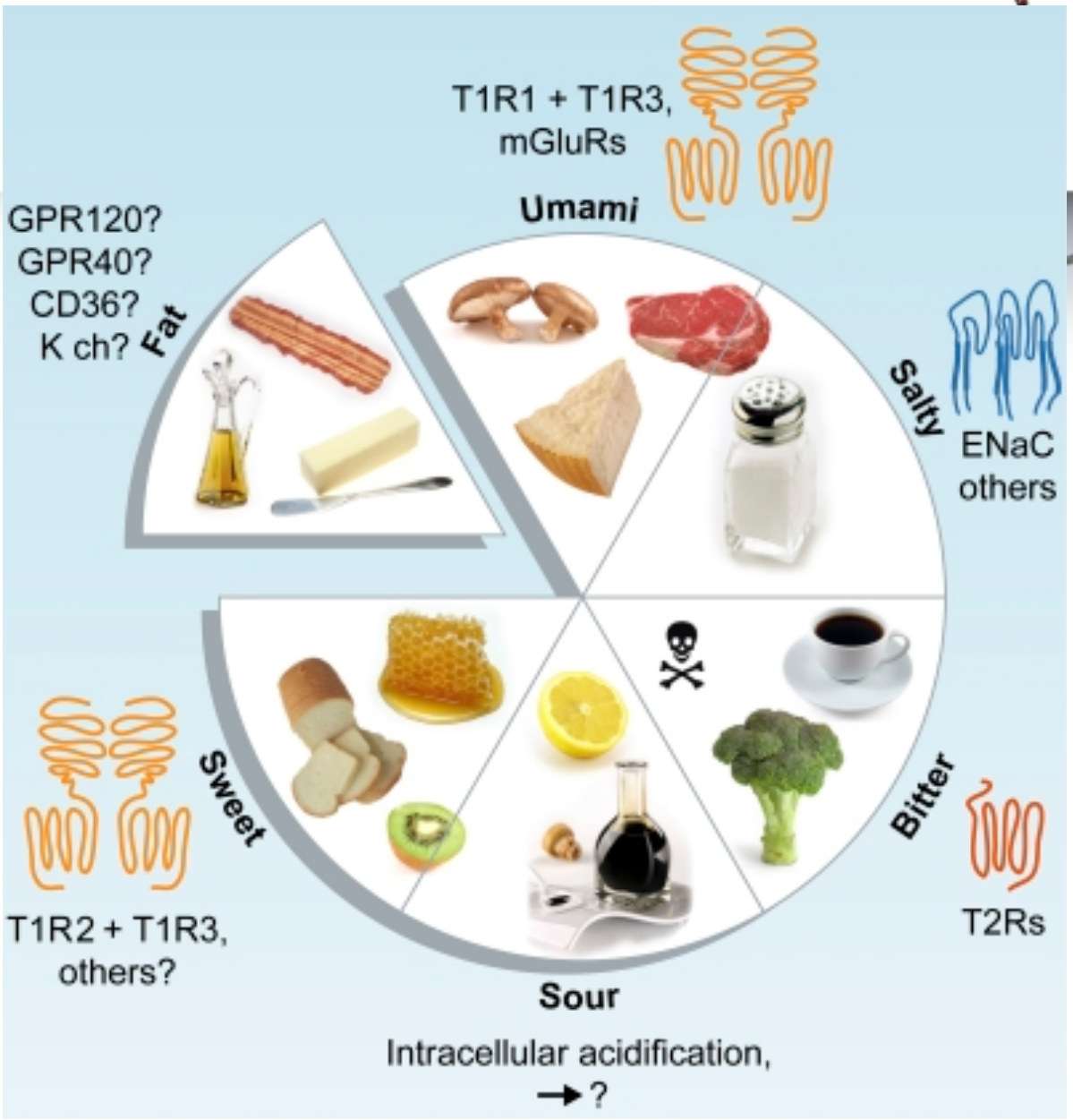
Singh N. et al. *Biochem Biophys Res Commun*. 2011 Mar 4;406(1):146-51. Epub 2011 Feb 12.

Potential Bitter Compounds to Modulate in Diet & Supplements

- Green tea catechins
- Soy isoflavones
- Hops polyphenols
- Caffeine
- Bitter melon
- Berberine
- Fenugreek

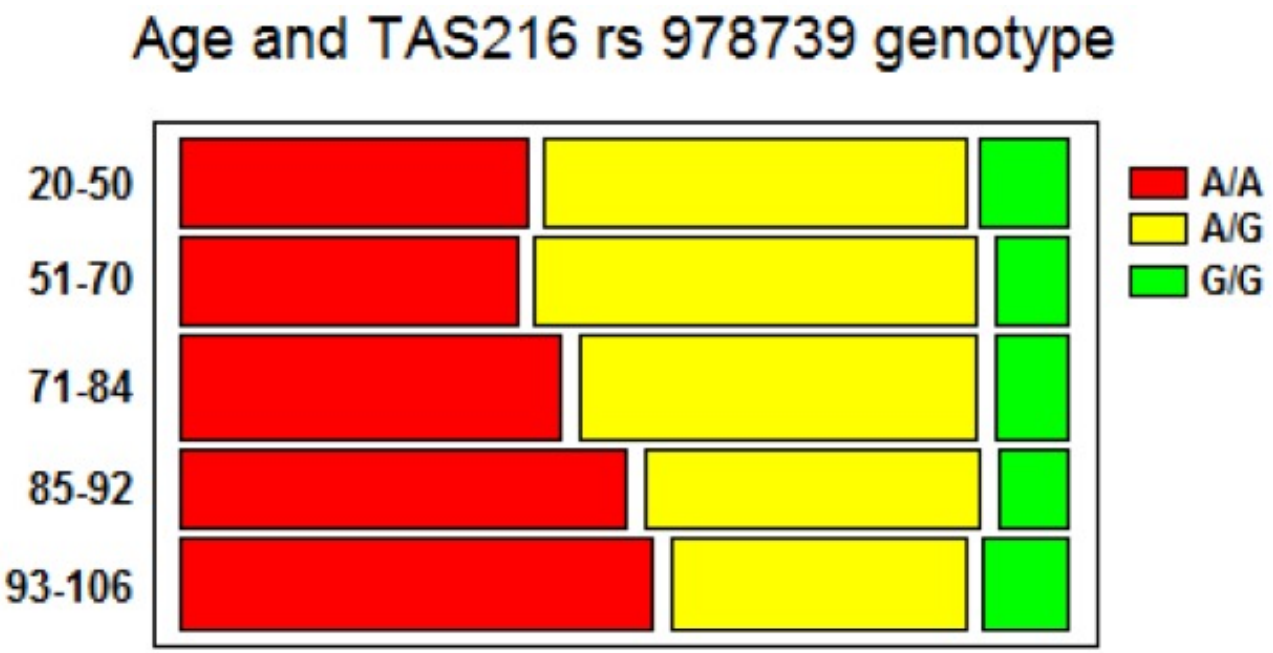
Bitter database of compounds: Ayana Wiener; Marina Shudler; Anat Levit; Masha Y. Niv. BitterDB: a database of bitter compounds. *Nucleic Acids Research 2011; doi: 10.1093/nar/gkr755*;

TASTE RECEPTORS



J Cell Biol. 2010 August 9; 190(3): 285–296.

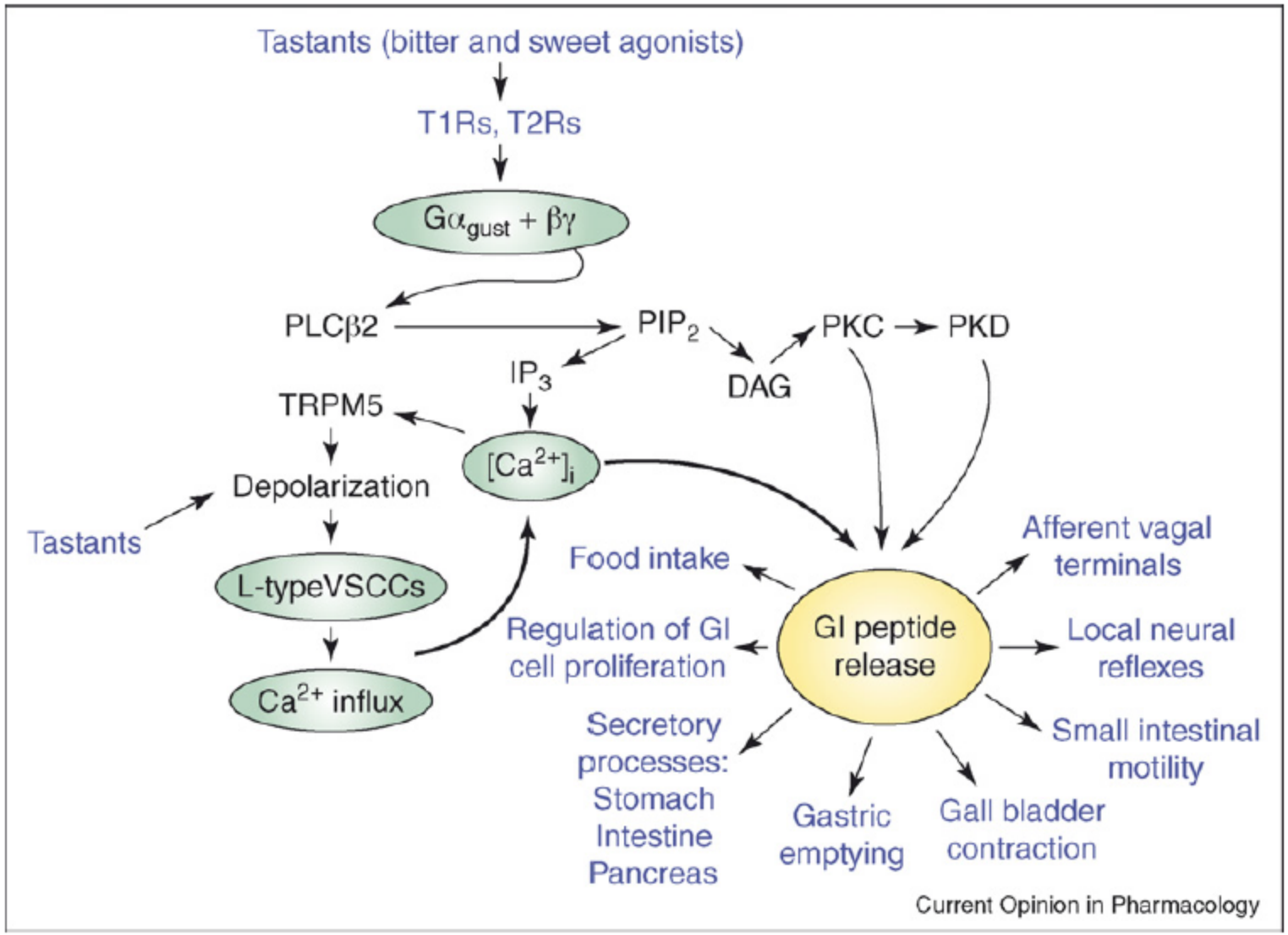
BITTER TASTE RECEPTOR POLYMORPHISMS AND HUMAN AGING



In particular, the frequency of A/A homozygotes increases gradually from 35% in subjects aged 20 to 70 up to 55% in centenarians.

PLoS One. 2012;7(11):e45232. doi: 10.1371/journal.pone.0045232.Epub 2012 Nov 2.

Gut effects of bitter tastants



Current Opinion in Pharmacology 2007, 7:557–562

Bitter tasters have lower BMI

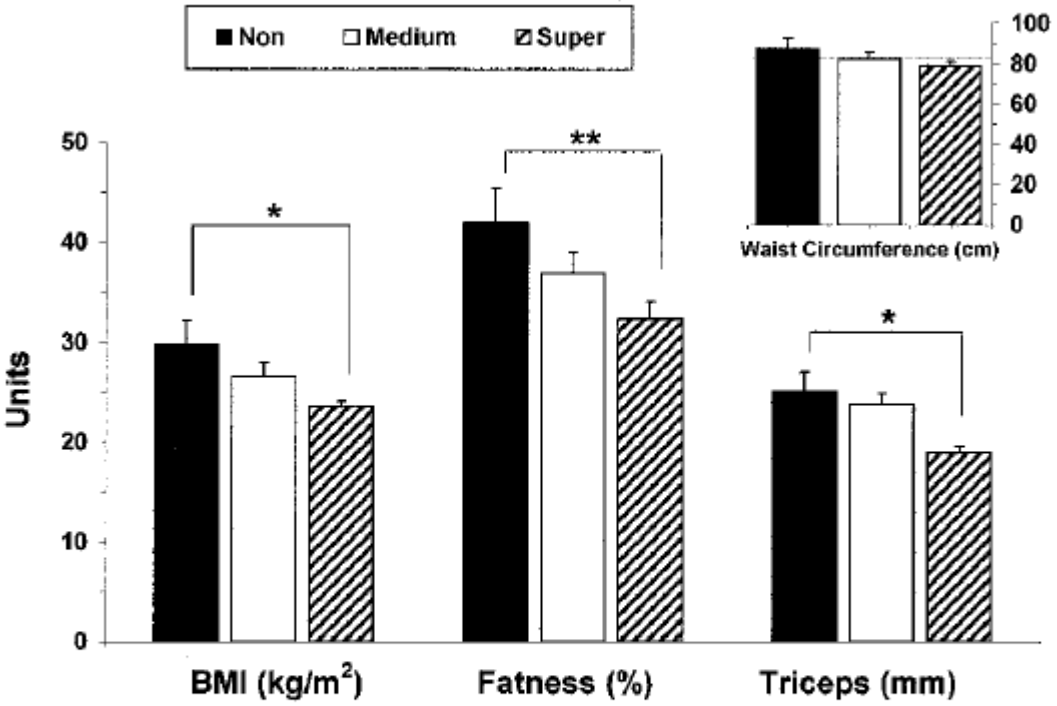


Figure 2: Mean adiposity measures in women classified by PROP phenotype. Nontaster women had significantly higher BMI, body fatness, and triceps skinfold than supertaster women. No group differences were found for WC (see inset). * $p < 0.05$; ** $p < 0.01$.

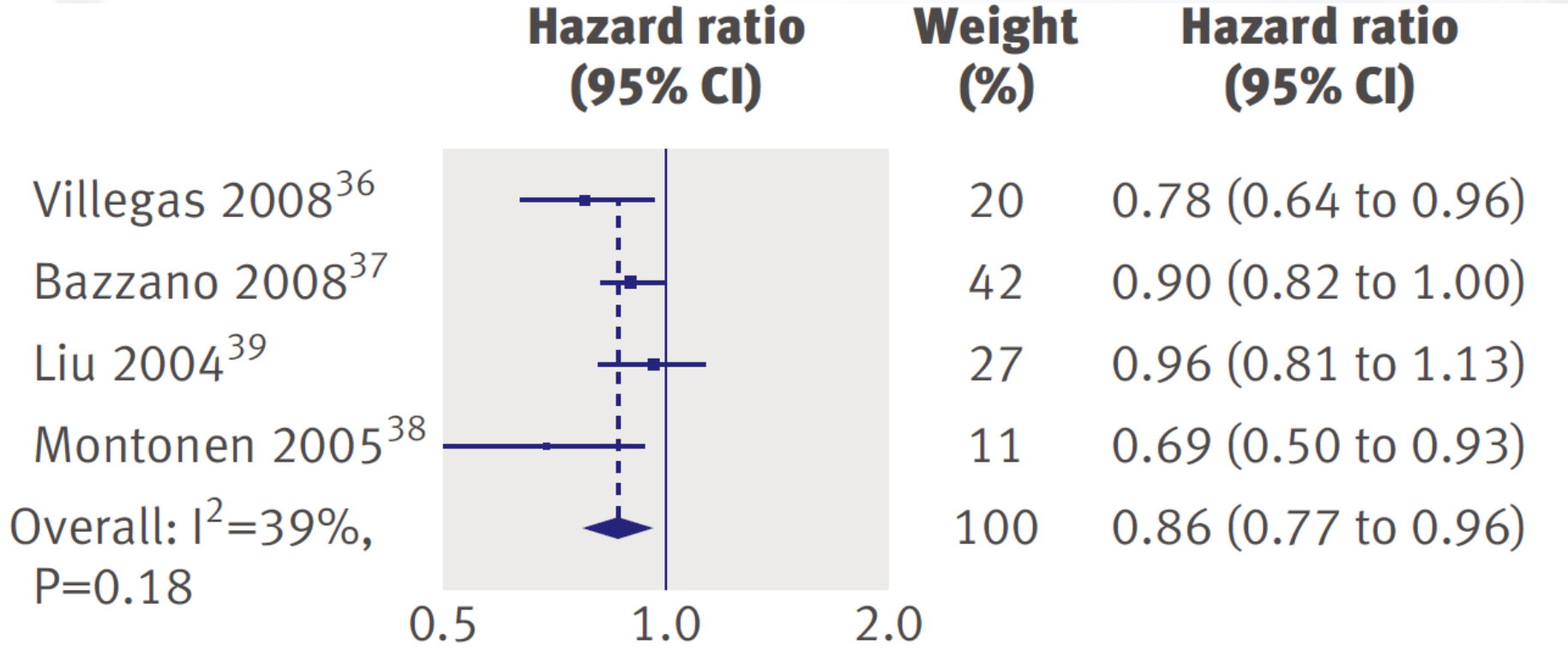
GOLDSTEIN, GRETCHEN L., HENRYK DAUN, AND BEVERLY J. TEPPER. Adiposity in middle-aged women is associated with genetic taste blindness to 6-npropylthiouracil. *Obes Res. 2005;13:1017–1023.*

Do polymorphisms in chemosensory genes matter for human ingestive behavior?

TAS2R38 predicts variation in bitterness of synthetic pharmaceuticals (e.g., propylthiouracil) and natural plant compounds (e.g., goitrin), and this variation associates with differential intake of alcohol and vegetables.

Food Qual Prefer. 2013 Dec;30(2):202-216.

Green, leafy vegetables & T2DM



"An increase of 1.15 servings a day was associated with a 14% decrease in incidence."

Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. BMJ. 2010 Aug 18;341:c4229.

To soy or not to soy?

Dietary Soy and Cancer

- Population differences
- Type of soy
- Type of tumor
- Polymorphisms
  - This study shows that, under conditions of reduced glucuronidation, dietary genistein exhibits a strongly increased estrogenic effect. Toxicol Appl Pharmacol. 2012 Nov 1;264(3):335-42. doi: 10.1016/j.taap.2012.09.013. Epub 2012 Sep 20.
- Epigenetic mechanisms of isoflavones
- Gut microflora conversion to metabolites

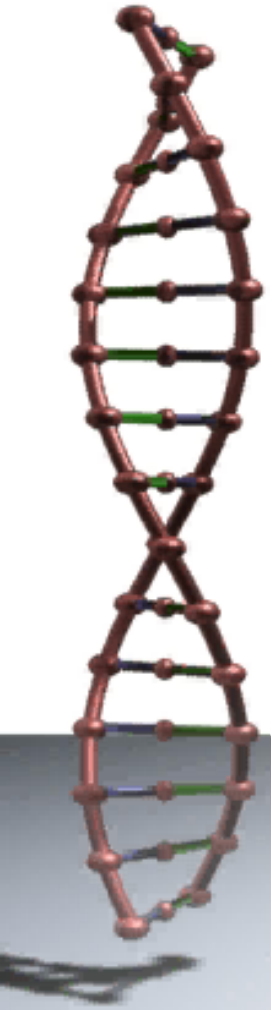
Fish oil supplementation

Omega-3 Fatty Acids and APOE

- APOE genotype response to EPA and DHA
- APOE4 carriers may experience an increase in total cholesterol and LDL-C with DHA supplementation

"High dose DHA supplementation is associated with increases in total cholesterol in E4 carriers, which appears to be due to an increase in LDL-C and may in part negate the cardioprotective action of DHA in this population subgroup."

Atherosclerosis. 2010 Mar;209(1):104-10. doi: 10.1016/j.atherosclerosis.2009.08.024. Epub 2009 Aug 21.



Detoxification Pathway Polymorphisms

Food Intolerances

- Involvement of immune system
- Possible enzyme deficiency or inadequacy
- Detoxification of colonic bacteria-generated metabolites
- Individual food substances and food classes – histamines, sulfites, nightshades, gluten, phenylethylamine (PEA) in chocolate, casein, lactose, oxalates

Individualized Toxin Exposure

- Air
- Food
- Water
- Drugs
- Radiation
- Internally-generated metabolites
  - Inflammation, lipid peroxidation, oxidative stress, disease states, infections, and microflora

TAILORING FOODS TO EXPOSOMIC PATHWAYS

1. Phase I Cytochrome Systems
2. Phase II Conjugation Enzymes
3. Antioxidant Response Element/Nrf2
4. Metallothionein Response Element

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http://dx.doi.org/10.1155/2015/760689

Hindawi

Review Article

Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application

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Academic Editor: H. K. Biesalski

Research into human biotransformation and elimination systems continues to evolve. Various clinical and *in vivo* studies have been undertaken to evaluate the effects of foods and food-derived components on the activity of detoxification pathways, including phase I cytochrome P450 enzymes, phase II conjugation enzymes, Nrf2 signaling, and metallothionein. This review summarizes the research in this area to date, highlighting the potential for foods and nutrients to support and/or modulate detoxification functions. Clinical applications to alter detoxification pathway activity and improve patient outcomes are considered, drawing on the growing understanding of the relationship between detoxification functions and different disease states, genetic polymorphisms, and drug-nutrient interactions. Some caution is recommended, however, due to the limitations of current research as well as indications that many nutrients exert biphasic, dose-dependent effects and that genetic polymorphisms may alter outcomes. A whole-foods approach may, therefore, be prudent.

1. Introduction

Food-based nutrients have been and continue to be investigated for their role in the modulation of metabolic pathways involved in detoxification processes. Several publications to date have leveraged cell, animal, and clinical studies to demonstrate that food-derived components and nutrients can modulate processes of conversion and eventual excretion of toxins from the body [1]. In general, the nature of these findings indicates that specific foods may upregulate or favorably balance metabolic pathways to assist with toxin biotransformation and subsequent elimination [2, 3]. Various whole foods such as cruciferous vegetables [2, 4, 5], berries [6], soy [7], garlic [8, 9], and even spices like turmeric [10, 11] have been suggested to be beneficial and commonly prescribed as part of naturopathic-oriented and functional medicine-based therapies [12, 13].

While these foods are important to note, the science in this active area of inquiry continues to evolve to reveal new findings about food-based nutrients and their effect on health. Thus, the purpose of this review article is to summarize the science to date on the influence of whole foods, with a special focus directed towards phytonutrients and other food-based components, on influencing specific metabolic detoxification pathways, including phase I cytochrome enzymes, phase II conjugation enzymes, antioxidant support systems, and metallothionein upregulation for heavy metal metabolism. Based on this current science, the paper will conclude with clinical recommendations that may be applied in a personalized manner for patients via the discretion of a qualified health professional.

2. The Metabolic Pathways of Detoxification

Discussion of physiological pathways for detoxification has been mainly centered around phase I and phase II enzyme systems. This review will cover phase I cytochrome P450

J Nutr Metab. 2015;2015:760689. doi: 10.1155/2015/760689. Epub 2015 Jun 16. Review.

In vivo example phytonutrient INDUCERS of CYP1 enzymes

Enzyme	Food or Bioactive	Type of Study	Reference
CYP1A1	Cruciferous vegetables	Clinical	Lord et al., 2002; Ioannides, 1999
	Resveratrol[1]	Clinical	Chow et al., 2010
	Green and black tea	In vivo	Yao et al., 2014
	Curcumin[2]	In vivo	Bansal et al., 2014
	Soybean	In vivo	Bogacz et al., 2014
	Garlic oil	In vivo	Chen et al., 2003
	Fish oil	In vivo	Chen et al., 2003
	Canthaxanthin & Astaxanthin[3]	In vivo	Ioannides, 1999
	B-Apo-8'-carotenal[4]	In vivo	Ioannides, 1999
CYP1A2	Cruciferous vegetables	Clinical	Peterson et al., 2009
	Green and black tea	In vivo	Yao et al., 2014
	Chicory root	In vivo	Rasmussen et al., 2012
	Canthaxanthin & Astaxanthin[3]	In vivo	Ioannides, 1999
	B-Apo-8'-carotenal[4]	In vivo	Ioannides, 1999
	Allyl sulphides[5]	In vivo	Ioannides, 1999
CYP1B1	Curcumin (dietary)[2]	In vivo	Bansal et al., 2014
	Cruciferous vegtables	In vivo	Horn et al., 2002

J Nutr Metab. 2015;2015:760689. doi: 10.1155/2015/760689. Epub 2015 Jun 16. Review.

In vivo example phytonutrient INHIBITORS of CYP1 enzymes

Enzyme	Food or Bioactive	Type of Study	Reference
CYP1A1	Black raspberry	In vivo	Aiyer & Gupta, 2010
	Blueberry	In vivo	Aiyer & Gupta, 2010
	Ellagic acid	In vivo	Celik et al., 2013; Aiyer & Gupta, 2010
	Black soybean	In vivo	Zhang et al., 2013
	Theaflavins (black tea)	In vivo	Moon et al., 2006
	Curcumin	In vivo	Thapliyal & Maru, 2001
CYP1A2	Apiaceous vegetables	Clinical	Peterson et al., 2010
	Quercetin	Clinical	Chen et al., 2009
	Daidzein	Clinical	Moon et al., 2006
	Grapefruit	Clinical	Ioannides, 1999
	Genistein	In vivo	Moon et al., 2006
	Equol	In vivo	Moon et al., 2006
	Chamomile and peppermint tea	In vivo	Maliakal & Wanwimolruk, 2001
	Dandelion tea	In vivo	Thapliyal & Maru, 2001
CYP1B1	Curcumin (implant)	In vivo	Bansal et al., 2014

J Nutr Metab. 2015;2015:760689. doi: 10.1155/2015/760689. Epub 2015 Jun 16. Review.

In vivo example phytonutrient INDUCERS of Glutathione S-transferases (GSTs)

Enzyme	Food or Bioactive	Type of Study	Reference
GSTs	Cruciferous vegetables[1]	Clinical, observational	Navarro et al, 2009; Wark et al., 2004; Lampe et al., 2000
	Allium vegetables[2]	Clinical	Lampe et al., 2002
	Resveratrol[3]	Clinical	Chow et al., 2010
	Habitual fruit and vegetable consumption	Observational	Wark et al., 2004
	Citrus	Observational, in vivo	Perez et al., 2010; Wark et al., 2004
	Garlic	In vivo	Chen et al., 2003; Wu et al., 2002; Guyonnet et al., 2001
	Fish oil	In vivo	Chen et al., 2003;
	Black soybean	In vivo	Zhang et al., 2013
	Purple sweet potato	In vivo	Hwang et al., 2011
	Curcumin[4]	In vivo	Iqbal et al., 2003
	Green tea	In vivo	Newsome et al., 2014
	Rooibos tea	In vivo	Marnewick et al., 2003
	Honeybush tea	In vivo	Marnewick et al., 2003
	Ellagic acid[5]	In vivo	Celik et al., 2013
	Rosemary	In vivo	Lin et al., 2014
	High-CLA ghee	In vivo	Chinnadurai et al., 2013
	Genistein (kidney GSTs)	In vivo	Froyen et al., 2009

J Nutr Metab. 2015;2015:760689. doi: 10.1155/2015/760689. Epub 2015 Jun 16. Review.

Cruciferae Interact with the *UGT1A1*28* Polymorphism to Determine Serum Bilirubin Levels in Humans[1,2]

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*Interdisciplinary Graduate Program in Nutritional Sciences, Department of Epidemiology, University of Washington, Seattle, WA and †Fred Hutchinson Cancer Research Center, Seattle, WA 98109

ABSTRACT UDP-glucuronosyltransferase (UGT) 1A1 is a conjugating biotransformation enzyme that plays a role in maintaining levels of endogenous compounds (e.g., bilirubin) and handling exogenous compounds, including carcinogens. The *UGT1A1*28* polymorphism results in decreased *UGT1A1* promoter activity due to 7 thymine-adenine (TA) repeats instead of the commonly found 6 repeats. Studies indicate that foods from the botanical families *Cruciferae* (e.g., broccoli), *Rutaceae* (citrus), *Liliaceae* (e.g., onions), and *Leguminosae* (legumes) may increase UGT activity. We investigated, in an observational study, whether foods from these botanical groups were associated with increased UGT1A1 activity as indicated by serum bilirubin concentrations and whether the effect varied by *UGT1A1*28* genotype, comparing those homozygous for the $[TA]_7$-repeat allele (7/7) to homozygous wild-types (6/6) and heterozygotes (6/7) combined. Healthy volunteers completed 3-d food records. Blood samples were drawn for genomic DNA collection and bilirubin measures. For total, direct, and indirect bilirubin measures, there was no significant association with any botanical group independently. There was a significant inverse association between all 3 bilirubin measures and interaction of *UGT1A1*28* genotype with *Cruciferae* intake ($P < 0.02$ for each measure); individuals with the 7/7 genotype had reduced bilirubin concentrations with increased intake of cruciferous vegetables, whereas individuals with the 6/6 or 6/7 genotype did not. With regard to UGT1A1-conjugated carcinogens (e.g., heterocyclic amines, polycyclic aromatic hydrocarbons), individuals with decreased UGT1A1 activity due to the 7/7 genotype may be at greater risk for carcinogenesis, but our results imply that they also may have greater opportunity to decrease that risk through dietary intervention. J. Nutr. 135: 1051–1055, 2005.

KEY WORDS: • *UGT1A1* • *polymorphism* • *chemoprevention* • *Cruciferae* • *bilirubin*

UDP-glucuronosyltransferases (UGTs)[4] are a superfamily of phase II biotransformation enzymes that catalyze the transfer of the glucuronyl group from 5′-disphosphoglucuronic acid to endogenou
less toxic
major UG
bin (1), a
susceptibi
Grant and
(the most
exogenous

flavones, many of which are found in the diet (3). Thus UGTs play an important role in the maintenance of steady-state levels of endogenous compounds and the handling of exoge-

total serum bilirubin concentration compared to 7/7 homozygotes (*UGT1A1*28*) (9). Corroborating these in vivo differences, enzyme studies with human liver tissue demonstrated that bilirubin-glucuronide formation by UGT1A1 was ~80%

[1] Present
Seattle, WA
(2004) Diet
morphism. A
[2] Suppor
training grant
the Universi
Environmental Health (NIEHS P30ES07033), the Clinical Research Center Facility at the University of Washington, and by the National Institutes of Health grant M01-RR-0037.

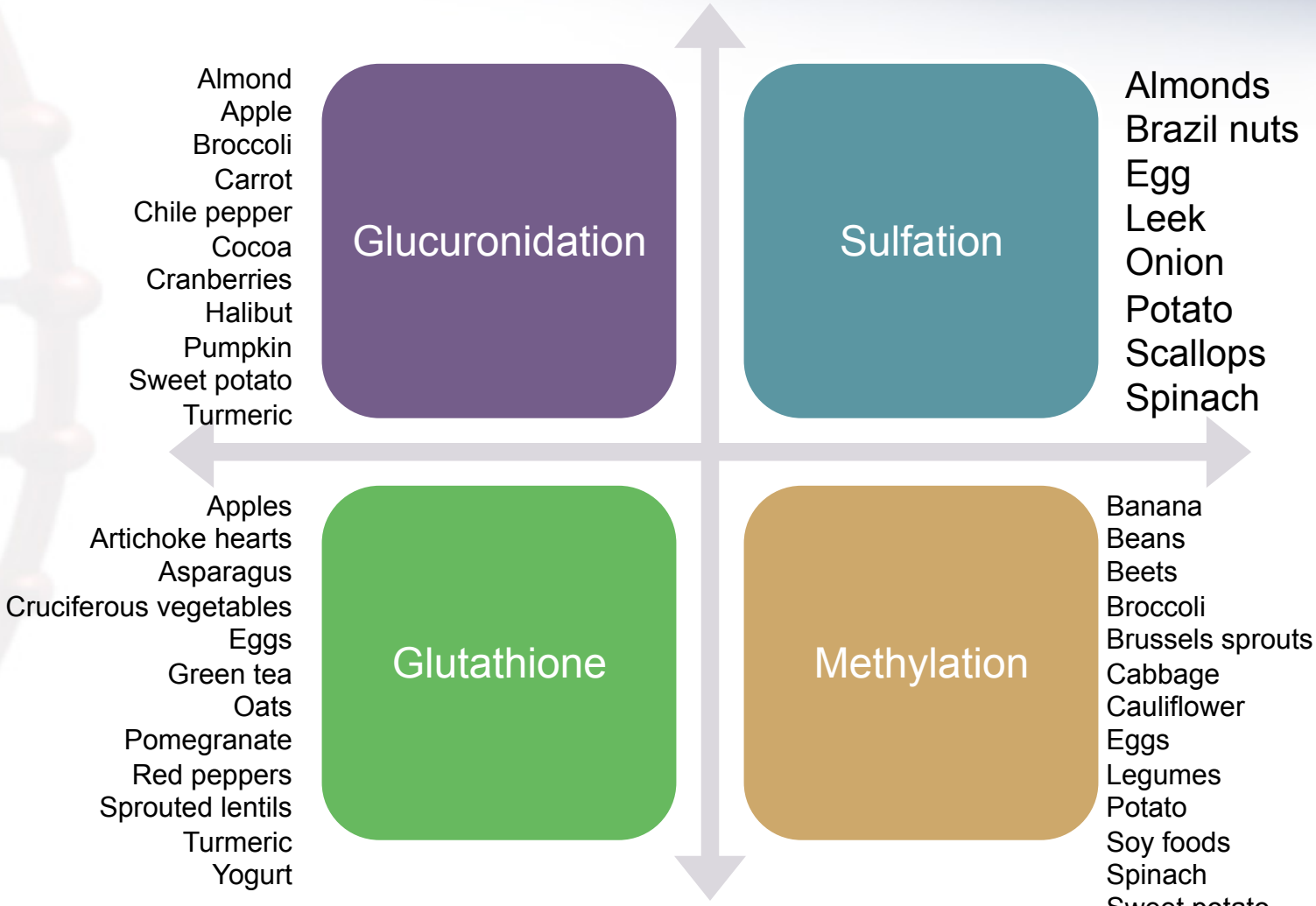
[3] To whom correspondence should be addressed. E-mail: jlampe@fhcrc.org.

[4] Abbreviations used: AhR, aryl hydrocarbon receptor; TA, thymine-adenine; UGT, UDP-glucuronosyltransferase.

Individuals with decreased UGT1A1 activity may be at greater risk for carcinogenesis, but they may modulate their risk through dietary intervention with cruciferous vegetables.

J Nutr, 2005, Vol 135: 1051-1055

Foods for Personalization of Metabolic Detoxification Pathways



Source: The Detox Prescription, Woodson Merrell, MD, 2013

THE FUTURE OF NUTRITION:

Interface between nutrition with lifestyle, psychology, environment, and physiology/genes

A typical patient's experience with Personalized Lifestyle Medicine

INITIAL

- Genetic tests run by major labs
- SNP evaluation
- Laboratory biomarkers
- Evaluation of physical symptomatology
- Assessment of lifestyle factors
  - Social networks
  - Stressors

ONGOING

- Tracking using applications
- Virtual coaches

Telemedicine for obesity

"When comparing patients who received more than one visit with either form of consultation, the TM [telemedicine] group demonstrated substantially more improvement than the FTF [face-to-face] group in improving nutrition (88% versus 65%), increasing activity (76% versus 49%), and decreasing screen time (33% versus 8%)."

Telemed J E Health. 2013 Aug 27. [Epub ahead of print]

Personalized Lifestyle Medicine Prescription

Therapeutic Modality	Intervention
Food & Supplements	• No alcohol, reduced carbohydrate • Organically-grown foods • Phytoestrogenic foods • Foods with aromatase inhibitory qualities • Phytonutrient-dense foods to reduce inflammation and to protect skin (carotenoids) • Phytomethylators
Activity	Regular moderate exercise
Stress	Stress reduction practices (e.g., meditation, yoga)
Environment	Low-toxin load; Nutritional detoxification twice annually

Supplementary Resources

- http://www.nutritionandgenetics.org/
- Genes and Nutrition Journal http://link.springer.com/journal/12263
- Journal of Nutrigenetics and Nutrigenomics http://www.karger.com/Journal/Home/232009
- Frontiers Journal: http://www.frontiersin.org/Nutrigenomics
- Ferguson LR. Nutrigenomics approaches to functional foods. J Am Diet Assoc. 2009 Mar;109(3):452-8. http://www.ncbi.nlm.nih.gov/pubmed/19248861
- Berná G1, Oliveras-López MJ2, Jurado-Ruíz E3, Tejedo J4, Bedoya F5, Soria B6, Martín F7. Nutrigenetics and Nutrigenomics Insights into Diabetes Etiopathogenesis. Nutrients. 2014 Nov 21;6(11):5338-5369. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4245593/

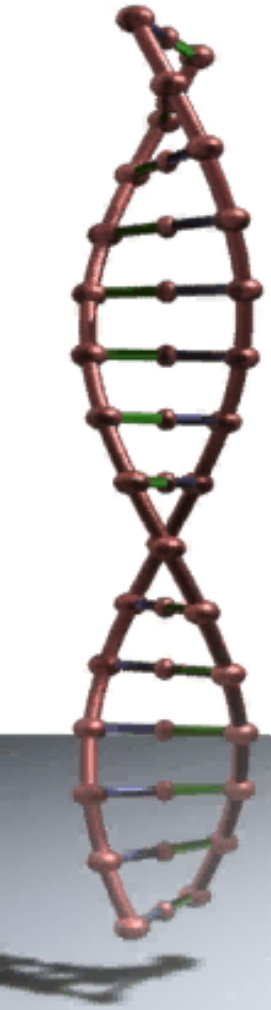
Summary

- There is a lot we now know about genes.
- There is a lot we still don't know about genes and modulation of the epigenome.
- There is still less we know about nutrigenomic application to clinical medicine.
- Food (and eating) is (are) filled with informational signals delivered to our cells.
- Don't rely solely on nutrigenetic testing for clinical application.
- See the whole picture of the patient and apply principles of personalized lifestyle medicine.

Presentation Clinical Actions

After participating in this presentation, clinicians should be better able to:

- Discuss the value of genetic testing in clinical practice
- Discuss how foods can be tailored to genes in a personalized way



Thank You!

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