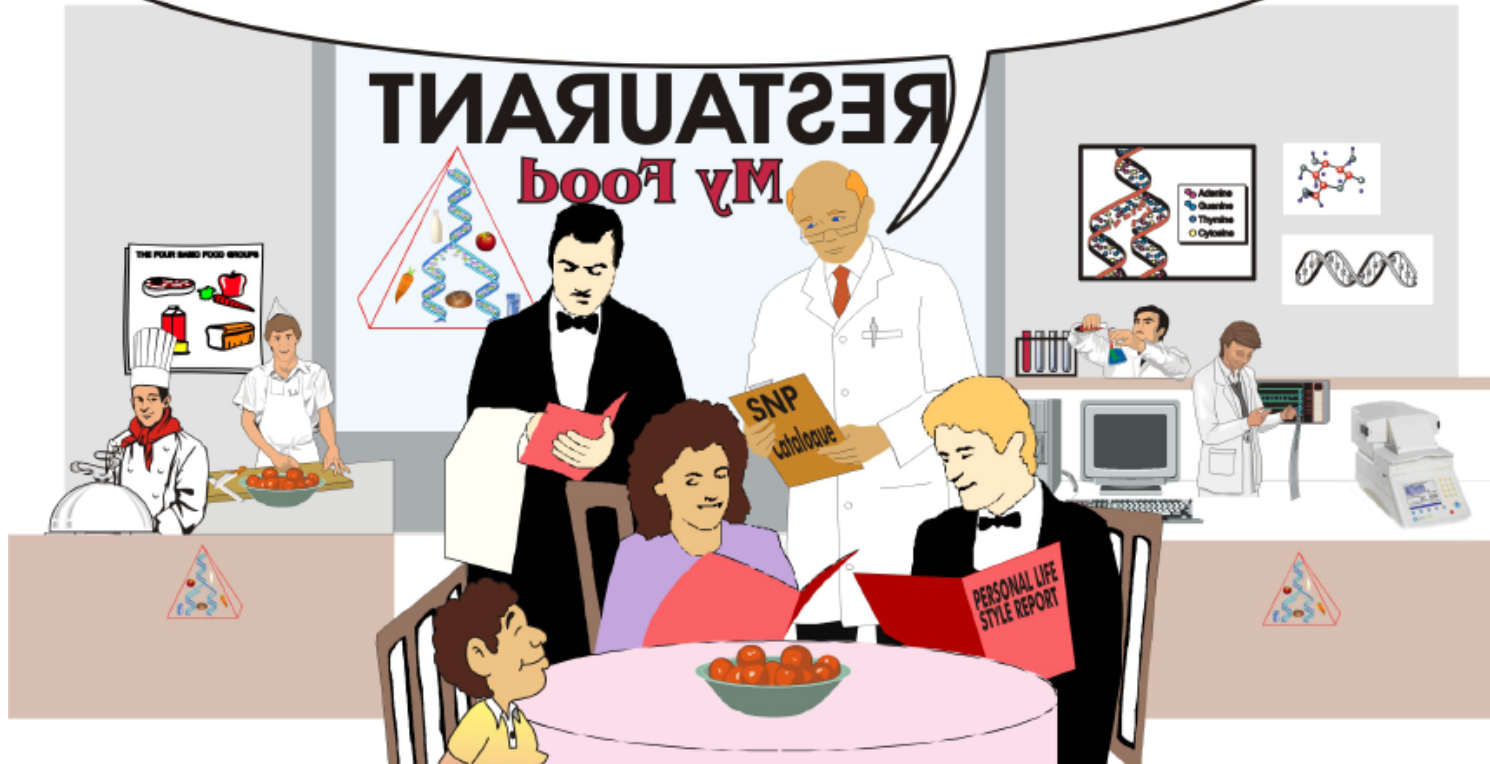


Nutrigenomics: Science or Fiction?

Mrs. Smith, based on your genetic profiles we propose that you and your son finish this dinner with a cup of coffee. Green tea would be most appropriate for Mr. Smith!



Dr. Guy Vergères
Agroscope Liebefeld-Posieux,
Federal Research Station for Animal
Production and Dairy Products, Switzerland

Content of presentation

From HUGO, the Human Genome Organization to NUGO, the European Nutrigenomics Organization

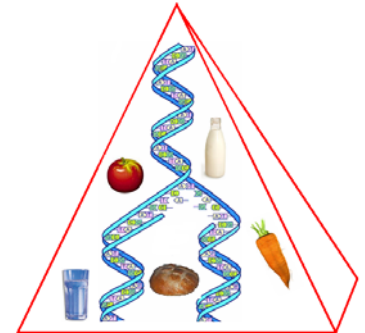
- *An overview of the science of nutrigenomics*

From bench to counter

- *Marketing applications of nutrigenomics*

From vision to realization

- *Issues related to the development of nutrigenomics*



The Paradigm of Molecular Biology

DNA



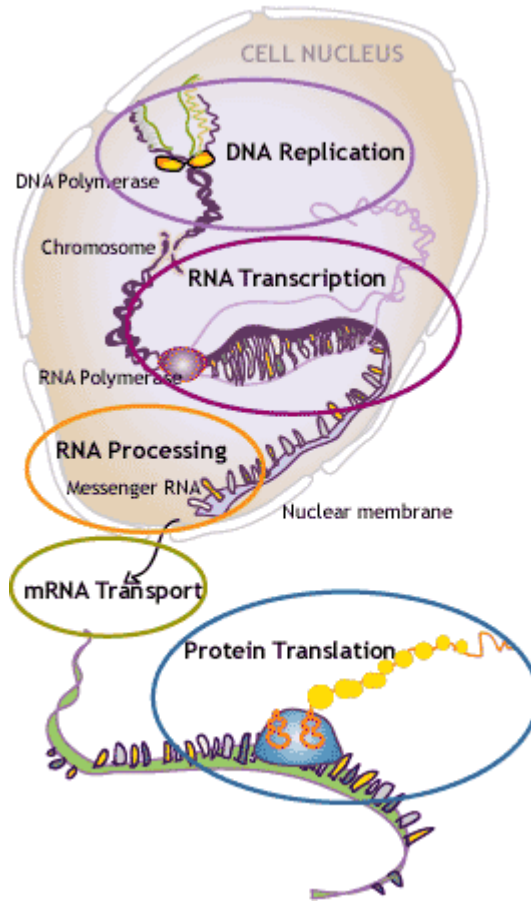
RNA



Protein



Metabolite



Phenotype

<http://nobelprize.org/medicine/educational/dna/>

The Paradigm of Modern Molecular Biology

DNA



RNA



Protein

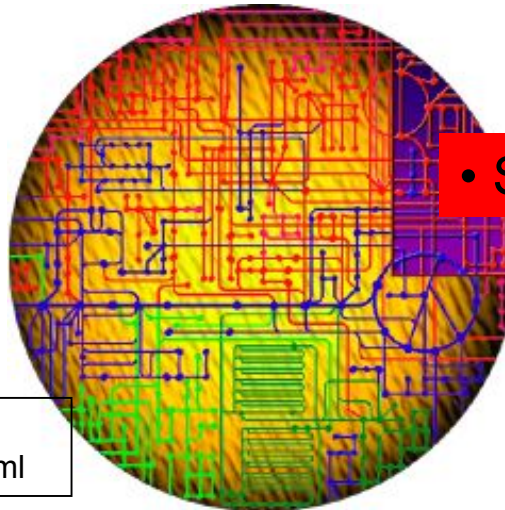


Metabolite • Metabolomics

- Genomics
- Genetics
- Epigenetics
- Transcriptomics
- Proteomics

Information („bit“) • Bioinformatics

Phenotype



• Systems Biology

Calvano et al 2005 Nature 437:1032-7
<http://pubs.acs.org/cen/coverstory/8120/8120biology.html>

The Science of Nutrigenomics

DNA



RNA



Protein

- Genomics
- Genetics
- Epigenetics
- Transcriptomics

Bioinformatics

Information

Metabolite • Metabolomics

Calvano et al 2005 Nature 437:1032-7
<http://pubs.acs.org/cen/coverstory/8120/8120biology.html>

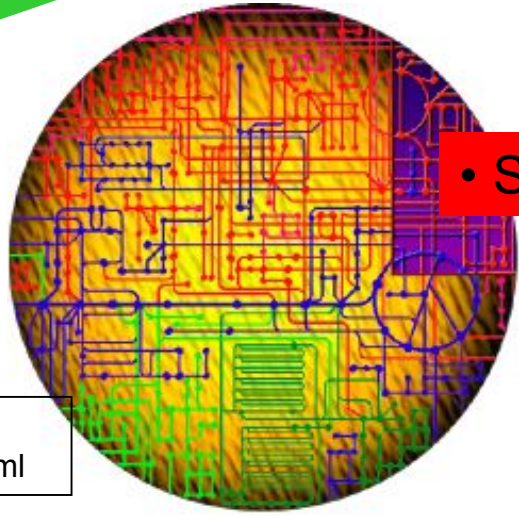
Molekulare Diagnostik 2006, Zürich / 03.03.2006 / www.alp.admin.ch
G. Vergères / guy.vergeres@alp.admin.ch

Phenotype



Modulatory action of diet

• Systems Biology



Genomics

DNA

- 3 billion base pairs
- 25'000 genes



RNA



Protein



Metabolite

Ezzell C
Genome sequencing
HUGO to go international
Nature 1989 339:3

Landers ES et al
Initial sequencing and analysis of the human genome
Nature 2001 409:860-921



Genetics

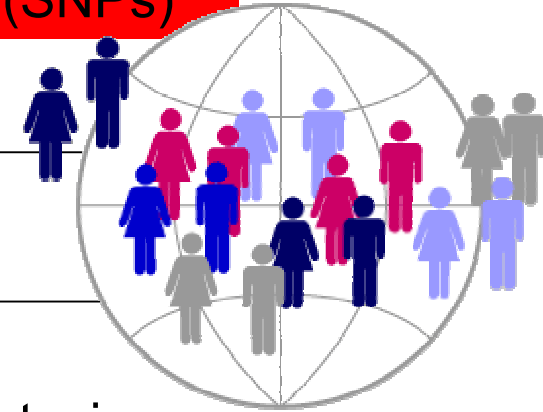
DNA

- ~ 3 million single nucleotide polymorphisms (SNPs)



RNA

The International HapMap Consortium
Nature 2003 426:789-96

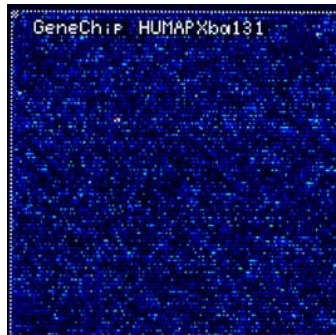


Protein

High-throughput technologies for SNP genotyping



Metabolite



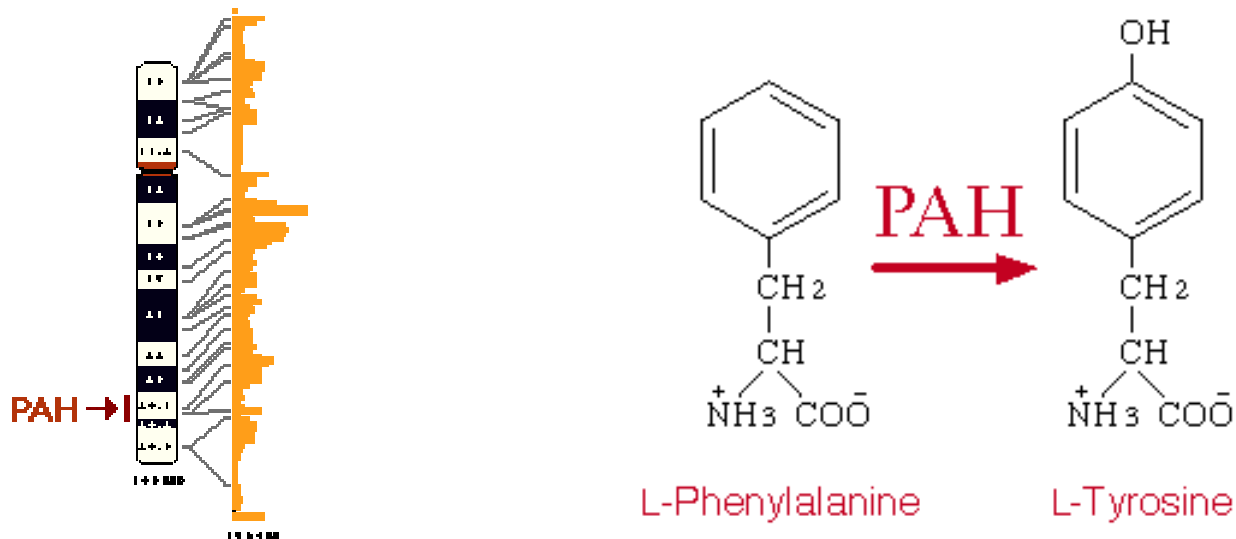
Towards personalized science

- Your genome on a DVD?
- Groups, e.g. ethnic groups

http://www.statistics.gov.uk/focuson/ethnicity/default_print.asp

Genetics and Nutrition: Phenylketonuria

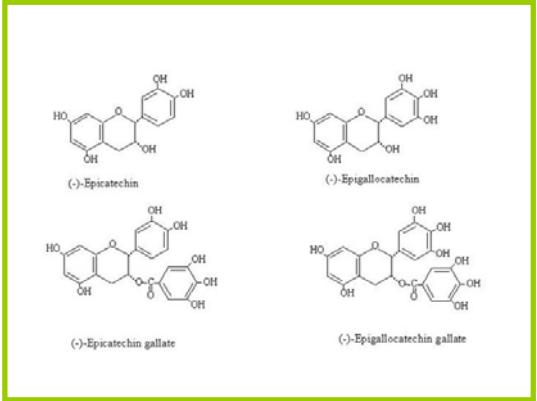
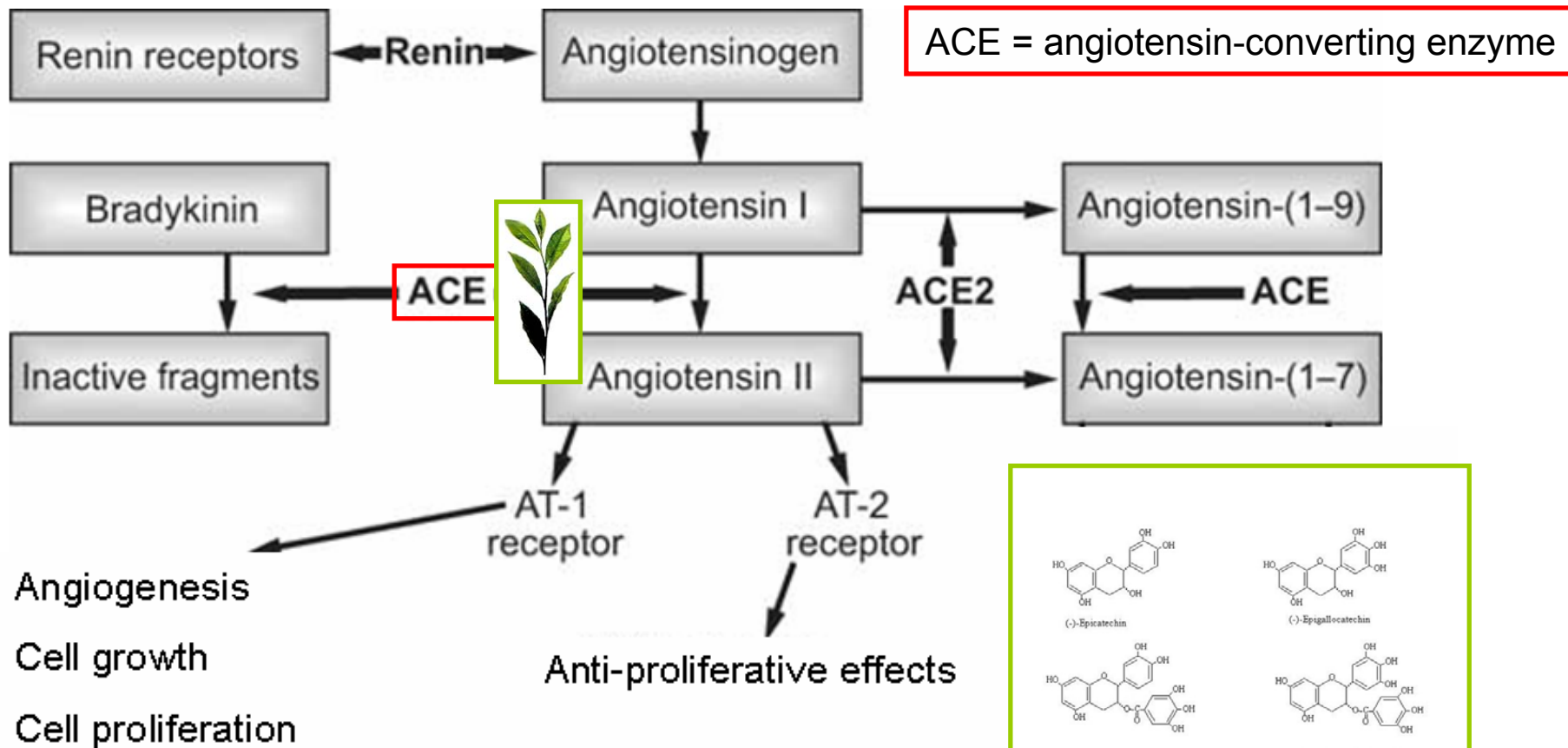
Since 1991 newborns are screened for deficiency of phenylalanine hydroxylase to identify those susceptible to phenylketonuria (PKU)



PKU babies are placed on a phenylalanine-restricted diet

<http://www.ncbi.nlm.nih.gov/SCIENCE96/gene.cgi?PAH>

ACE Polymorphism, Green Tea Intake, and Breast Cancer



<http://www.nature.com/ncpcardio/journal/v1/n1/images/ncpcardio0012-f1.jpg>

ACE Polymorphism, Green Tea Intake, and Breast Cancer



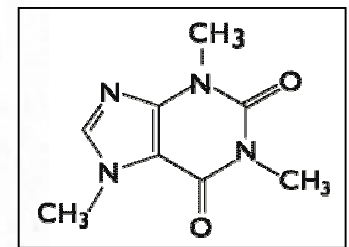
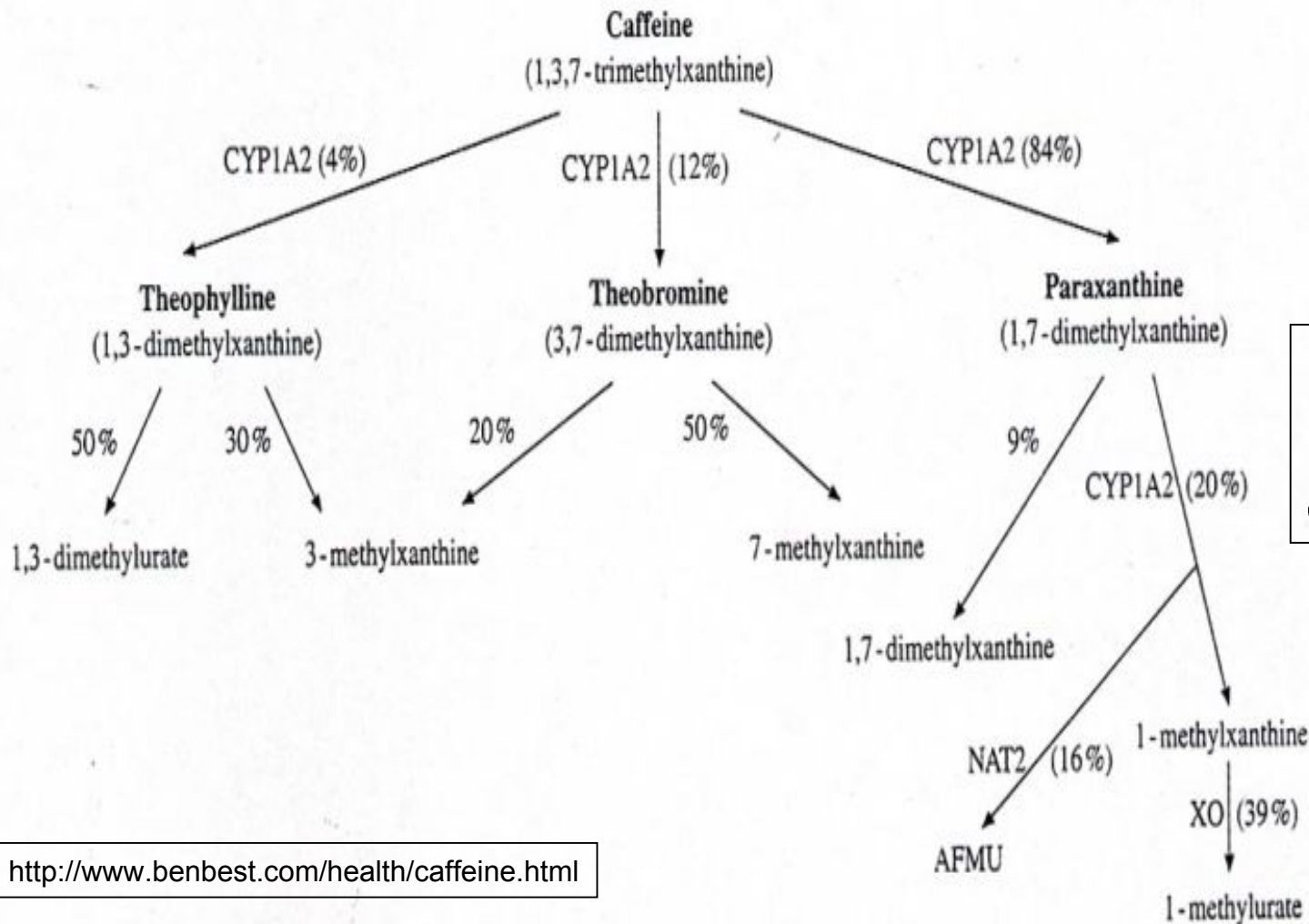
The Singapore Chinese Health Study

ACE genotypes	Cases	Controls	Drinking habit	Breast cancer risk	95% CI
all women	174	397	non-drinkers	1.00	
	123	268	monthly	1.00	0.75 - 1.32
	83	194	weekly	0.91	0.66 - 1.26
low-activity ACE	129	345	non-drinkers	1.00	
	109	239	monthly	1.18	0.86 - 1.60
	74	169	weekly	1.11	0.79 - 1.57
high-activity ACE	42	44	non-drinkers	1.00	
	11	28	monthly	0.33	0.13 - 0.82
	8	24	weekly	0.29	0.10 - 0.79

CI: confidence interval

Yuam JM. Carcinogenesis. 2005 26:1389-94

Detoxification of Caffeine by Cytochrome P450





<http://www.benbest.com/health/caffeine.html>

CYP1A2 Genotype, Caffeine Intake, and Risk of Myocardial Infarction

520 cases with first non fatal acute myocardial infarction (MI)
530 population-based controls

Risk = Odds ratio for MI between the group with >400mg caffeine per day and the group with ≤400mg caffeine per day



CYP1A2 genotype	Risk = Odd Ratio [>400mg] / [≤400mg]	95% CI
all	1.64	1.18 - 2.28
slow metabol. (734C)	 2.33	1.43 - 3.79
rapid metabol. (734A)	 1.38	0.78 - 2.44

Adapted from: **Poster presentation** by M. Cornelis, A. El-Sohehy and H. Campos
CYP1A2 genotype modifies the association between caffeine intake and risk of myocardial infarction
Experimtnal Biology 2004 Washington, DC - http://select.biosis.org/faseb/eb2004_data/FASEB004706.html

Low-Fat Dietary Pattern and Risk of Cardiovascular Disease

Women's Health Initiative Randomized Controlled Dietary Modification Trial (n = 48'835)

Dietary intervention (8.1 years) that reduced total fat intake and increased intakes of vegetables, fruits, and grains

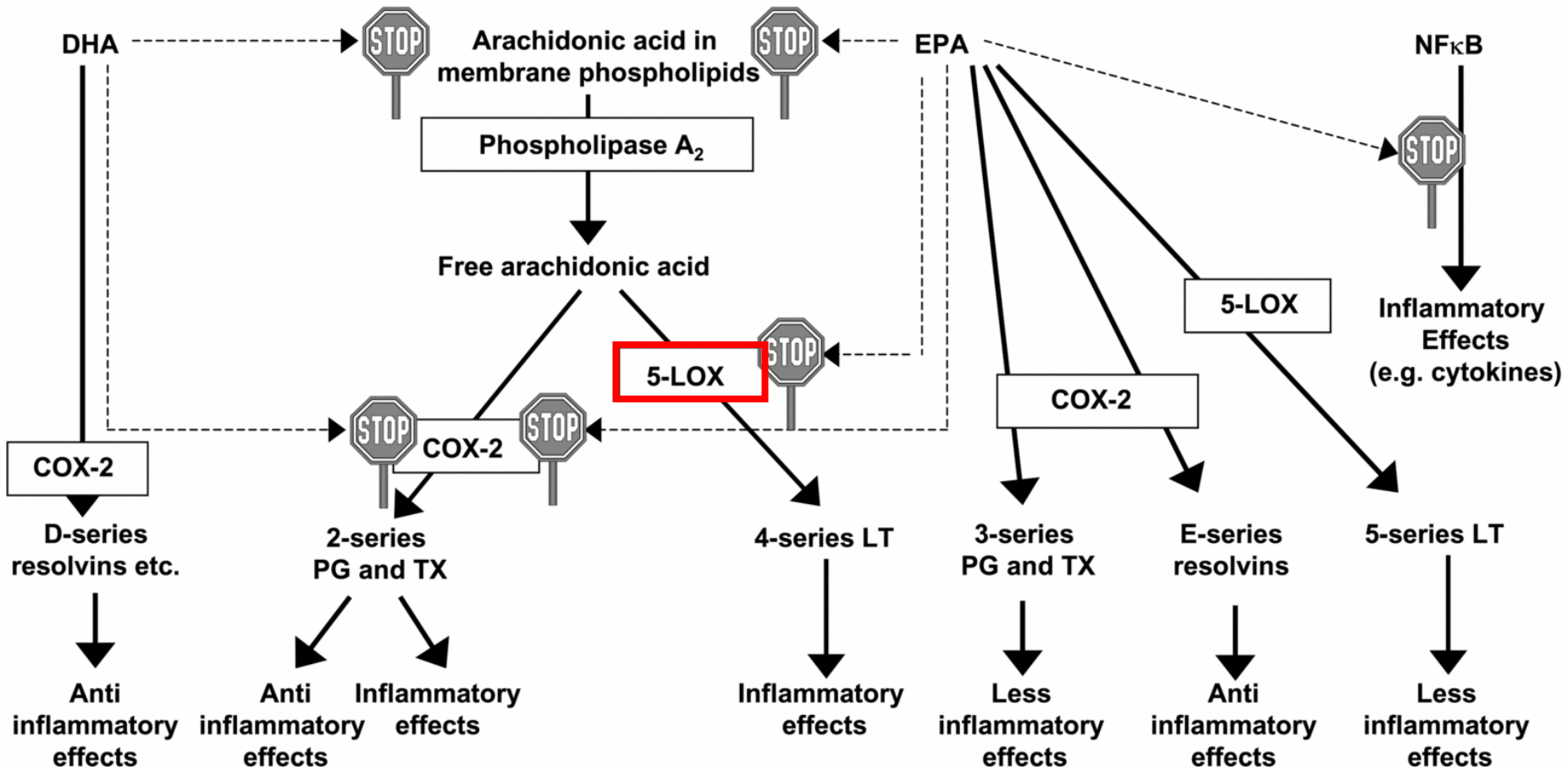
- No significant reduction of risk of cardiovascular diseases (CVD) (coronary heart disease, stroke) in postmenopausal women
- Only modest effects on CVD risk factors

Conclusion

More focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk

Howard BW et al. JAMA. 2006 295:655-66

Long-chain Polyunsaturated Fatty Acids (PUFAs) and Inflammation



<http://www.benbest.com/health/essfat.html>

5-LOX = arachidonate 5-lipoxygenase

Arachidonate 5-Lipoxygenase (5-LOX) Promoter Genotype and Atherosclerosis

5-LOX promoter:

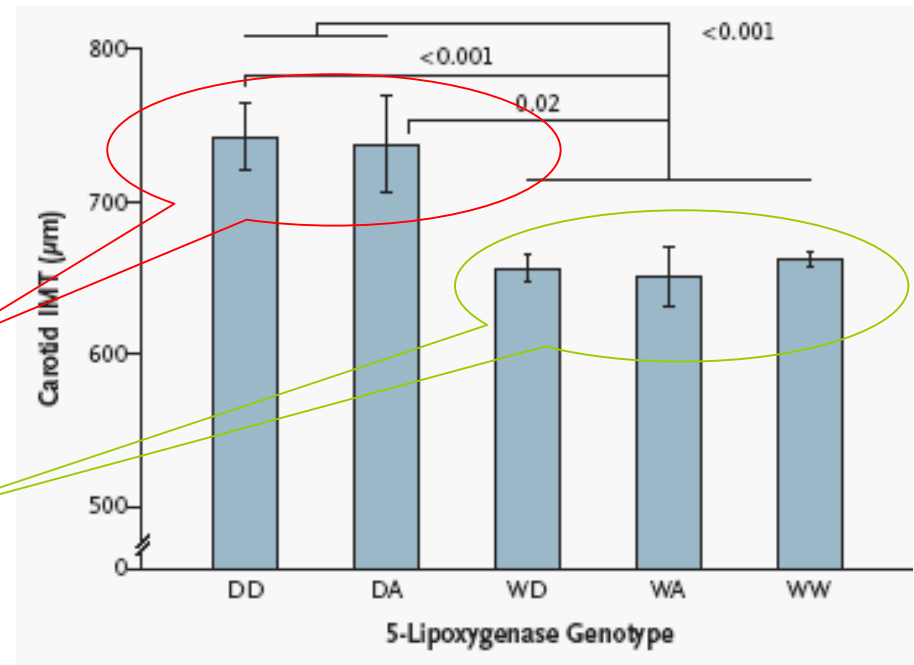
W: common

D: deletion

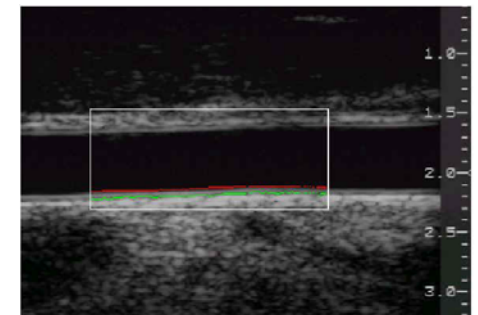
A: addition

Carriers of two variant alleles
DD or DA: n = 28 (6%)

Carriers of common allele
(WW, WA, or WD): n = 442 (94%)

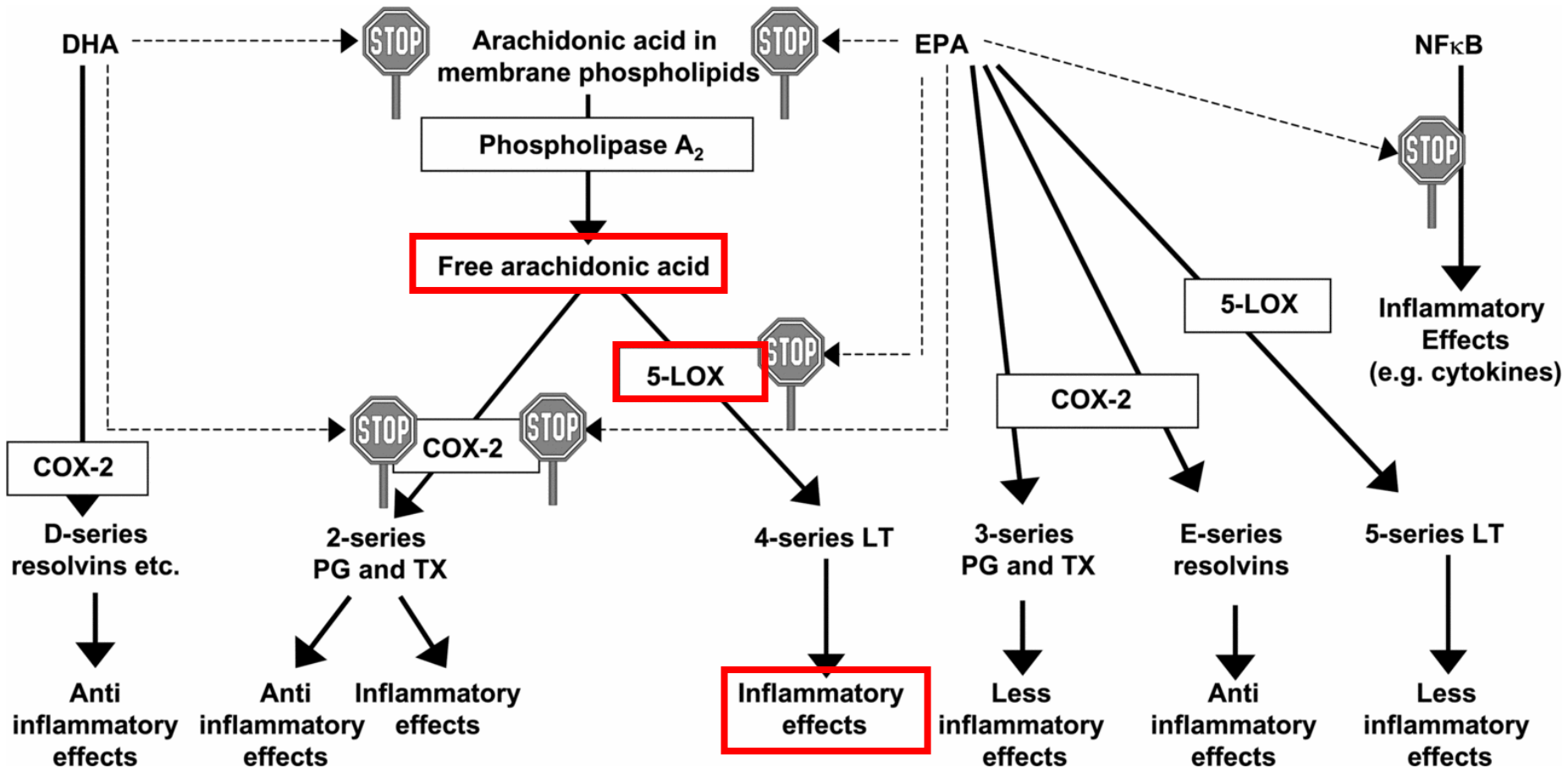


Carotid IMT =
carotid intima-media
thickness



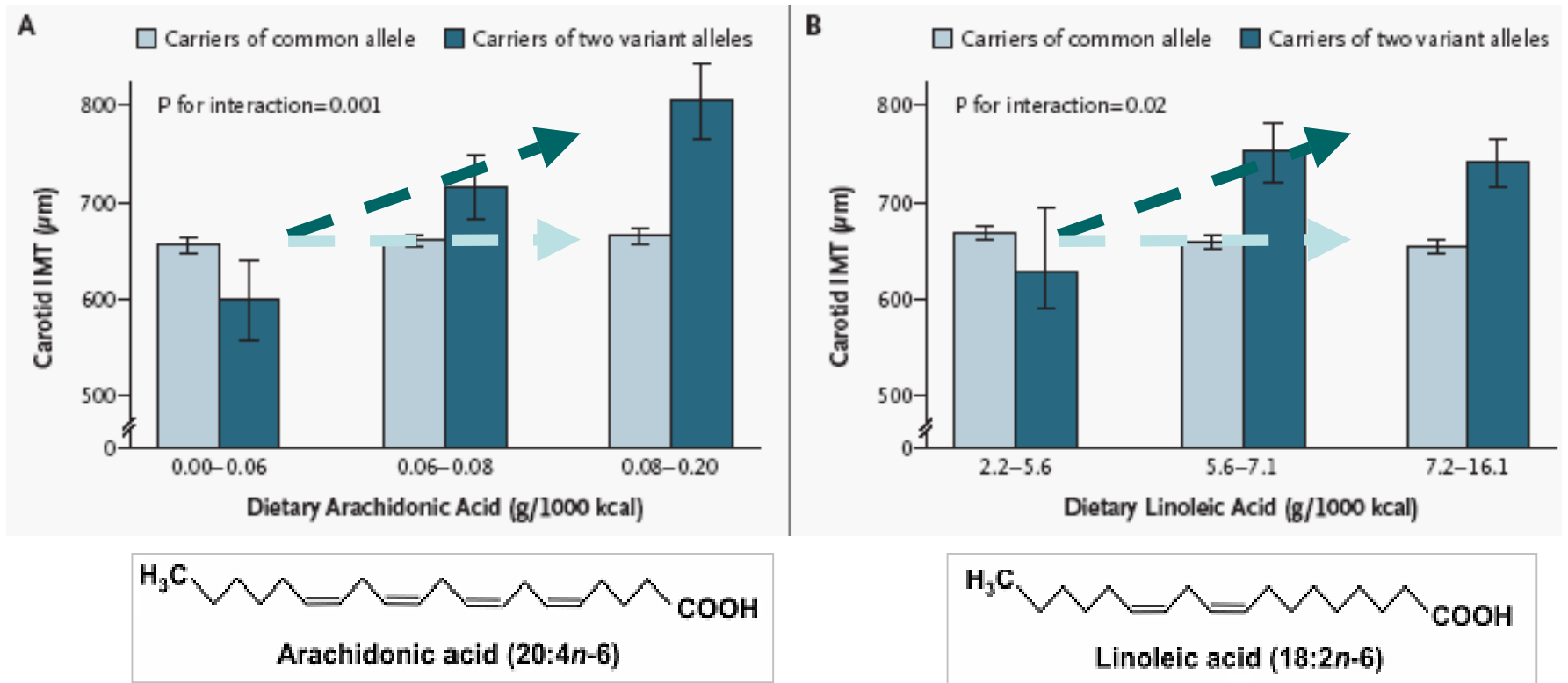
Dwyer JH et al. N Engl J Med. 2004 350:29-37;
<http://www.fac.org.ar/cvirtual/cvirteng/cienteng/cieng/cic0606i/isimon.htm>

Long-chain PUFAs and Inflammation



Graphic:
<http://www.benbest.com/health/essfat.html>

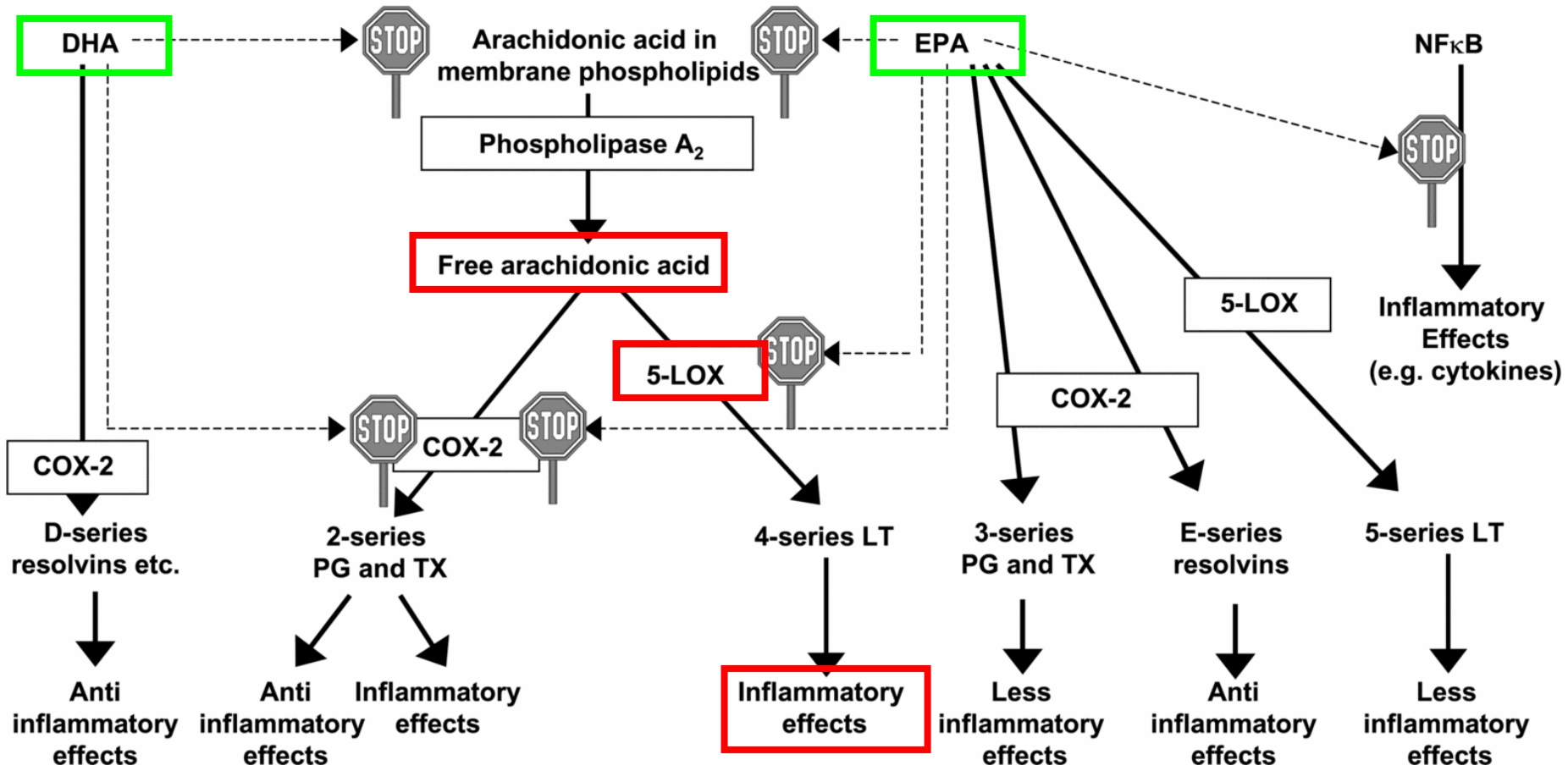
5-Lipoxygenase Promoter Genotype, Dietary PUFAs, and Atherosclerosis



➤ Atherosclerotic effect of n-6 PUFA among carriers of two variant alleles?

Dwyer JH et al. N Engl J Med. 2004 350:29-37

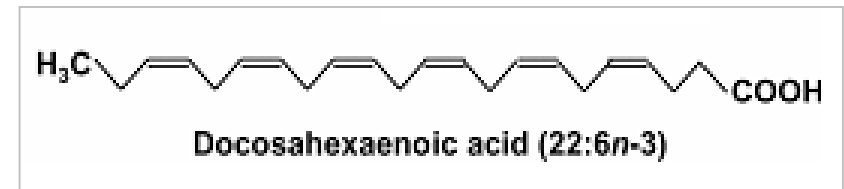
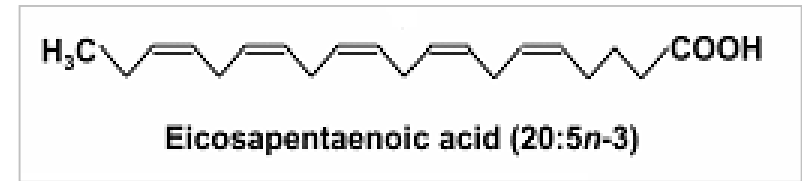
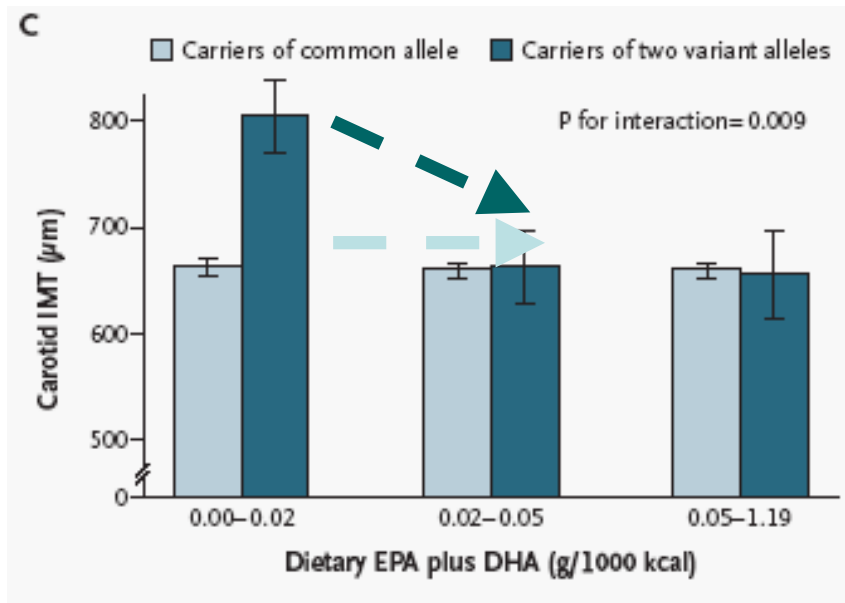
The Current View of Anti-inflammatory Actions of Long-chain *n*-3 PUFAs



<http://www.benbest.com/health/essfat.html>

EPA = Eicosapentaenoic acid
DHA = Docosahexaenoic acid

5-Lipoxygenase Promoter Genotype, Dietary PUFAs, and Atherosclerosis



- Antiatherosclerotic effect of n-3 PUFA among carriers of two variant alleles?

Dwyer JH et al. N Engl J Med. 2004 350:29-37

Epigenetics

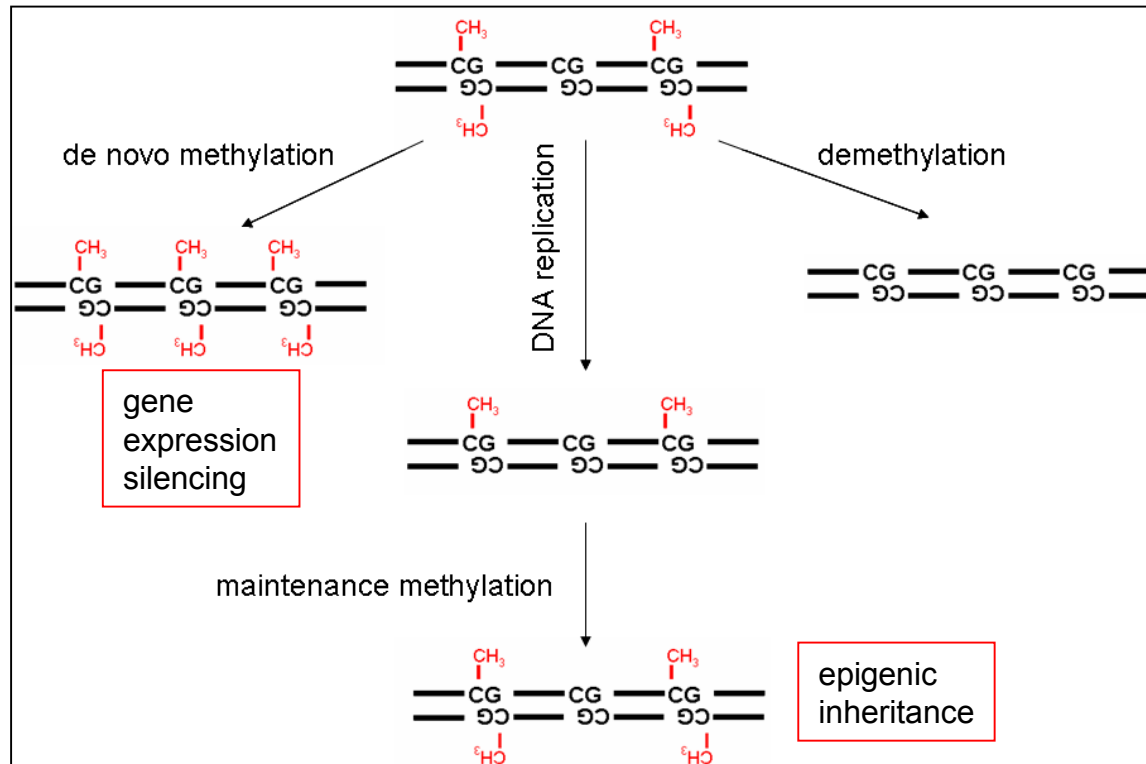
DNA

- Hundred thousands of hypermethylated CpG islands

RNA

Protein

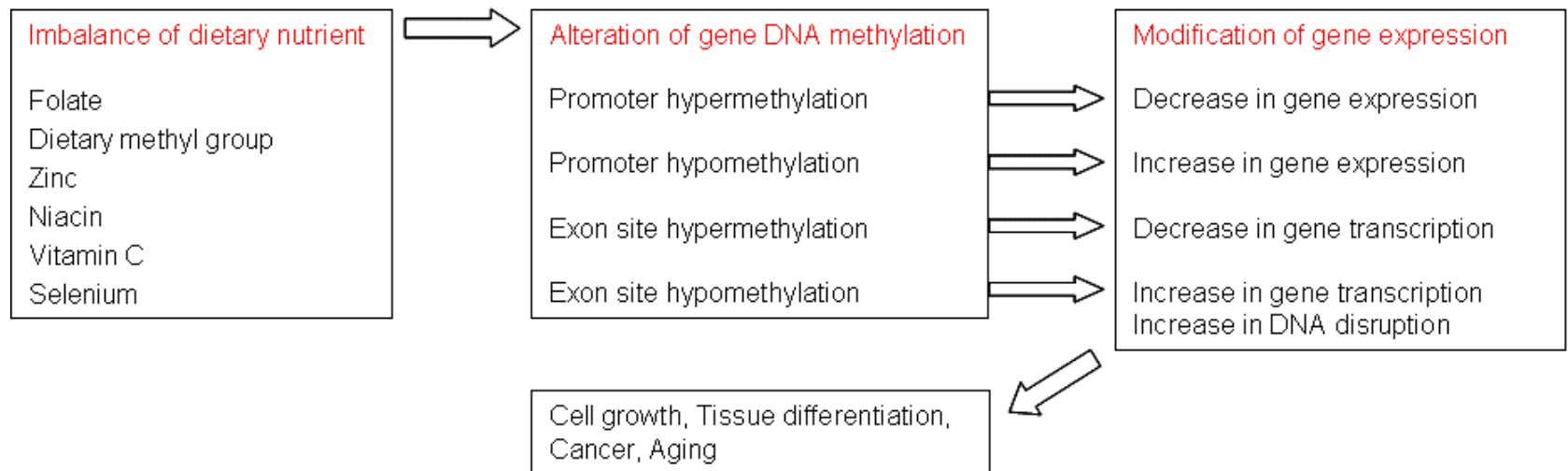
Metabolite



<http://www.wellcome.ac.uk/en/genome/thegenome/hg02b002.html>

Epigenetics and Nutrition: Nutrient-induced DNA Methylation

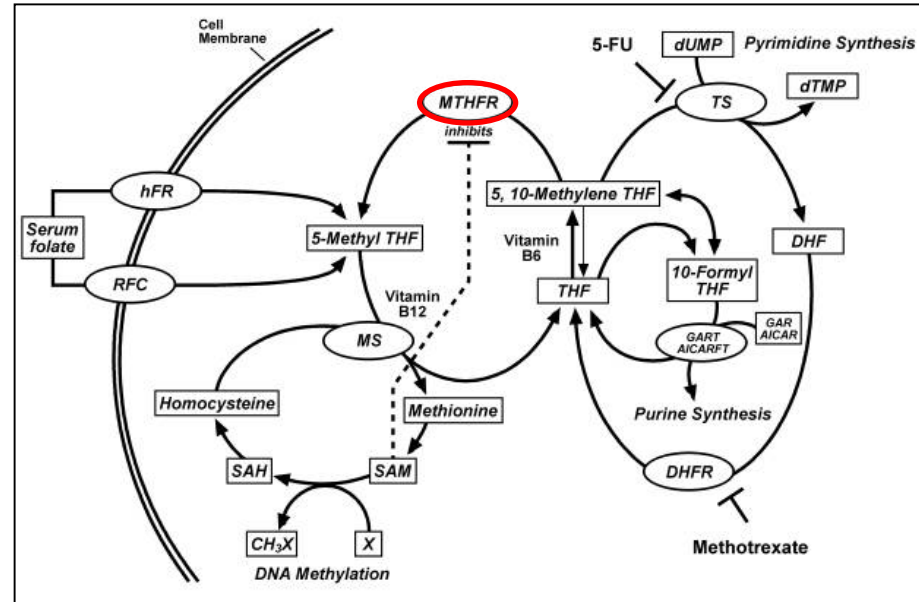
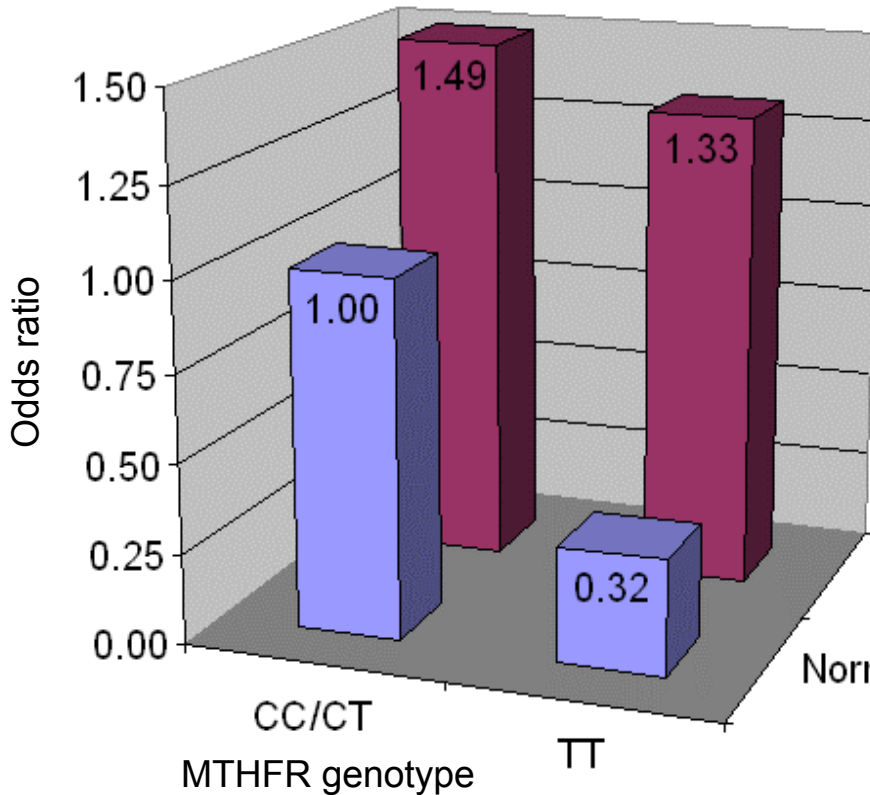
Many micronutrients (folate as methyl donor) and vitamins are critical for DNA synthesis/repair and maintenance of DNA methylation patterns



Friso S and Choi SW; J Nutr. 2002 132:2382S-2387S

Folate Status, MTHFR Genotype, and Colorectal Cancer Risk

Physician's Health Study



Deficient serum folate (<3ng/ml)

Normal serum folate (>3ng/ml)

MTHFR = methylene tetrahydrofolate reductase

Bailey LB. J Nutr. 2003 133:3748S-3753S
http://www.cdc.gov/genomics/hugenet/reviews/tables/MTHFRLeuk_Tables.htm

Early Nutritional Effects on Epigenetic Gene Regulation: the Agouti Mice Model

Hypomethylation:
high risk of cancer,
diabetes, and obesity;
reduced lifespan



Yellow Slightly mottled Mottled Heavily mottled Pseudo-agouti

Hypermethylation:
lower risk of cancer,
diabetes, and obesity;
prolonged life

Maternal supplements (methyl donors: folate, ...) affects the phenotype of offspring by influencing the degree of CpG methylation at the agouti locus

➤ Role of prenatal nutrition in prevention of chronic diseases?

Waterland RA & Jirtle RL 2003 Mol Cell Biol 23:5293-5300

Transcriptomics

DNA



RNA

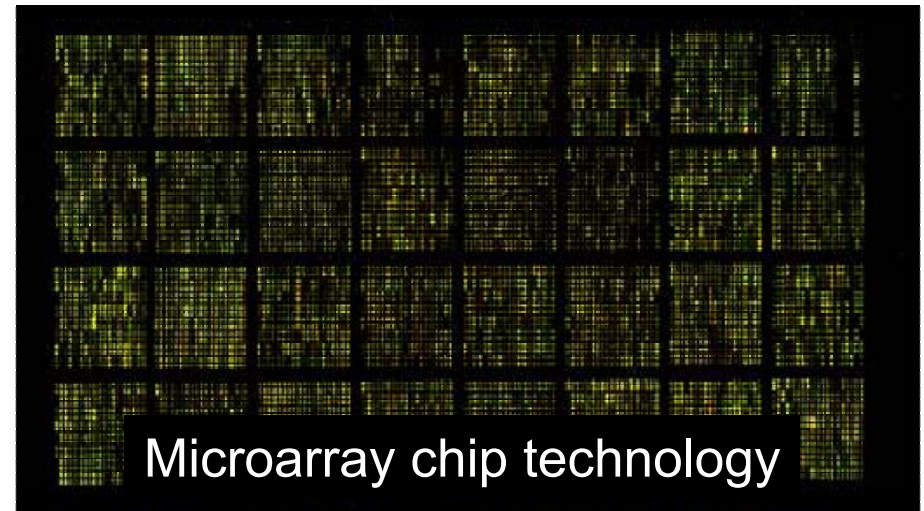
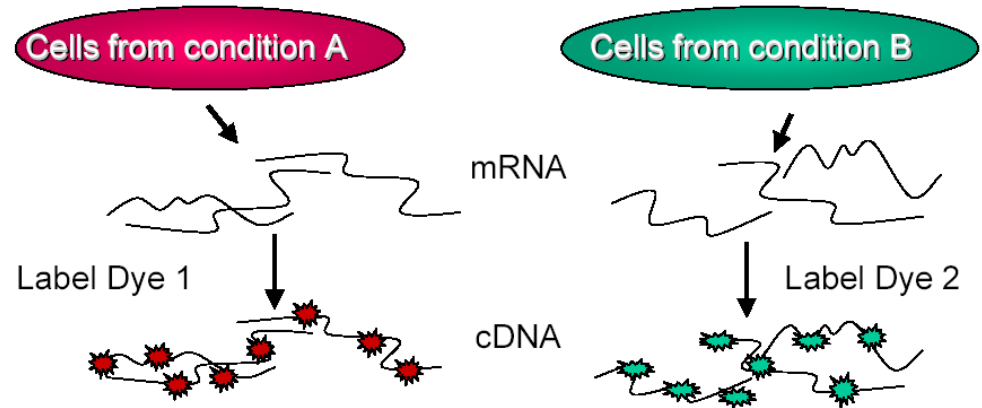
• ~ 100'000 mRNAs



Protein



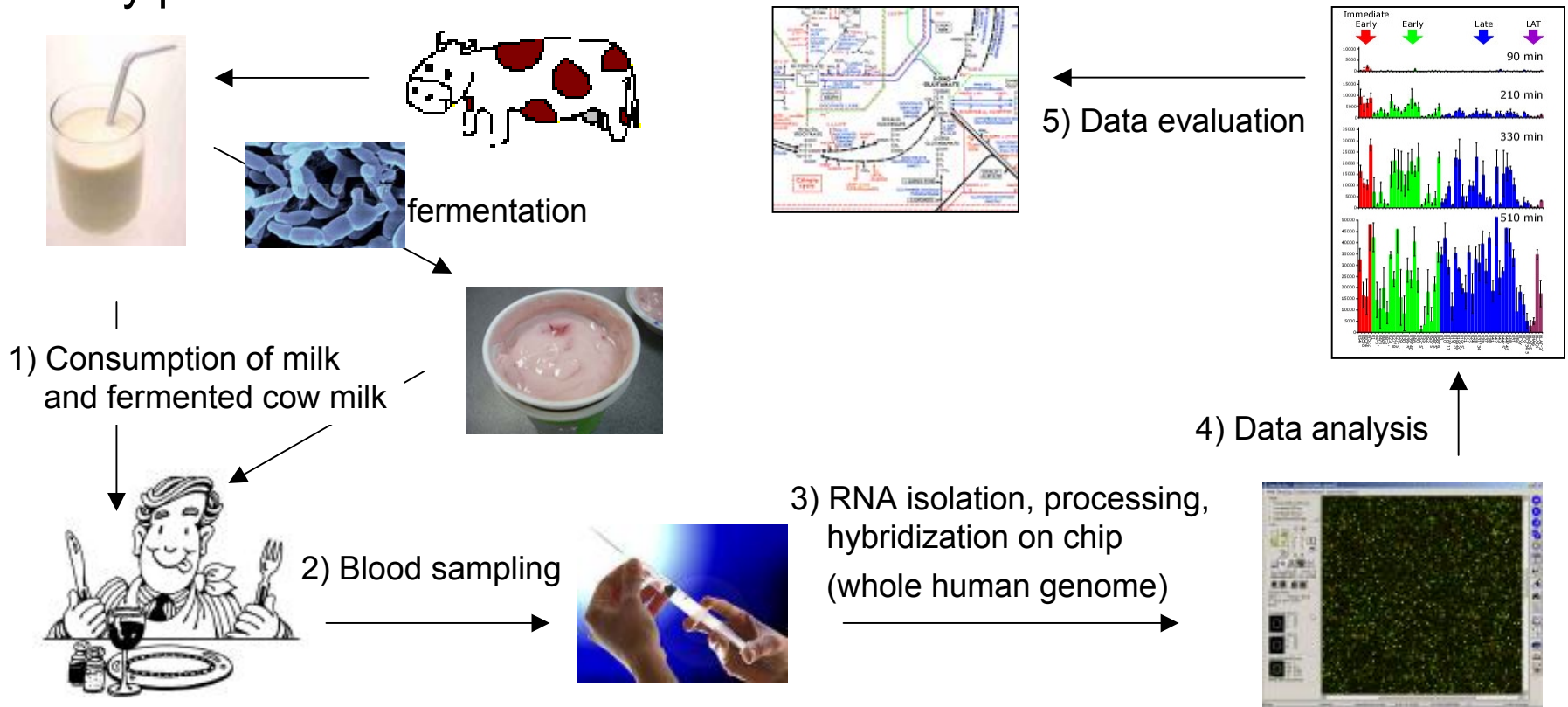
Metabolite



http://soybeangenomics.cropsci.uiuc.edu/files/NSF_Web_Microarrayresults.pdf

Transcriptomics and Nutrition: The Blood Cell Transcriptome as a Biomarker

Gene expression profiling of humans exposed to fermented dairy products



G. Vergères, Agroscope Liebefeld-Posieux, 2006

Proteomics (and nutrition?)

DNA



RNA

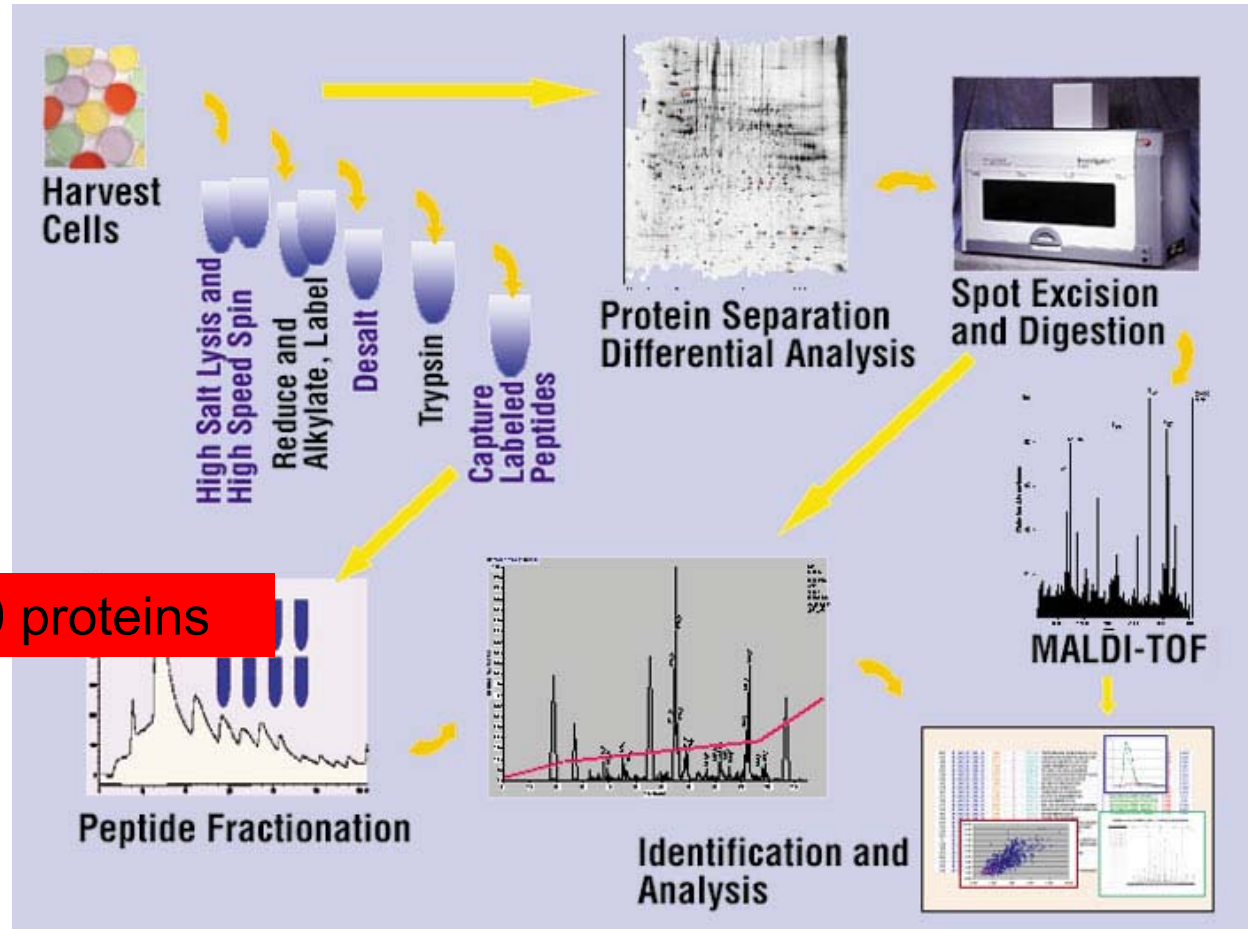


Protein

• ~1'000'000 proteins



Metabolite



http://www.genpromag.com/images/0306/gp36app_a_lrg.jpg

Metabolomics (and nutrition?)

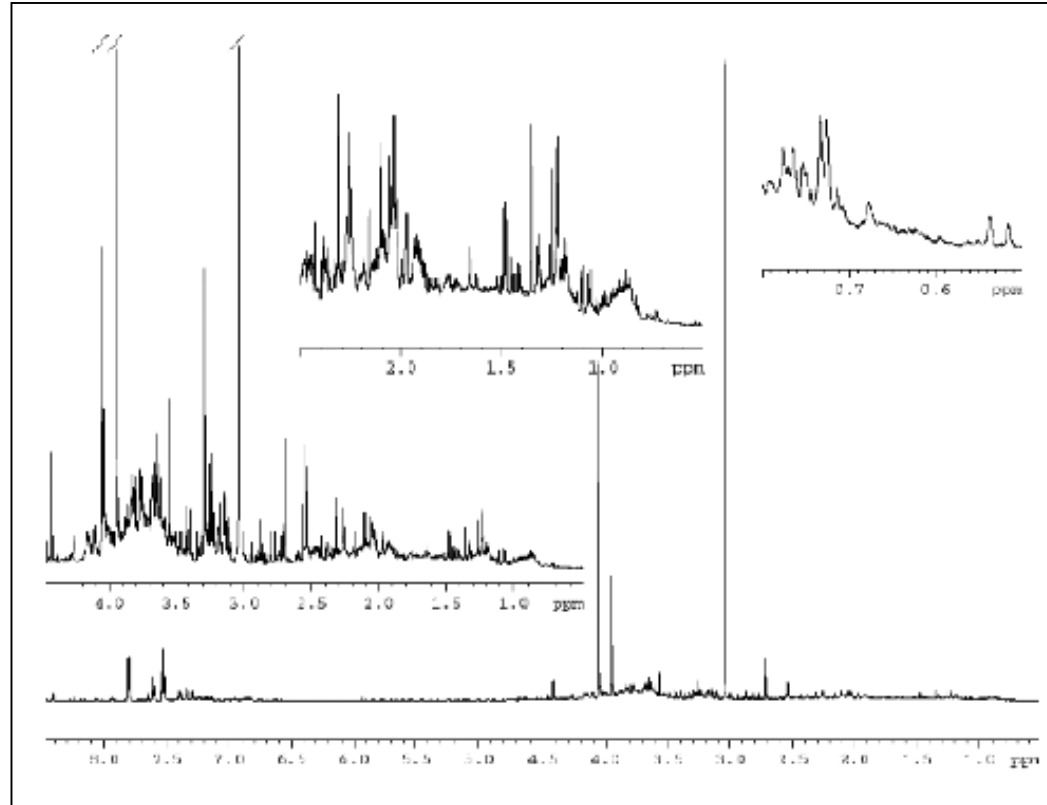
DNA



RNA



Protein



Metabolite

- Thousands of metabolites

http://www.touchbriefings.com/pdf/855/fdd041_metabomatrix_tech.pdf

Key Concepts in Nutrigenomics

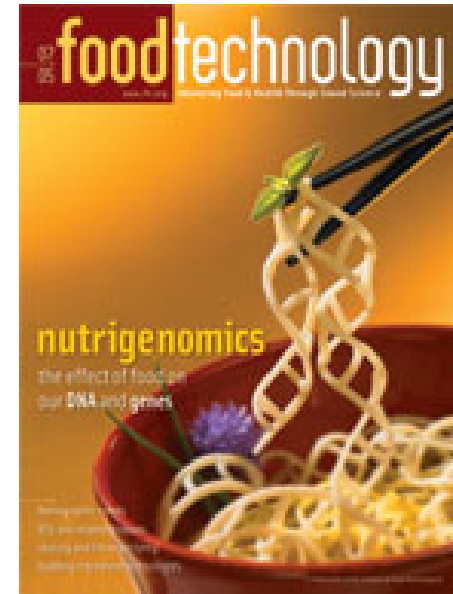
Nutrigenomics is the application of the omics sciences (genomics, transcriptomics, proteomics and metabolomics) to nutrition research

Diet is a major risk factor for five of the leading causes of death: coronary heart disease, cancer, diabetes mellitus, stroke, atherosclerosis

Nutrigenomics is aimed at preventing chronic diseases by the diet whereas pharmacogenomics aims at treatment using drugs

This requires understanding, and ultimately regulating, a multitude of nutrient-related interactions at the gene, protein and metabolic levels

Nutrigenetics investigates variations in selected genes to provide personalized advice about nutrition and health



Marketing of Nutrigenomics

Selected nutrigenomics companies

GeneLink, NuGenix

Great Smokies Diagnostic Lab

Sciona

Seryx

Product lines

Nutrigenetic Profile™

Genovations™

Cellf™ Genetic Assessment

Signature Genetics™

Selected Company Profile: Sciona

Consumer Direct

Sciona sells nutrigenetic assessment kits directly to consumers through multilevel marketers, catalogs and via the Internet. Sciona has sold over 10,000 kits through these direct channels. Consumer feedback has been extremely positive to this novel way of adapting diet and lifestyle, based on a individual's genetic profile.

Retail Partners

www.pharmaca.com

www.eq-life.com

www.prairiestonerx.com

www.lundsmarket.com

www.byerlys.com

www.hy-vee.com

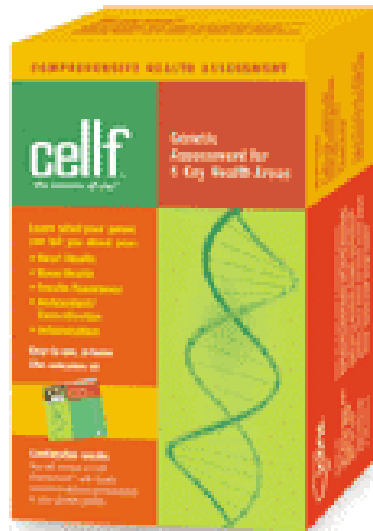
www.ukrops.com



<http://www.sciona.com>

Selected Company Profile: Sciona

Products



New Cellf Comprehensive Test

NEW! A combined analysis of nineteen genes that may play an important role in how your body manages bone health, heart health, antioxidant and detoxification, insulin resistance and inflammation. Perfect for those who want a complete snapshot of their overall risk profile and recommendations for achieving optimal health without a specific disease focus.

See Individual Product Specifications or **BUY NOW!**

<http://www.sciona.com>



Buy Now!

Selected Company Profile: Sciona



Heart Health

Gene Analyzed	Role of the Gene in Heart Health	Genetic Variation Screened For Variations Found in Your Gene	Percentage of Population with this Gene Variation*
MTHFR	Use of Folic Acid for DNA Synthesis or DNA Repair	C677T A1298C	28.7 30.0
MS_MTRR	Metabolism of Vitamin B12	A66G	47.3
MTR	Removal of Homocysteine	A2756G	17.4
CBS	Metabolism of Vitamin B6 and Removal of Homocysteine	C699T	28.0
MnSOD	Antioxidant Defense	C(-28)T	54.2
SOD3		T175C	
		C760G	
IL-6	Inflammatory Response	G(-174)C	36.3
TNF-α		G(-308)A	16.5
APOC3	Triglyceride Metabolism	C3175G	12.6
CETP	Cholesterol Metabolism	G279A	37.0
LPL		C1595G	9.9
eNOS	Blood Flow	G894T	35.6
ACE		DEL	61.0

<http://www.sciona.com>

Delivery of Nutrigenomics Services

PERSONAL LIFESTYLE REPORT

Your Personal Lifestyle Report highlights the ways in which your current habits are in line with healthy living and points out areas that may require special attention. Our recommendations are unique to you. While much of the advice may seem to be simple common sense, it was compiled with your specific genetic profile in mind.

For quick reference, our advice is summarized in this brief table. More detailed guidelines are found on the following pages, along with background information about specific foods and lifestyle choices.

Dietary/ Lifestyle Factors	Our advice
Folate	Increase intake of folate as variation in your genetic profile has been found
Vitamin B6	Increase intake of B6 on account of variation in your genetic profile
Vitamin B12	Increase intake of B12 in view of your personal profile
Fruit and vegetables	Incorporate servings of fruits and vegetables to your daily diet to complement your personal profile
Cruciferous vegetables	Add these vegetables to your diet to complement your personal profile

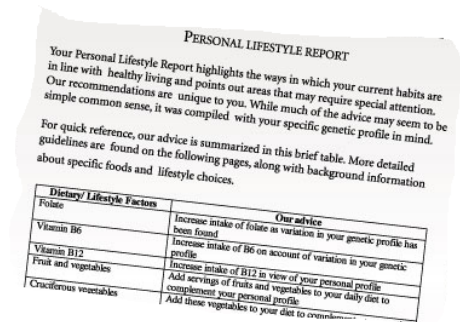
<http://www.the-scientist.com/2005/1/17/14/1/>

Delivery of Nutrigenomics Services

Predictive value of nutrigenomics testing is still limited

Predictive wellness or lifestyle tests are not advertised as being predictive for any specific disease, through there is sometime a known correlation between diseases and the genes analyzed

The tests are offered rather as useful for the promotion of healthy dietary choices

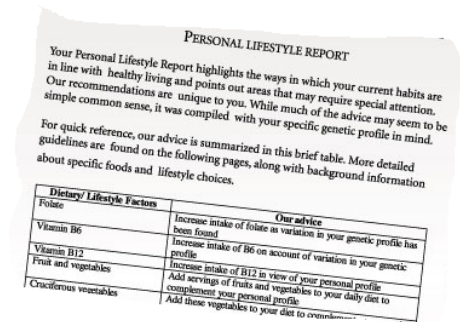


Nutrition and genes: science, society and the supermarket. The opportunities and ethical challenges of the new science of nutritional genomics. Canadian program on genomics and global health. 2004

The Consumer Market for Nutrigenomics Services

Survey results indicate that:

- Nearly half of Americans are ready to use diet-related products tailored to their health needs based upon their genetic make-up
- The consumer would be willing to pay up to US\$ 400 for a nutrigenetic test



<http://cogentresearch.com/whatsnew/cgatpr111303.html>
<http://www.sciona.com/sciona-corpoarte-brochure.pdf>

The Point of View of GeneWatch

GeneWatch UK is a not-for-profit group that monitors developments in genetic technologies from a public interest, environmental protection and animal welfare perspective

- Efficacy, safety, regulatory, and ethical issues of nutrigenomics are not resolved
- An action of GeneWatch in UK, forced Sciona to withdraw genetic tests combined with dietary advice from the Body Shop in 2001

Bottom line (GeneWatch):

- *“Buying nutrigenetic tests is a waste of money”*

www.genewatch.org

Scientific Issues in Nutrigenomics

Predictive value of genetic polymorphisms

- More than one gene plays a role in the development of most diseases
- Each gene appears to lead to small increases in susceptibility
- Genetic testing can indicate susceptibility, not future disease

Holistic view of nutrition

- Bioinformatic approach
- Large cohorts of subjects necessary (500'000!)

Closing the gap between claims of nutrigenomics companies and the knowledge gap in diet-gene interaction

1) Ferguson LR. and Kaput J. Food New Zealand 2004 29-36; 2) Nutrition and genes: science, society and the supermarket. The opportunities and ethical challenges of the new science of nutritional genomics. Canadian program on genomics and global health, 2004 .3) Lancet. 2003 361:567-71

Potential Benefits of Nutrigenomics

In chronic diseases a small number of genes may play a disproportionate role in disease development, and may be especially responsive to dietary manipulation

- Personalized recommendations for food as adjunct, possibly as replacement for prescription drugs
- Increased role for prevention in health management
- Health care saving

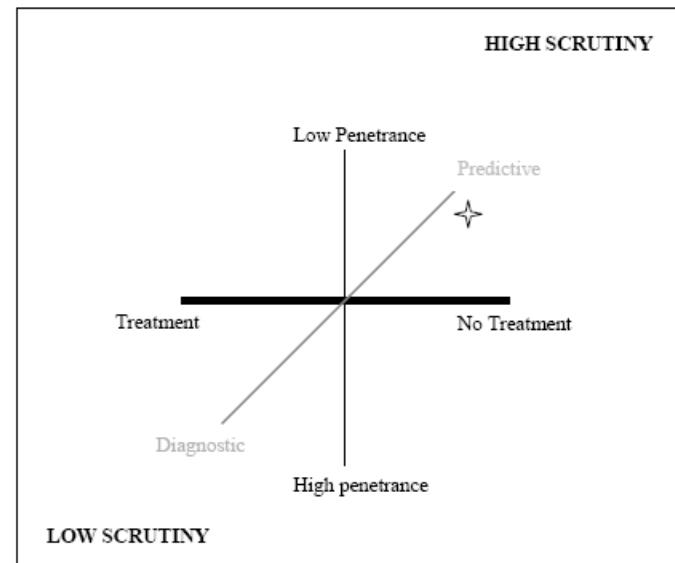
1) Ferguson LR. and Kaput J. Food New Zealand 2004 29-36; 2) Nutrition and genes: science, society and the supermarket. The opportunities and ethical challenges of the new science of nutritional genomics. Canadian program on genomics and global health. 2004

Criteria to Assess the Benefits and Risks of Genetic Tests (Validation)

Enhancing the oversight of Genetic Tests: Recommendation of the Secretary's Advisory Committee on Genetic Testing (SACGT), July 2000

Criteria

- Analytical validity
- Clinical validity
- Clinical utility
- Social consequences



http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf

Regulatory Aspects of Nutrigenomics

Debate on competences of regulatory agencies in the EU and USA in regulating genetic testing

The FDA assesses the clinical validity (but not the clinical utility) of genetic tests sold as kits. Tests that are provided as 'clinical laboratory services' are not assessed

As nutritional genomic research establishes more specific links between specific food and diseases, the line between food and drugs may become more blurred

➤ Regulation under which statutes?

Nutrition and genes: science, society and the supermarket. The opportunities and ethical challenges of the new science of nutritional genomics, 2004

Ethics and Socio-economics of Nutrigenomics

Informed consent

Confidentiality, storage and usage of data and samples

Familial consequences of genetic information

Testing of children, prenatal testing and epigenetics

Health disparities and genetic discrimination in subpopulations, including ethnic racial minorities, the poor, and the elderly

Non-medical use of genetic information by interested third parties, such as employers and insurers

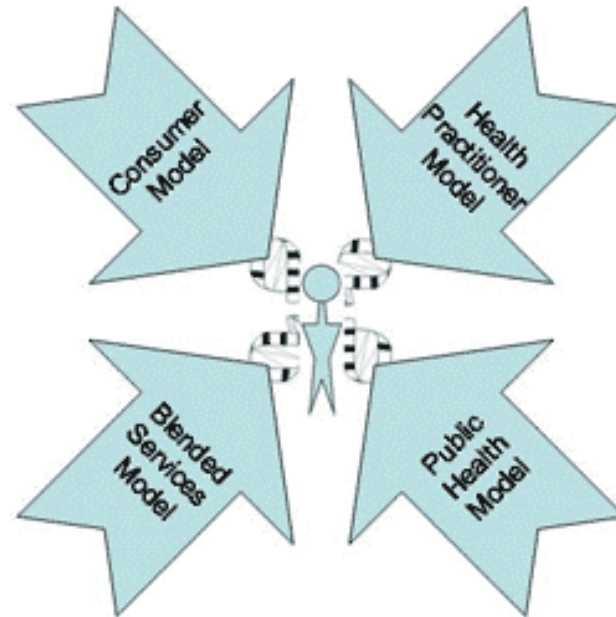
Risk of misleading thinking by consumer that „good genes“ can cope with a bad diet

Nutrition and genes: science, society and the supermarket. The opportunities and ethical challenges of the new science of nutritional genomics. Canadian program on genomics and global health. 2004

Alternatives for Providing Nutrigenomics Services

Four possible models:

- Consumer model
- Health practitioner model
- Blended services model
- Public health model



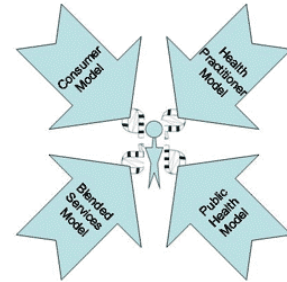
Bottom Line:

“The longer nutrigenomics resides in regulatory limbo between medicine and nutrition, physicians are more likely to be on the front lines educating the public about the nature of nutrigenomics ...”

Castle D. Clinical challenge posed by new biotechnology. Postgrad. Med. J. 2003; 79:5-66

Training in Nutrigenomics

Starting in Spring 2007, the Institute of Food Science and Nutrition of the Swiss Federal Institute of Technology Zürich will offer training in nutrigenomics at the Masters and postgraduate levels



7. Angaben zum Lehrinhalt und Lernziel

Voraussetzungen

Grundkenntnisse der allgemeinen und experimentellen Biologie und der Biochemie (Makromoleküle, Stoffwechselwege)

Inhalt

Einführung: von klassischer Ernährungsforschung zu Nutrigenomik. Das Paradigma der klassischen Molekularbiologie. Effekte von Nährstoffen auf biologische Stoffwechselwege. Einführung in die Biomics: Genomik, Transkriptomik, Proteomik, Metabolomik, Systembiologie. Anwendung der Omics in der Entwicklung von Biomarkern für Ernährungswissenschaften. Nutrigenomik und Management chronischer Krankheiten. Nutrigenomik in der Entwicklung von Richtlinien für die tägliche Nährstoffzufuhr. Nutrigenetik in der Entwicklung individualisierter Ernährungsformen. Omics in Lebensmittelwissenschaften und Biotechnologie. Omics und Lebensmittelsicherheit. Ethik und Sozioökonomie der Nutrigenomik

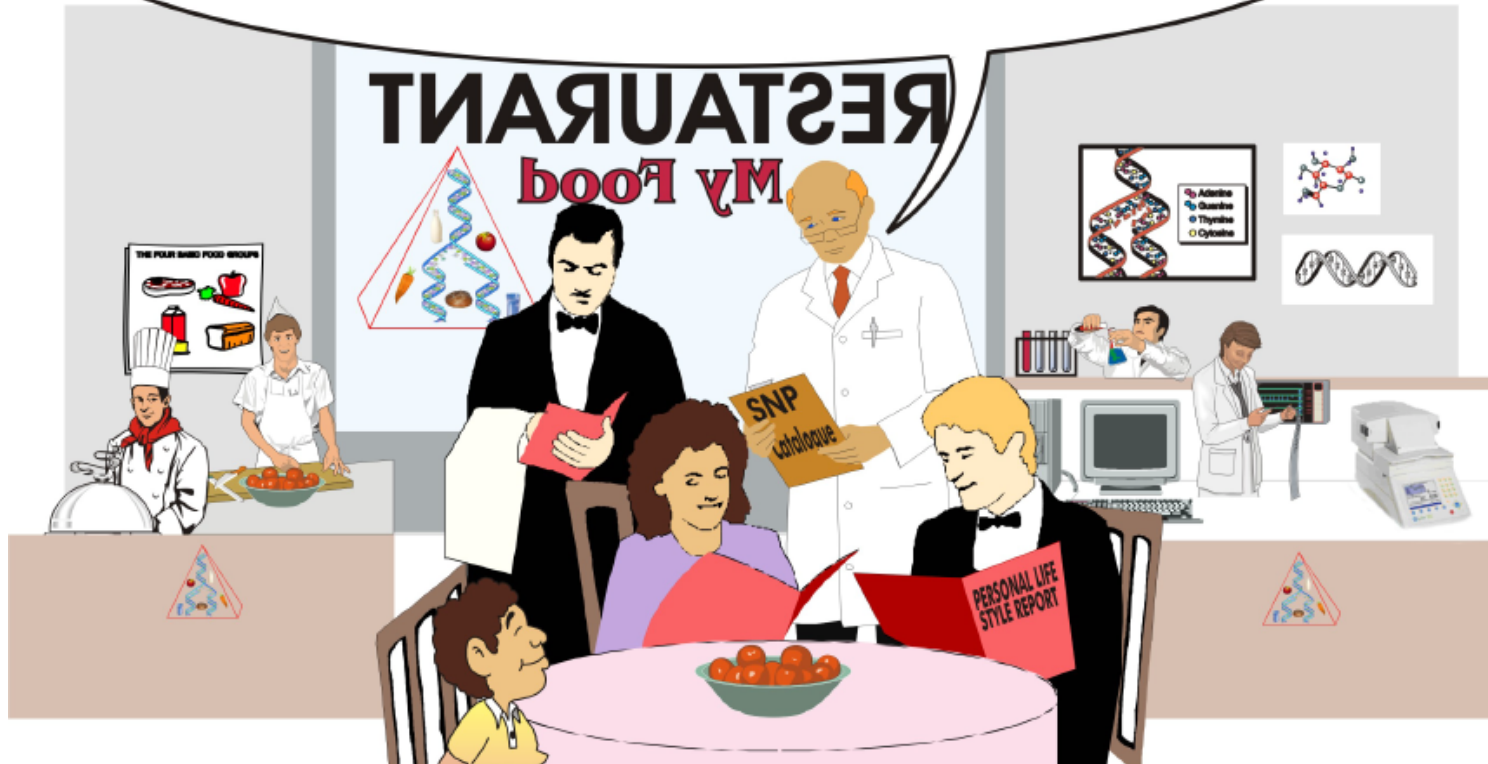
Lernziel

Vermittlung des Beitrages verschiedener Fachgebieten der „Life Sciences“ zu der Ernährungsforschung



Nutrigenomics: Science or Fiction?

Mrs. Smith, based on your genetic profiles we propose that you and your son finish this dinner with a cup of coffee. Green tea would be most appropriate for Mr. Smith!



Cartoon design: Corinne Papilloud