Nutrient Requirements as Complex Traits – What Consumers Will Need to Know

Patrick J. Stover, PhD
The Janet and Gordon Lankton Professor of Nutrition
Director, Division of Nutritional Sciences, Cornell University

Disclosures

AFFILIATION/FINANCIAL INTERESTS (prior 12 months)	ORGANIZATION
Grants/Research Support:	NIH: T32-DK007158 R37DK58144; ODS Supplement HD059120
Scientific Advisory Board/Consultant:	NHSc-Pamlab; Biofortis, Marabou Foundation, ASN Board; National Academy of Sciences Chronic Disease Endpoints Committee
Speakers Bureau:	None
Stock Shareholder:	TIAA
Owner	MetabolicSolutions LLC

What should we expect from the food supply?

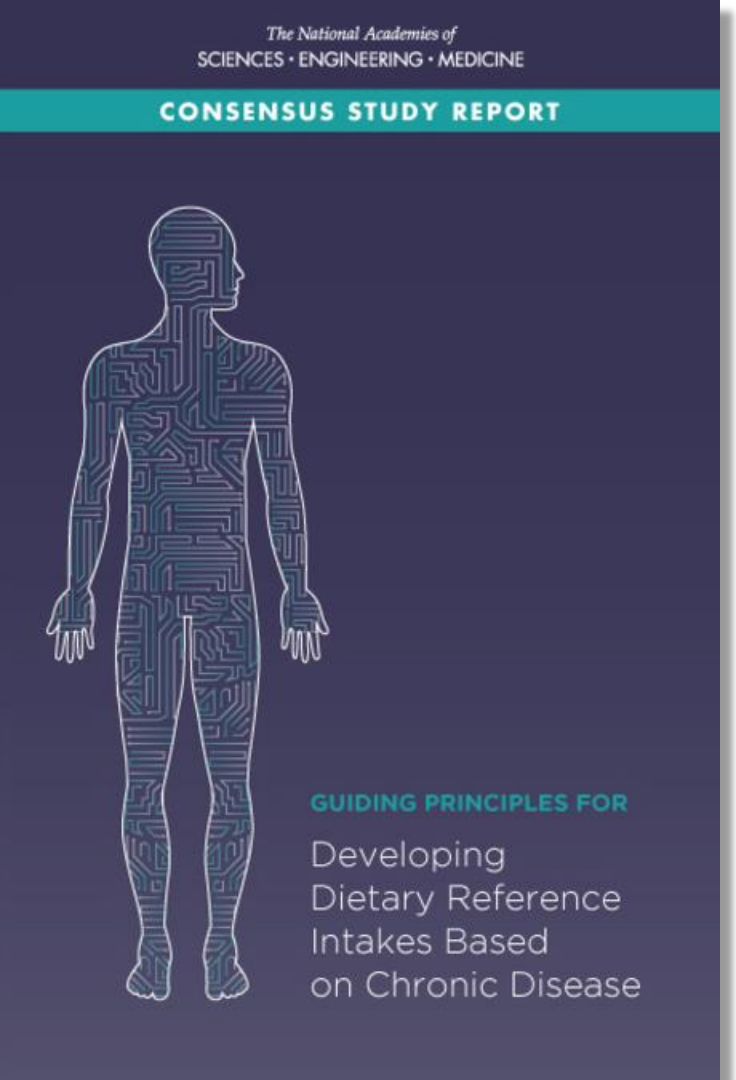
Engineering the Food Supply:

- Diet diversification
- Fortification (Chem/Bio)
- Supplements, etc

Dietary and Nutrient Recommendations:

- *Adequate for what?*

- Nutritional Status/Avoid Deficiency
- Metabolic Function
- Other Function
- Chronic Disease Prevention
- Disease Management



Chronic Disease Endpoints
- Challenges -

- Few chronic diseases are affected by:
  - single nutrients
  - single pathways
- Consider systems/networks over pathways
- Establish system readouts as biomarkers (integrative biomarkers)
- Consider DRIs as ranges in lieu of point estimates
- Understand biomarkers of aging – system decay
- “GRADE” standards of evidence

Nutrient Needs in Chronic Disease

Activity

Examining Special Nutritional Requirements in Disease States: A Workshop

Type: Stand Alone Workshop

Topics: Diseases, Food and Nutrition

Board: Food and Nutrition Board

Activity Description

An ad hoc committee will plan a two-day public workshop exploring the evidence for special nutritional requirements in disease states and medical conditions that cannot be met with a normal diet and the workshop will explore how these requirements may apply to the management of chronic or acute conditions or diseases that include inborn errors of metabolism, burns or surgical trauma, cancer, inflammatory bowel disease, traumatic brain injury, and other non-communicable diseases or medical conditions. The workshop will explore the currently available evidence used to determined potential nutritional requirements that are not encompassed within normal population variation, and how nutritional interventions affect the overall clinical management of diseases in terms of patient safety, efficacy and access. The workshop discussions will encompass the strengths and limitations of different types of evidence (e.g. clinical, non-clinical) in establishing whether special nutritional requirements exist for a given disease or medical condition and in establishing the safety and efficacy of such therapies. The committee will plan and organize the workshop, select and invite speakers and discussants, and moderate the discussions. A summary of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously undertaken by the Institute of Medicine (IOM).

Planning Committee Members

- Barbara Schneeman, Chair

✚ View Full Planning Committee Roster

Staff

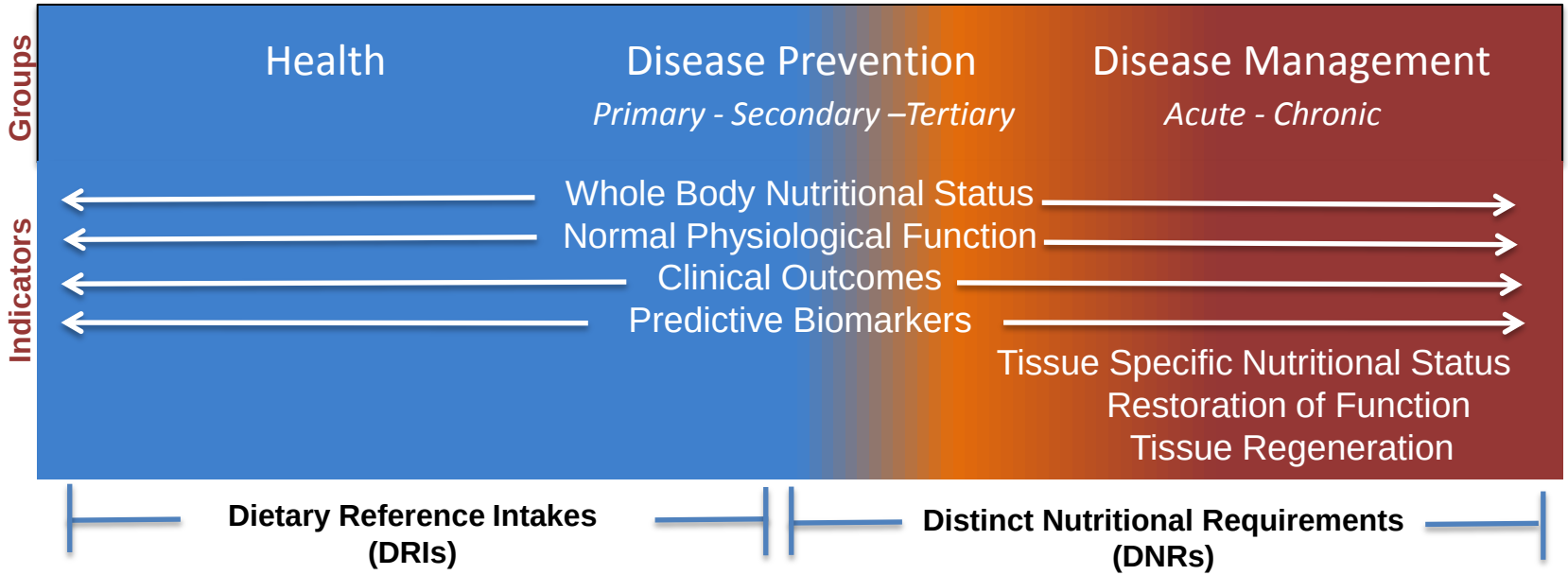
- Maria Oria, Study Director

✚ View Full Study Staff Roster

Sponsors

- National Institute of Diabetes and Digestive and Kidney Diseases
- Health Canada
- Office of Dietary Supplements National Institutes of Health
- American Society for Nutrition
- Academy of Nutrition and Dietetics
- U.S. Food and Drug Administration
- Crohn's and Colitis Foundation
- National Institutes of Health/National Cancer Institute

Classifying and Evaluating Human Nutrient Needs



Dietary Requirements as Complex Traits

Physiological Processes	Modifiers and Sensitizers
Absorption	Disease
Catabolism	Epigenetics
Excretion	Food Matrix
Metabolism	Genetics
Stability	Nutrient-Nutrient Interactions
Transport	Pharmaceuticals
Bioactivation	Toxins
Energetic State	Age/Physiological Decay
Nutrient Storage	Microbiome/Pregnancy/Sex

American Society for Nutrition Nutrition Research Priorities

Variability in Responses to Diet & Food

Achieving personalized nutrition with dietary recommendations tailored to each person's needs.

Healthy Growth, Development and Reproduction

Understanding how nutrition during critical, early periods of development (including pregnancy) impacts future health.

Health Maintenance

Improving health with noncommunicable disease prevention and weight maintenance.

Medical Management

Slowing disease progression through nutrition with improved responses to therapy and survival rates.

Nutrition-Related Behaviors

Understanding how the human brain influences food choice and nutrition-related behaviors.

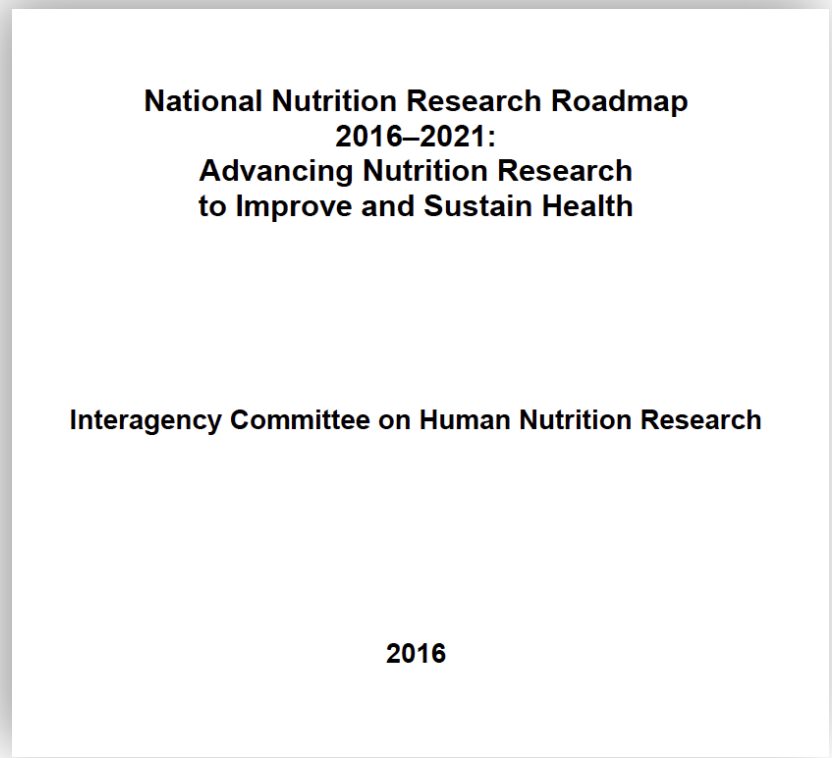
Food Supply & Environment

Realizing the potential of the food environment to improve diet and lifestyle choices.

Responders vs. Non-responders

Olhorst et. al. (2013) *Am J Clin Nutr* doi: 10.3945/ajcn.113.067744

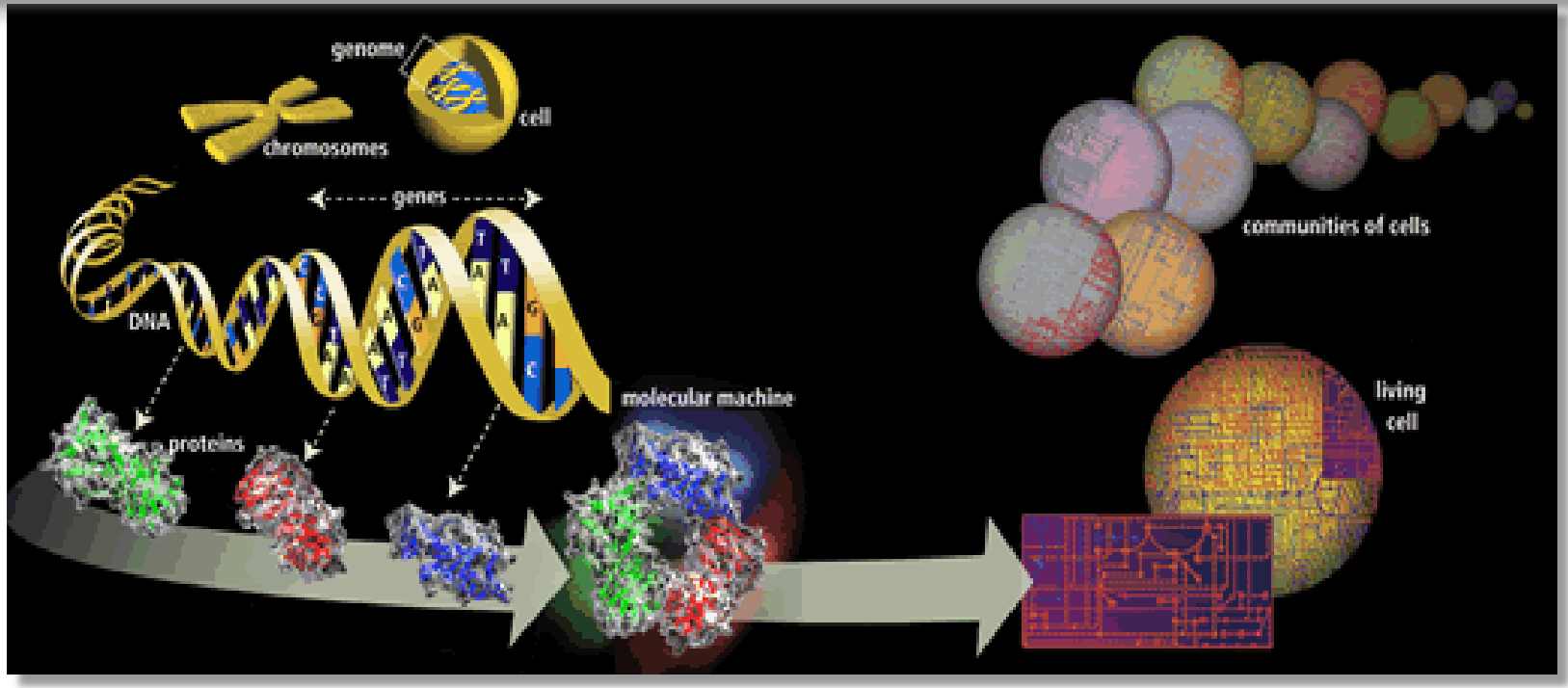
National Nutrition Research Roadmap 2016–2021



Question 1: How can we better understand and define eating patterns to improve and sustain health?
Question 1 Topic 1 (Q1T1): How do we enhance our understanding of the role of nutrition in health promotion and disease prevention and treatment?
Question 1 Topic 2 (Q1T2): How do we enhance our understanding of individual differences in nutritional status and variability in response to diet?
Question 1 Topic 3 (Q1T3): How do we enhance population-level food- and nutrition-related health monitoring systems and their integration with other data systems to increase our ability to evaluate change in nutritional and health status, as well as in the food supply, composition, and consumption?
Question 2: What can be done to help people choose healthy eating patterns?
Question 2 Topic 1 (Q2T2): How can we more effectively characterize the interactions among the demographic, behavioral, lifestyle, social, cultural, economic, occupational, and environmental factors that influence eating choices?
Question 2 Topic 2 (Q2T2): How do we develop, enhance and evaluate interventions at multiple levels to improve and sustain healthy eating patterns?
Question 2 Topic 3 (Q2T3): How can simulation modeling that applies systems science in nutrition research be used to advance exploration of the impact of multiple interventions?
Question 2 Topic 4 (Q2T4): How can interdisciplinary research identify effective approaches to enhance the environmental sustainability of healthy eating patterns?
Question 3: How can we develop and engage innovative methods and systems to accelerate discoveries in human nutrition?
Question 3 Topic 1 (Q3T1): How can we enhance innovations in measuring dietary exposure, including use of biomarkers?
Question 3 Topic 2 (Q3T2): How can basic biobehavioral science be applied to better understand eating behaviors?
Question 3 Topic 3 (Q3T3): How can we use behavioral economics theories and other social science innovations to improve eating patterns?
Question 3 Topic 4 (Q3T4): How can we advance nutritional sciences through the use of research innovations involving Big Data?

https://www.google.ch/?gfe_rd=cr&ei=Og8SWOLrLcHCaNn8gOAN#q=national+nutrition+roadmal

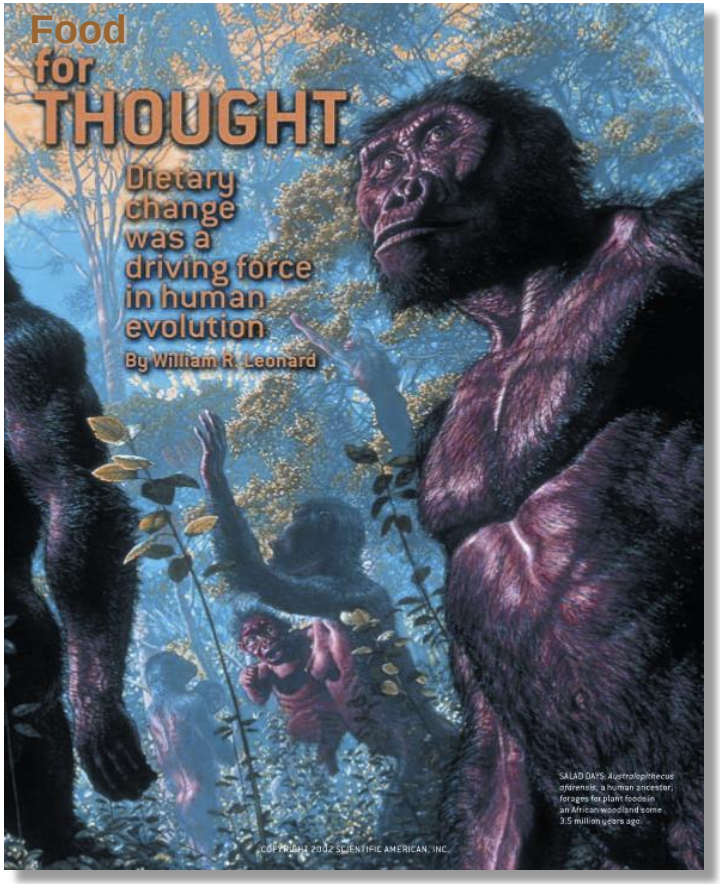
Human Genome Project (1990-2003)



- Assemble & understand cellular networks, their variation → manipulation by inputs (drugs, nutrients)

http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml

Human Genetic Variation
Nutrition and Evolution



Genome Primary Sequence
Genome Programming
Gene Expression

Human Genome ⇄ **Dietary Components**

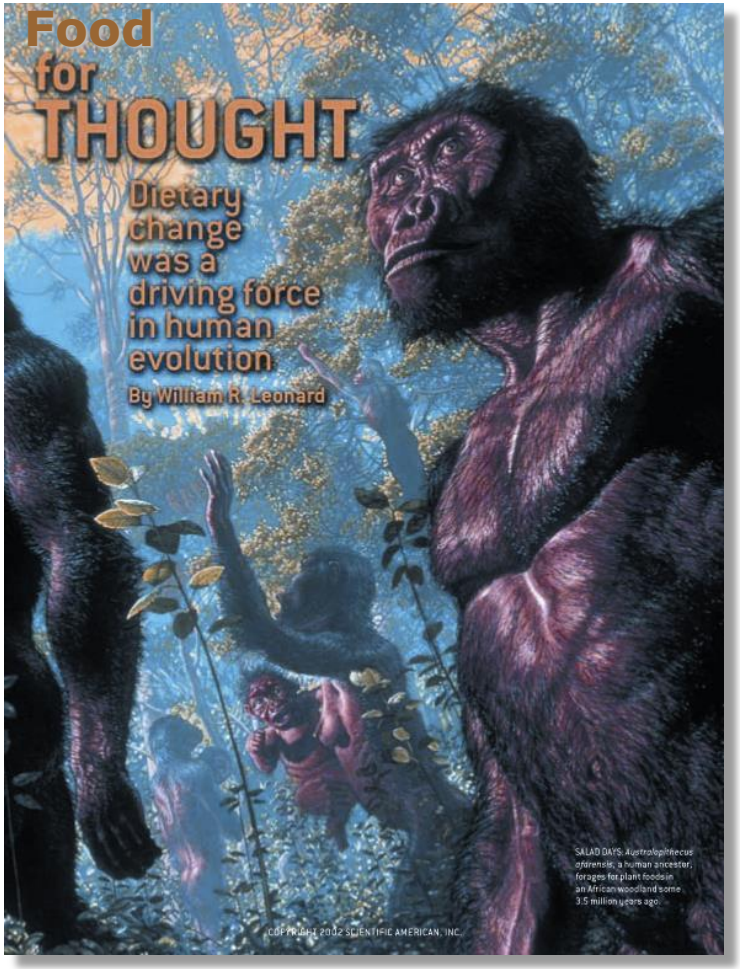
Food Intolerances
Dietary Requirements
Susceptibility to metabolic disease

Scientific American November 13, 2002 William R. Leonard

Human Genetic Variation
Nutrition and Evolution

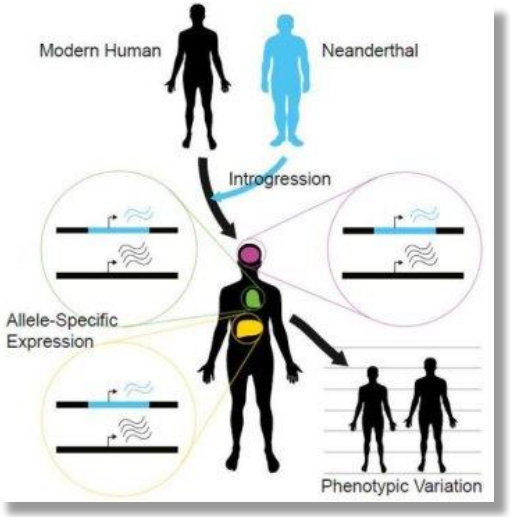
Gene Evolution and the Creation of Genetic Variation

- **Archaic Humans**
- **Mutation/Expansion**
  - **Selection**
  - **Drift**

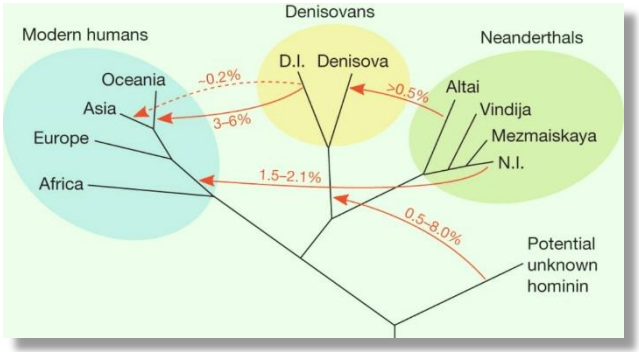


Diet-related genes Inherited from Archaic Humans?
500,000 ka

http://punnett.blogspot.co.uk/2016/04/neanderthal-y-chromosome-analysed.html

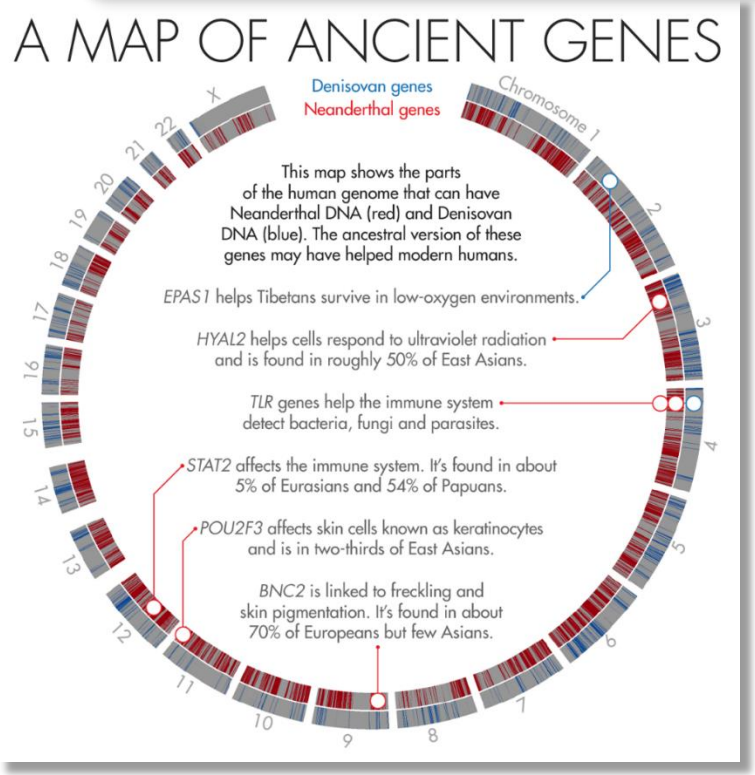


https://www.sciencedaily.com/releases/2017/02/170223124316.htm

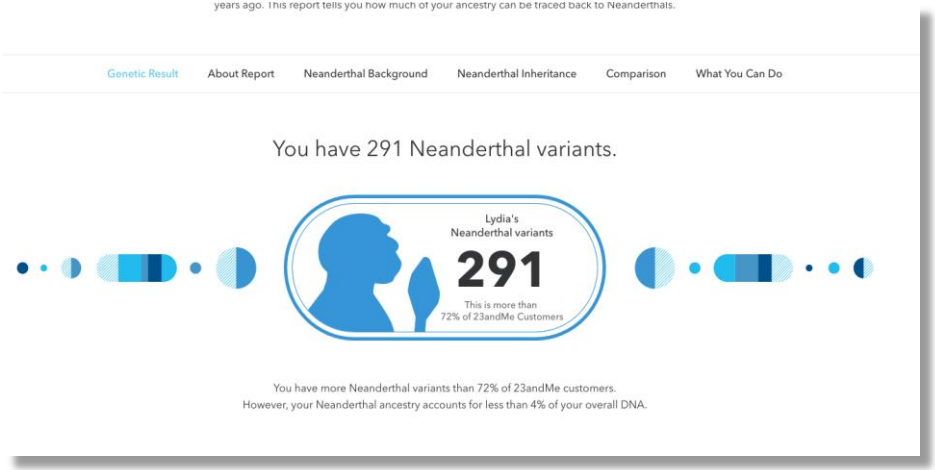


.http://www.sci-news.com/othersciences/anthropology/science-neanderthal-genome-fourth-lineage-01624.html

Diet-related genes Inherited from Archaic humans? 500,000 ka



https://www.quantamagazine.org/how-neanderthal-dna-helps-humanity-20160526/

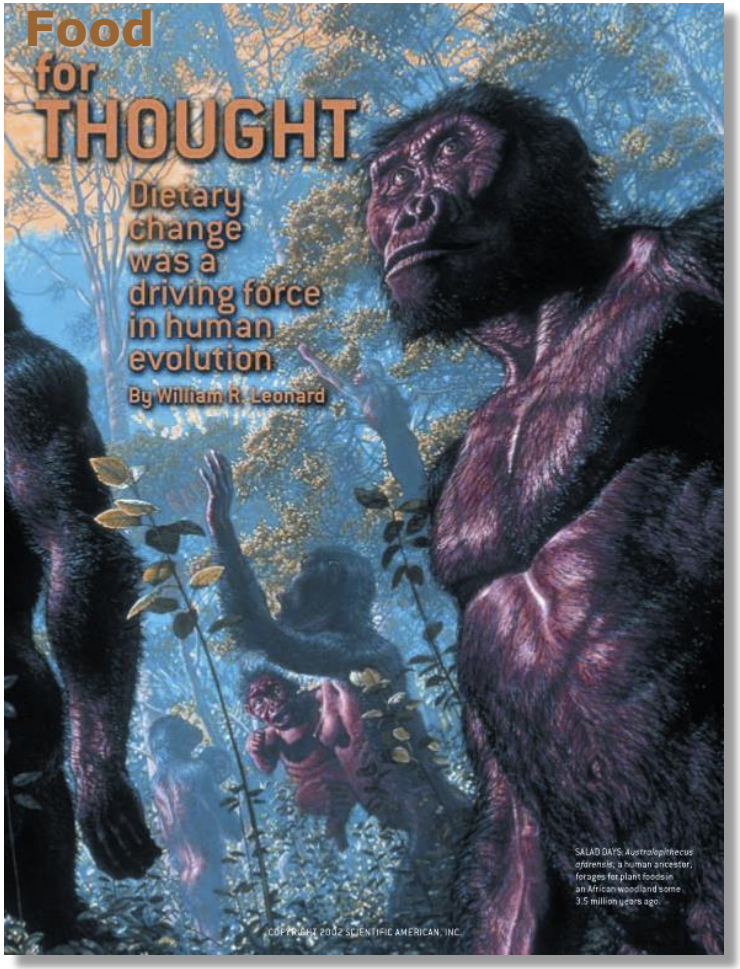


23 and me result page for Lydia
http://uk.businessinsider.com/best-dna-test-23andme-ancestry-national-geographic-2017-4?r=US&IR=T

Human Genetic Variation
Nutrition and Evolution

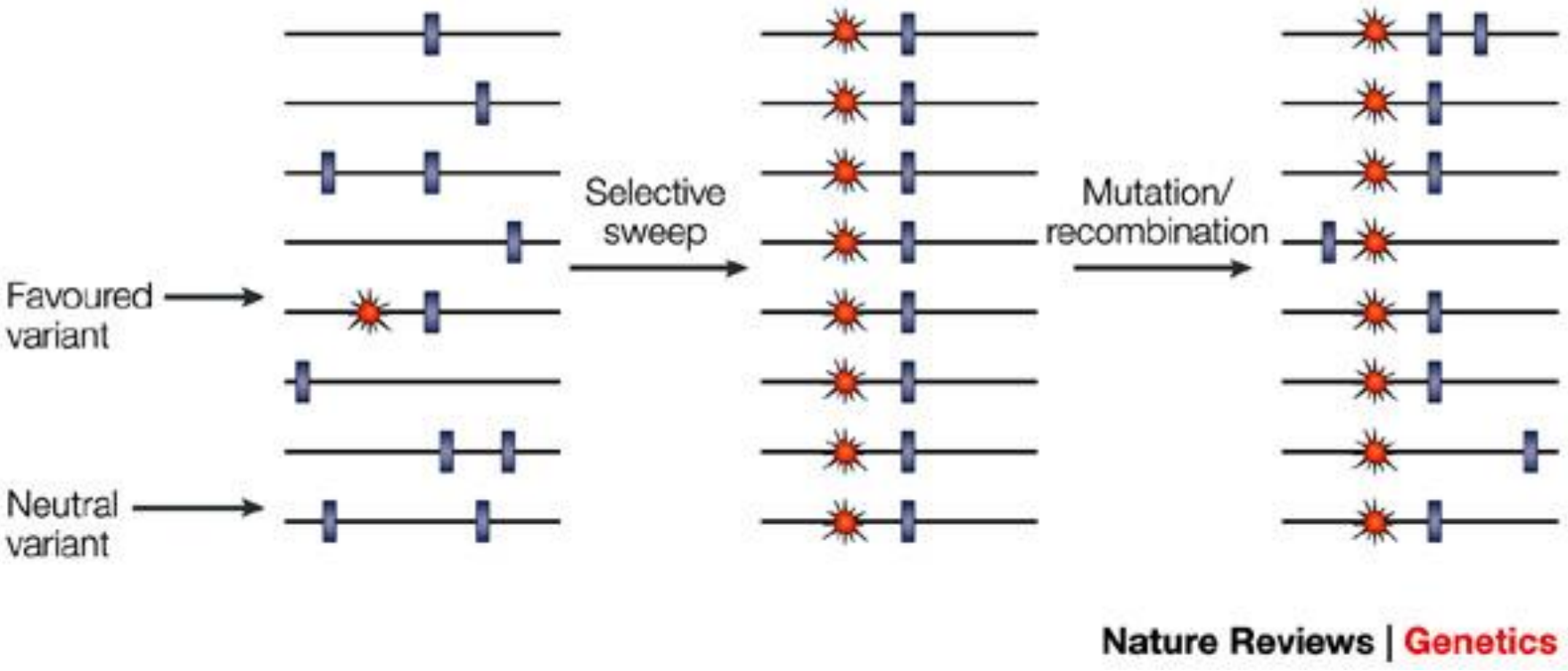
Gene Evolution and the Creation of Genetic Variation

- **Archaic Humans**
- **Mutation/Expansion**
  - **Selection**
  - **Drift**



Human Genetic Variation

Nutrition and Evolution
Selective Sweeps



Lactose Tolerance was enabled by Genetic Mutation and the Food Environment

BMC Evolutionary Biology 2010, **10**:36 https://doi.org/10.1186/1471-2148-10-36

Phenotype

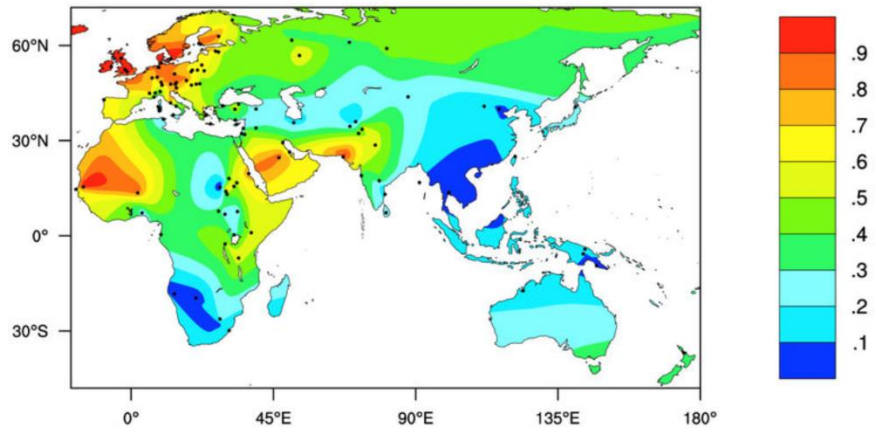


Figure 1
Interpolated map of Old World LP phenotype frequencies. Dots represent collection locations. Colours and colour key show the frequencies of the LP phenotype estimated by surface interpolation.

Genotype

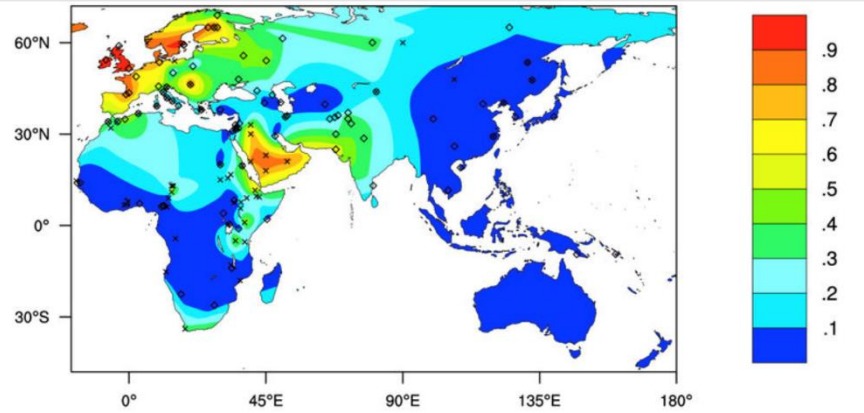
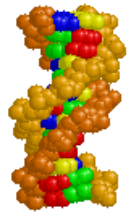
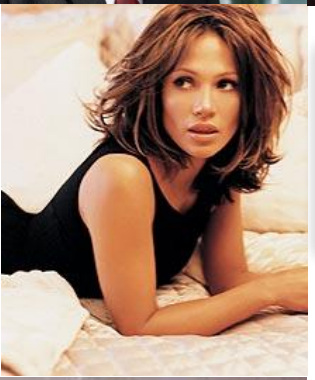


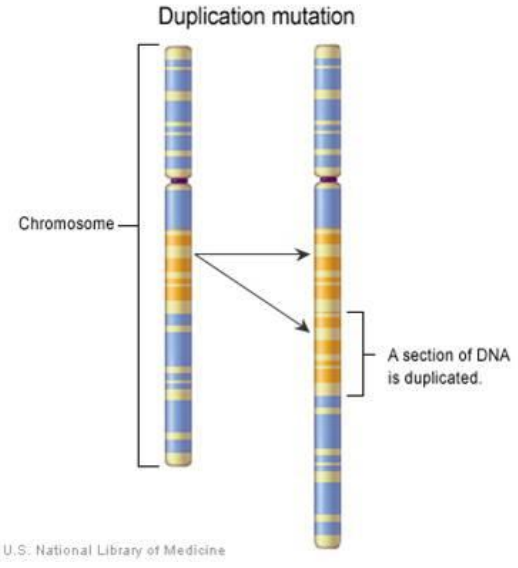
Figure 2
Predicted Old World LP phenotype frequencies based on LP-associated allele frequencies. LP frequency prediction assumes *Hardy-Weinberg* equilibrium and dominance. Crosses represent collection locations where all 4 currently known LP-associated alleles were genotyped, and diamonds represent collection locations where the only data on the -13,910 C>T allele is available. Colour key shows the predicted LP phenotype frequencies estimated by surface interpolation.

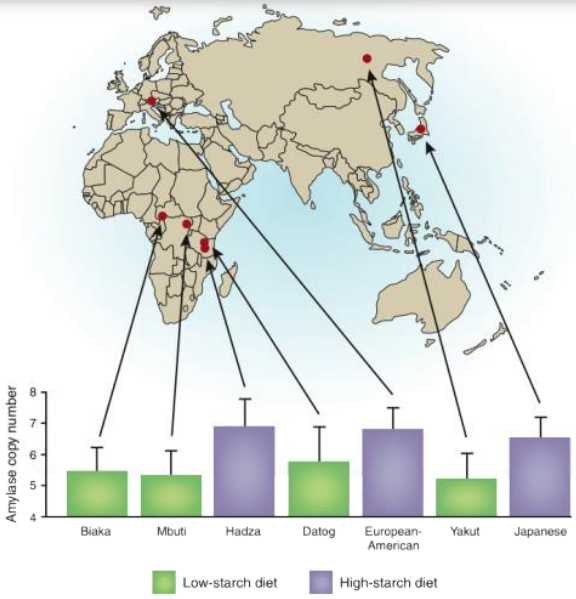




Andre The Giant

Amylase CNVs expanded in agrarian human populations to improve starch digestion





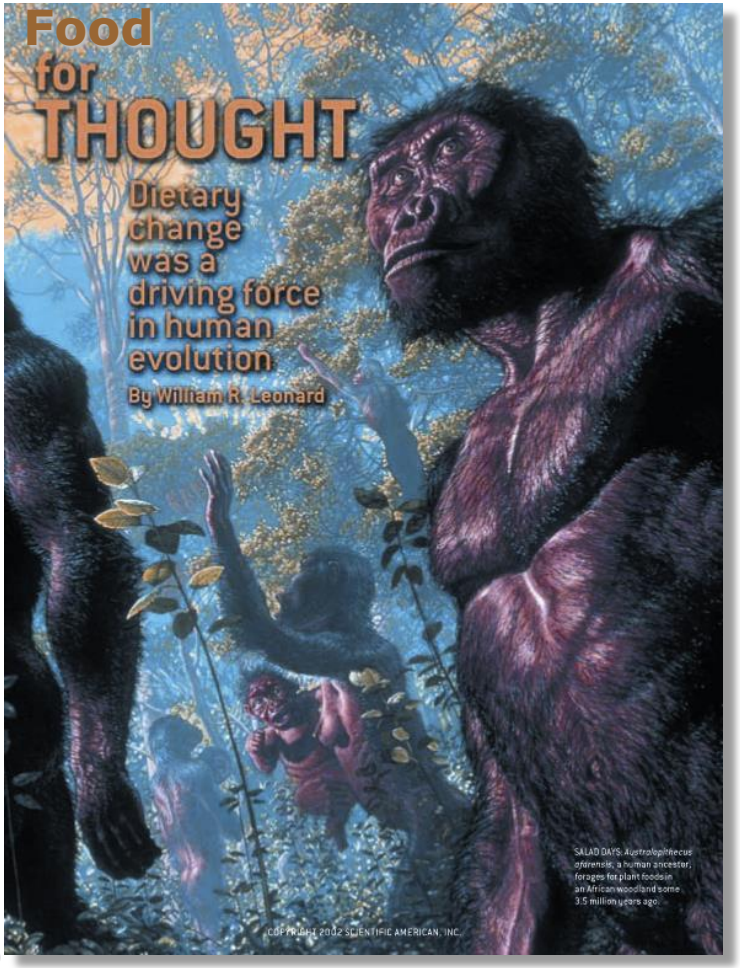
Diet-related genes that display genomic signatures of adaptive evolution by selection

Gene	Species/function	References
LCT	human lactose metabolism	*Am J Hum Genet 2004;74(6):1111-20*
ADH1B	human ethanol metabolism	*Am J Hum Genet 2002;71(1):84-99*
ALDH2	human ethanol metabolism	*Ann Hum Genet 2004;68(Pt 2):93-109*
HFE	human iron homeostasis	*Genetics 2003;165(1):287-97*
PPARg	human nuclear receptor	*Genome Res 2002;12(12):1805-14*
PTC	human bitter-taste receptor	*Am J Hum Genet 2004;74(4):637-46*
KEL	human protein metabolism	*PLoS Biol 2004;2(10):e286*
TRPV5	human calcium transport	*PLoS Biol 2004;2(10):e286*
TRPV6	human calcium transport	*PLoS Biol 2004;2(10):e286*
ABO	human protein metabolism	*PLoS Biol 2004;2(10):e286*
ACE2	human protein metabolism	*PLoS Biol 2004;2(10):e286*
CYP1A2	human arylamine metabolism	*Am J Hum Genet 2002;71(3):528-42*
G6PD	human NADP metabolism	*Am J Hum Genet 2002;71(5):1112-28*

Pathways

Amino acid metabolism	human, chimp	*Science 2003;302(5652):1960-3*
Amino acid transport	chimp	*Science 2003;302(5652):1960-3*
Purine metabolism	chimp	*Science 2003;302(5652):1960-3*

Stover, P.J. 2007. Human Nutrition and Genetic Variation. Food Nutr. Bull. 28:1, S101-S115. PMID: 17521122



Nutrigenomics and the Future of Nutrition

- Strong biological premise in concept
- Strength of effect/penetrance?
- Does it matter in public health?
- Does it matter to the individual consumer?

Benefit and Risks of MTHFR Polymorphism

COMMON Allele

Gene sequence	..GCG GGA GCC GAT …
Protein Sequence	.. Ala Gly Ala ASP…

677 C -> T Allele

Gene Sequence	..GCG GGA GTC GAT…
Protein Sequence	…Ala Gly Val Asp …

In utero Risk

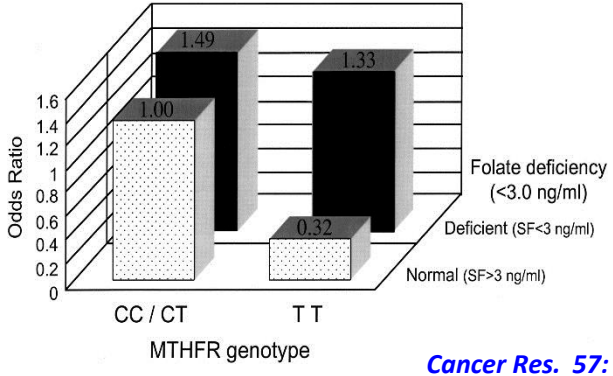
"T" allele

- Low folate status
- Higher folate requirement
- Birth defects
- Miscarriage

Adult Benefit

"T" allele

- Physician's Health Study – Colon Cancer Risk



Cancer Res. 57: 1098-1102

Allelic Frequency of the MTHFR 677 C->T Polymorphism

	(TT) Frequency
Mexicans	30%
Tuscanian (Italy)	30%
Africans	0%
African Amer	2%
Yemenite Jews	2%
Muslim Arab Israelis	16%
Asians	19%
Caucasians	9%

J. Nutr. 138: 67–72, 2008.

The Journal of Nutrition
Nutrient Requirements and Optimal Nutrition

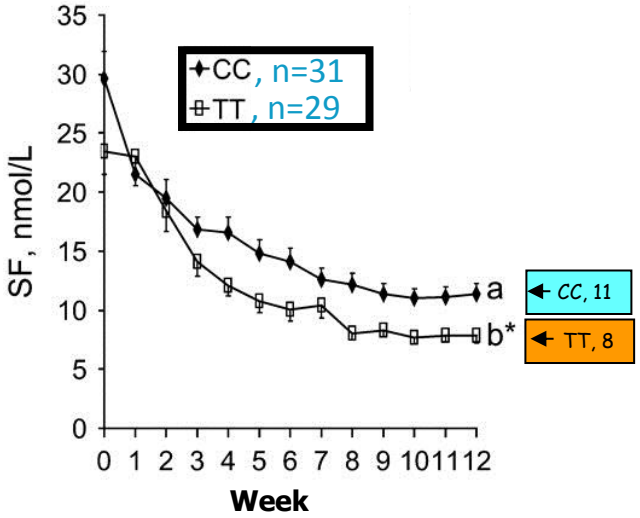
Folate Intake at RDA Levels Is Inadequate for Mexican American Men with the Methylenetetrahydrofolate Reductase 677TT Genotype[1–3]

Claudia Solis,[4] Kristin Veenema,[4] Alexandre A. Ivanov,[4] Sally Tran,[4] Rui Li,[4] Wei Wang,[5] David J. Moriarty,[6] Charles V. Maletz,[7] and Marie A. Caudill[8]*

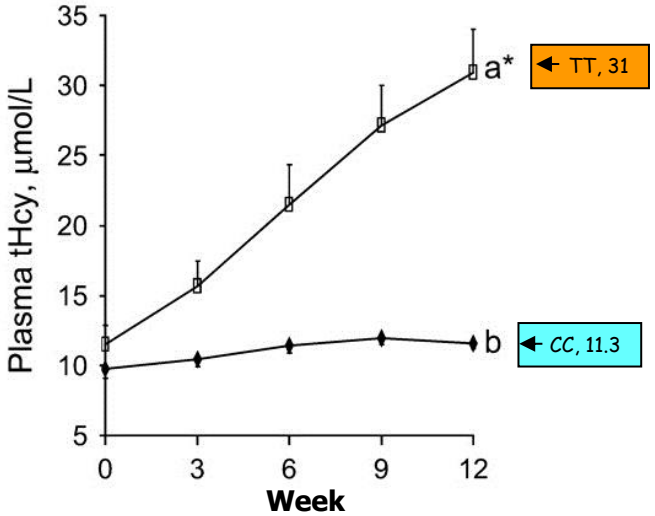
MTHFR 677TT Genotype Markedly Affects Biomarkers of Folate Status in Men Consuming the Folate RDA

Solis et al. JN 2008

Folate Treatment with 400 μg DFE/d

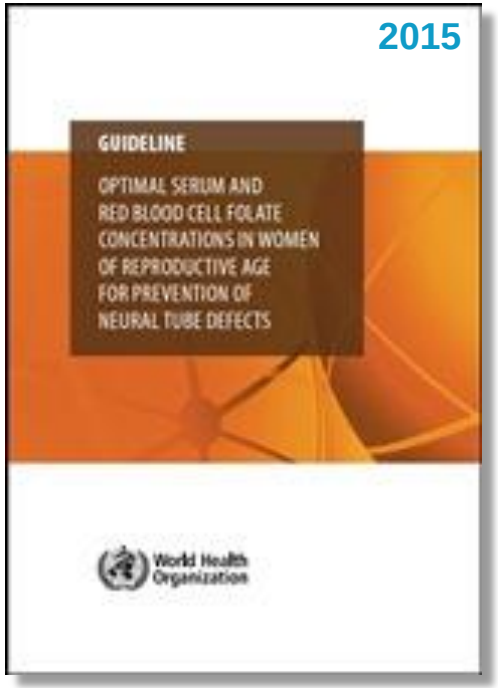


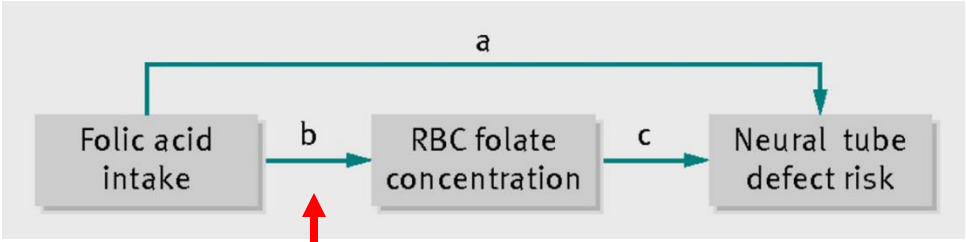
Deficient (<6.8 nmol/L)
34% TT (10 of 29)
16% *CC* (5 of 31)



Deficient (>14 μmol/L)
79% TT (23 of 29 men)
7% *CC* (2 of 31 men)

WHO Guidelines for Prevention of NTDs with Folate Bayesian Model

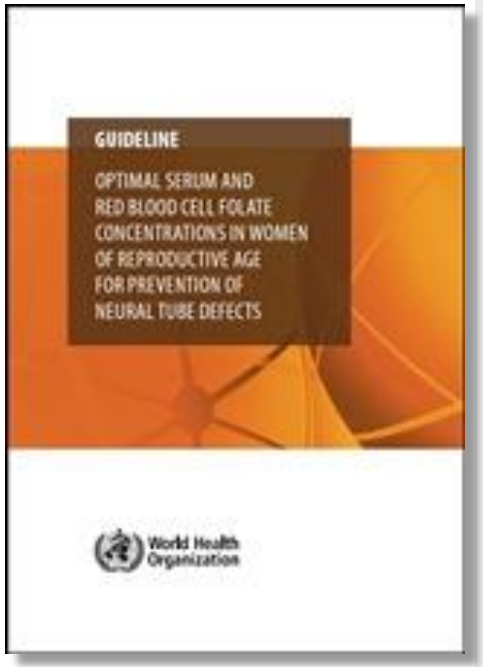


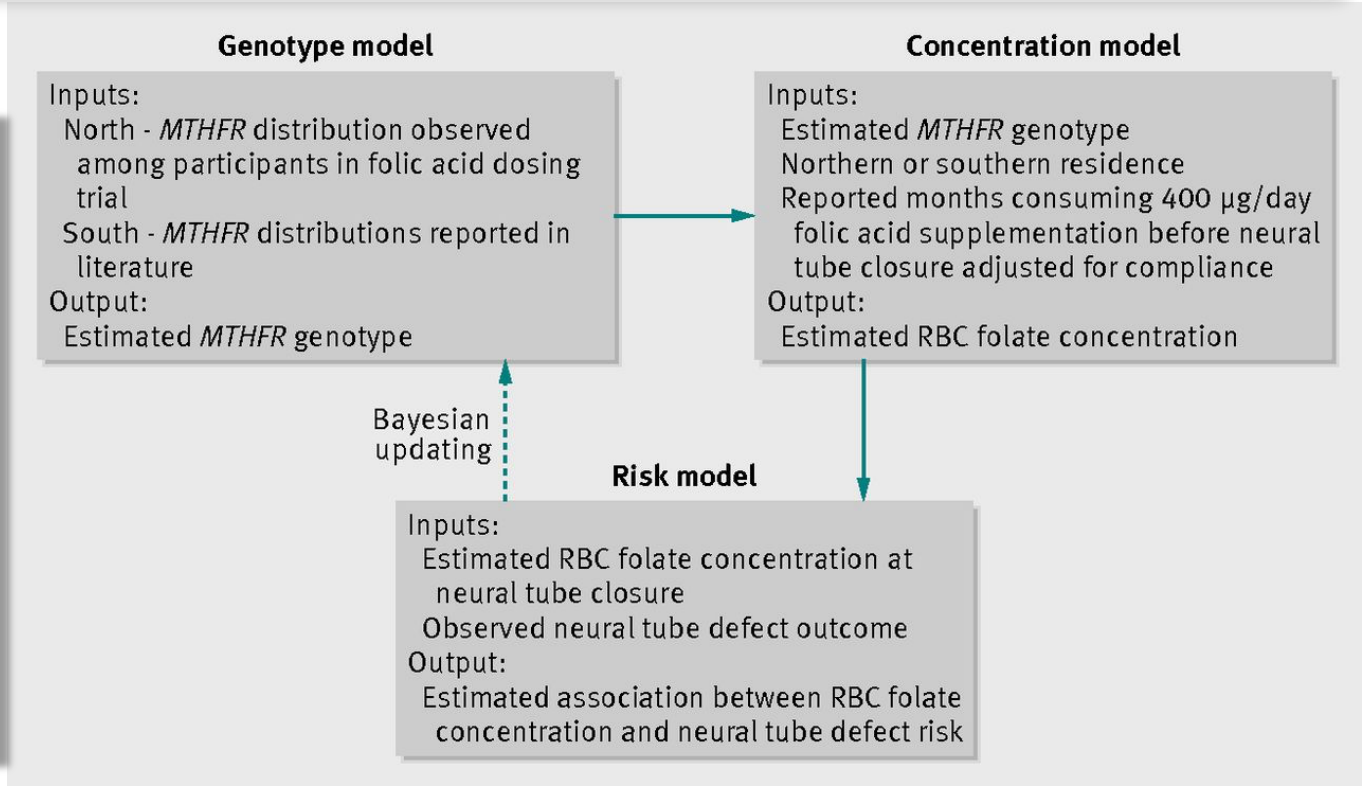


MTHFR Genotype

BMJ 2014; 349 :g4554

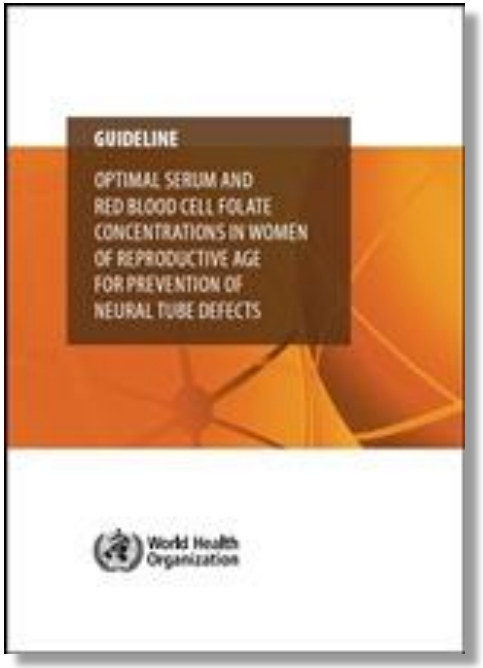
WHO Guidelines for Prevention of NTDs with Folate Bayesian Model

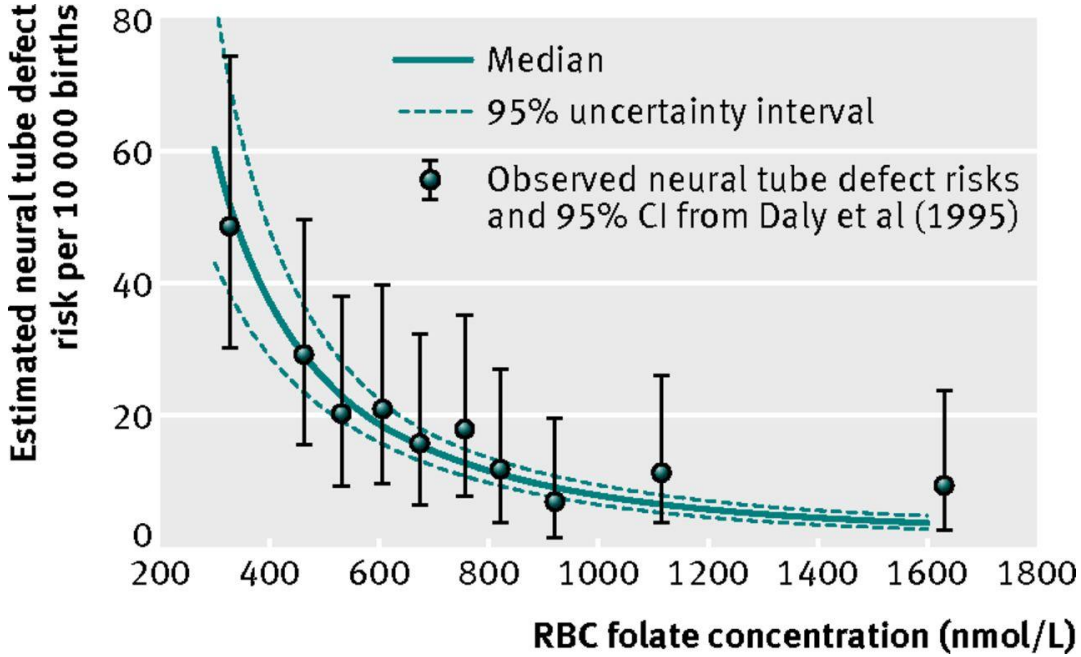




BMJ 2014; 349 :g4554

WHO Guidelines for Prevention of NTDs with Folate Bayesian Model





BMJ 2014; 349 :g4554

Precision Nutrition

What consumers will need to know

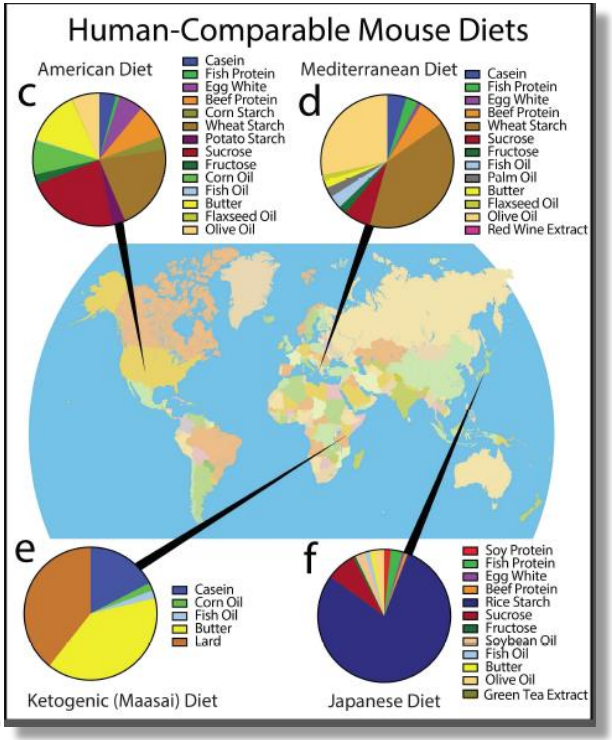
1. **Classification of Subgroups for Diets**
2. **Classification of Subgroups for Nutrients**

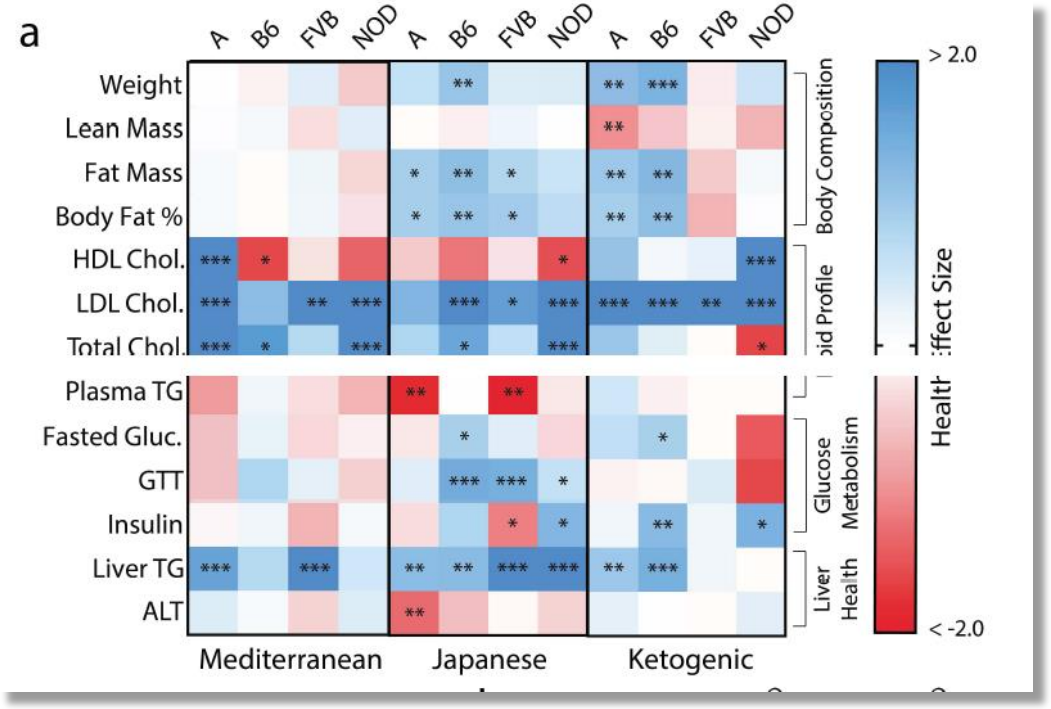
Redesign Process - Dietary Guidelines

How the DGA can better prevent chronic disease, ensure nutritional sufficiency for all Americans, and accommodate a range of individual factors, including age, gender, and metabolic health.

Improving Metabolic Health through Precision Dietetics in Mice

William T. Barrington[1,2], Phillip Wulfridge[3], Ann E. Wells[9], Carolina Mantilla Rojas[1], Selene Y.F. Howe[1], Amie Perry[4], Kunjie Hua[5], Michael A. Pellizzon[10], Kasper D. Hansen[3,6,7], Brynn H. Voy[9], Brian J. Bennett[5], Daniel Pomp[5], Andrew P. Feinberg[3], David W. Threadgill[1,4,8]*





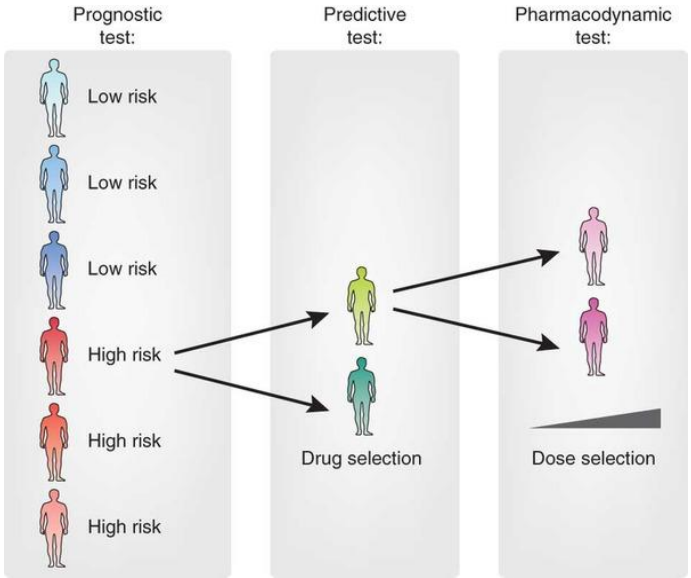
Genetics: Early Online, published on November 20, 2017 as 10.1534/genetics.117.300536

Precision Nutrition

What Consumers will need to know

1. **Classification of Subgroups for Diets**
2. **Classification of Subgroups for Nutrients**

Precision Medicine ⟷ Precision Nutrition
Biomarkers to Classify Population Subgroups



Classification:

a) **Sex, Pregnancy, Lactation, Age**

b) **Genetics, Exercise, Disease, etc …**

Does this make sense for a complex trait?

Nature Medicine. 17.3 (Mar. 2011): p304.

Precision Nutrition

What consumers will need to know

1. **Classification of Subgroups for Diets**
2. **Classification of Subgroups for Nutrients**
3. **~~Classification~~ →Real Time Personalized Readouts**
   - **Data will be readily accessible!**
   - **What guidance will we give?**
   - **Can Systems/Network Biology be applied?**

Point-of-Care Measurement of Nutrition-Related Biomarkers

Lab on a Chip. http://doi.org/10.1039/c6lc00393a

Nutrient Status Biomarkers
Functional Biomarkers
Chronic Disease Markers
Infectious Disease Markers

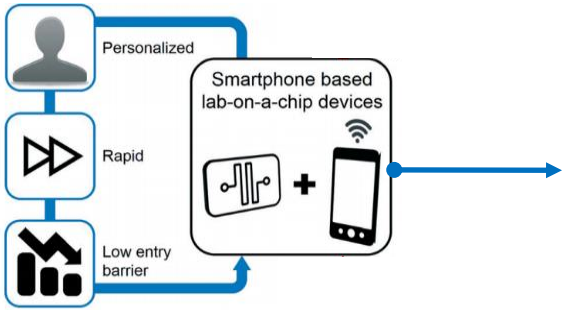
mobihealthnews | OysterLabs + manacloud

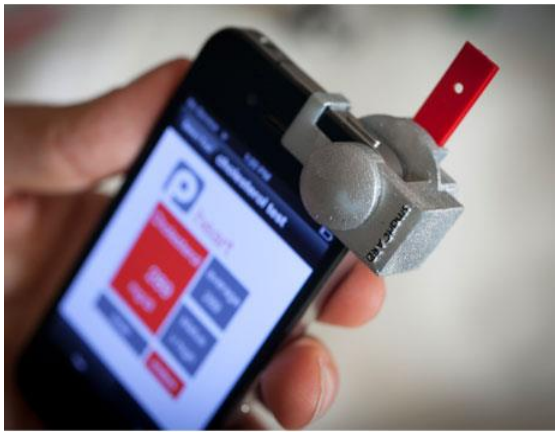
News About Advertise Research

Nutriphone hopes to commercialize smartphone-enabled vitamin D deficiency testing

By: Brian Dolan | Dec 12, 2013 Tweet 66 Share 43 Share 10

Tags: Biosense Technologies | chemical sensors | Cornell | mHealth Summit | Nutriphone | nutrition sensors | pHitPal | uChek | vitaMe Technologies |





SCIENTIFIC REPORTS

OPEN

A hybrid stochastic model of folate-mediated one-carbon metabolism: Effect of the common

Stochastic Model/Simulation – Infrastructure

- Entire One-Carbon Metabolism Network
  - compartmentalization
- Known Expression Ranges of all Enzymes
- Ranges for all Nutrient "Inputs"
- System/Network Level Biomarkers as "readouts"

Current Analyses

- Sensitivity Analyses for all Changes in Enzyme Levels
- Dynamic Range of Nutrient Inputs Required under Different Network States to Maintain Network Outputs.

folate cycle

Misselbeck, K., Marchetti, L., Field, M.S., Scotti, M., Priami, C., and Stover, P.J. (2017) *Sci. Rep.*, 7: 797.

First International Conference on Precision Nutrition and Metabolism in Public Health and Medicine

When: 21/09/2018 - 26/09/2018

Where: Chania, Crete, Greece

Conference Center: Avra Imperial Hotel

The cost of diet-related chronic disease may soon exceed $1 trillion per year in the United States (JAMA, 2017, v317, p1755), driving the need to understand the dose-response relationships among food components and chronic disease, and establish scientifically-grounded guidance for optimal dietary intakes. To achieve this goal, scientific and methodological transformations are needed: 1) to quantify comprehensively the dynamics of physiological systems, their decay with age, and their response to individual nutrient concentrations, 2) to understand the role of nutrients and the dynamic ranges of their interactions in biological networks in health and disease, and 3) to identify robust biomarkers of nutrient intake, status, function, and their connection to biomarkers of disease.

OPEN FOR ABSTRACT SUBMISSION UNTIL: