Research Strategies for Personalized Health

Developing 21st Century Science @ NIHS

EPEMED Webinar
16 November 2011

Nestlé Institute of Health Sciences

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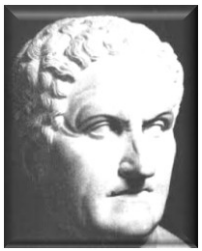
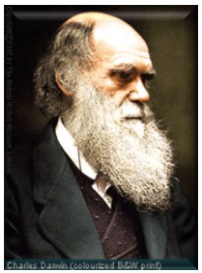
…food be your medicine

…aptitude of the body



…adapt to the environment



…inborn errors of metabolism

…biochemical individuality

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Outline

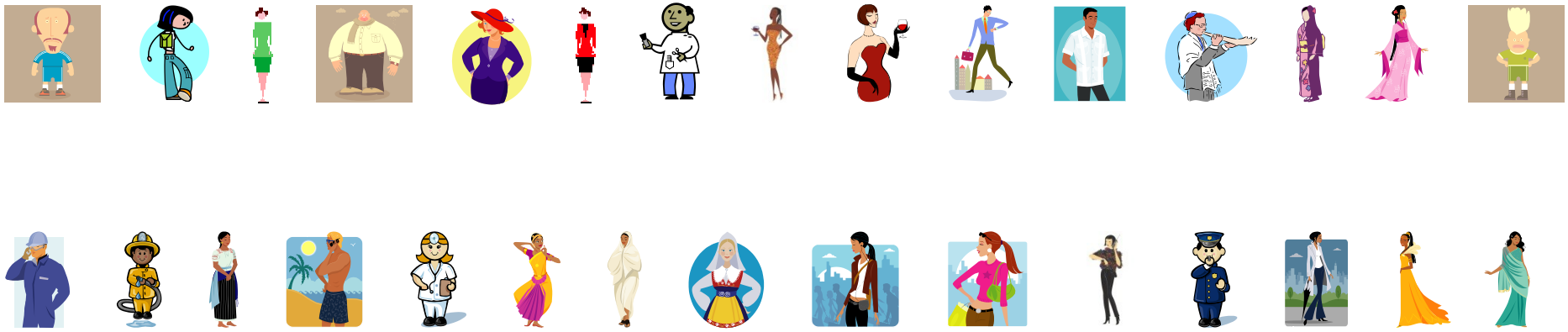
20th Century Science

21st Century Science

Acute and Long Term Challenges

International Projects & Harmonization

Facts & Challenges 20th Century Science



Genotype	Pheno	Pheno
A	6	9
B	2	2
C	8	3

$\sum$ Phenotype / 16 = Average Phenotype

A,B,C = variants of one gene or
A,B,C = variants of many genes

Phenotype /14 = Average Phenotype

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Facts & Challenges

Adult Hypolactasia

N. European

Indian children

Afr American kids

Indian adults

Mex American - adult

Cretans

Cypriots

N. American Jews

Mexicans - rural

SE Asians

Eskimo

Afr American - adult

Asian Americans

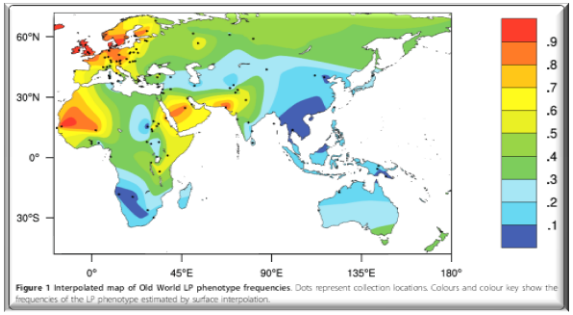
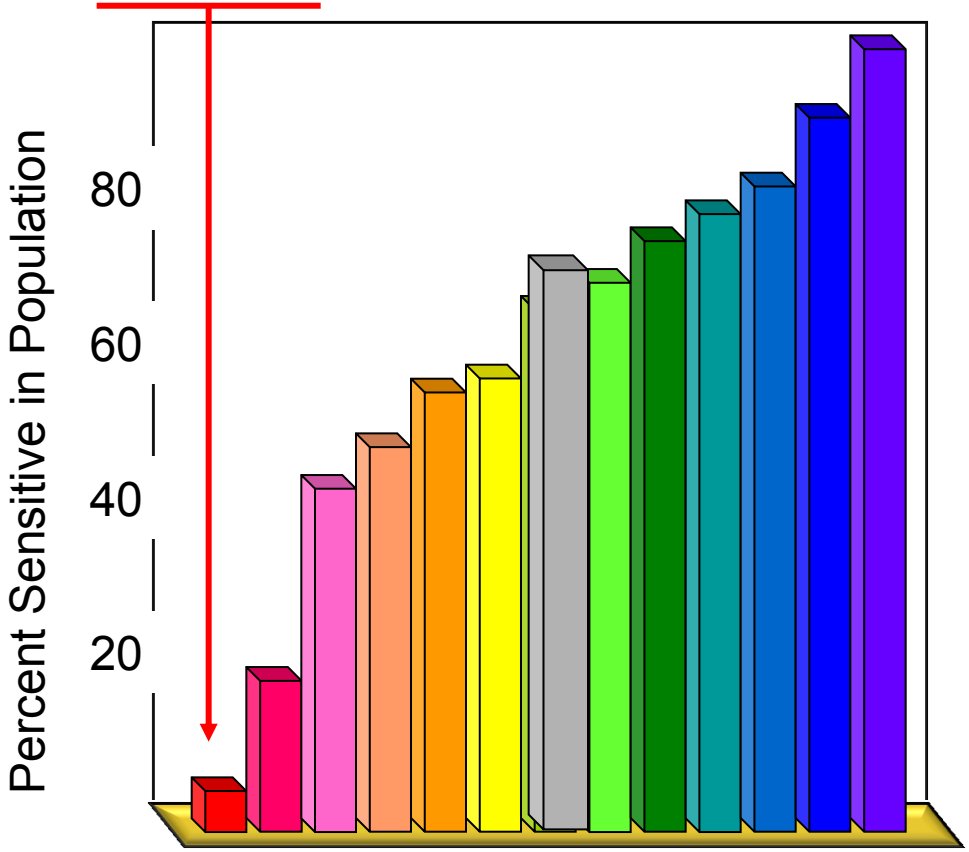


Figure 1 Interpolated map of Old World LP phenotype frequencies. Dots represent collection locations. Colours and colour key show the frequencies of the LP phenotype estimated by surface interpolation.

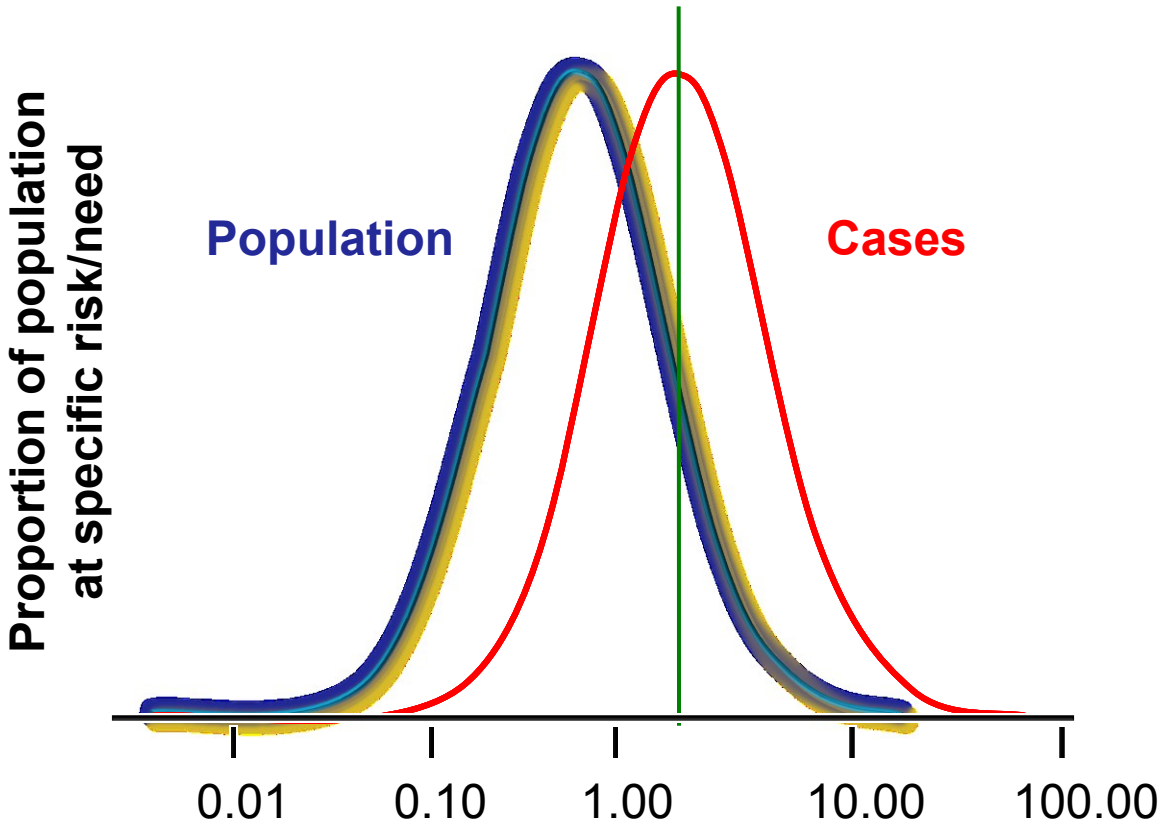
Itan *et al. BMC Evolutionary Biology* 2010, **10**:36
http://www.biomedcentral.com/1471-2148/10/36

C-13910T In Africa: G-14010C



Kaput and Rodriguez, *Physiological Genomics* 16, 166 (2004)

Facts & Challenges: 20th Century Science



http://science.cancerresearchuk.org/cri/research/population_studies/?version=2

Why a distribution of health or needs within a population ?

Why a distribution within cases or requirements?

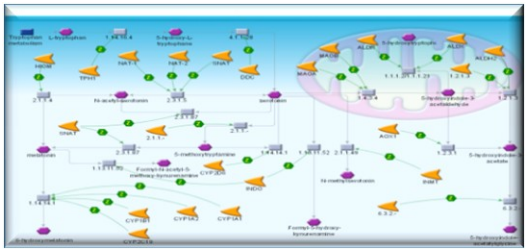
Is risk/intake as calculated for population useful for the individual??

What path to knowledge??

Facts & Challenges Complexity, Heterogeneity, Diversity

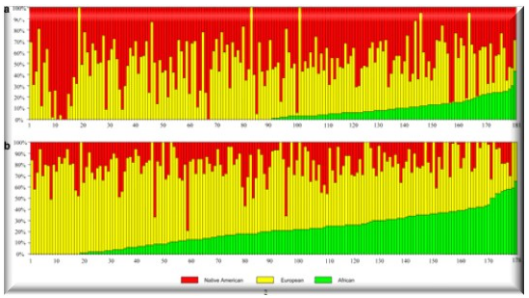
Nutritional

- Composition of agri-foods varies
- Culture & food preparation
- Food processing



Health & Disease

- Variable pathways to each



Genetic

- Humans are the same but different
- History & culture alter populations

Kaput et al, *NMCVD* 17, 89 (2007)

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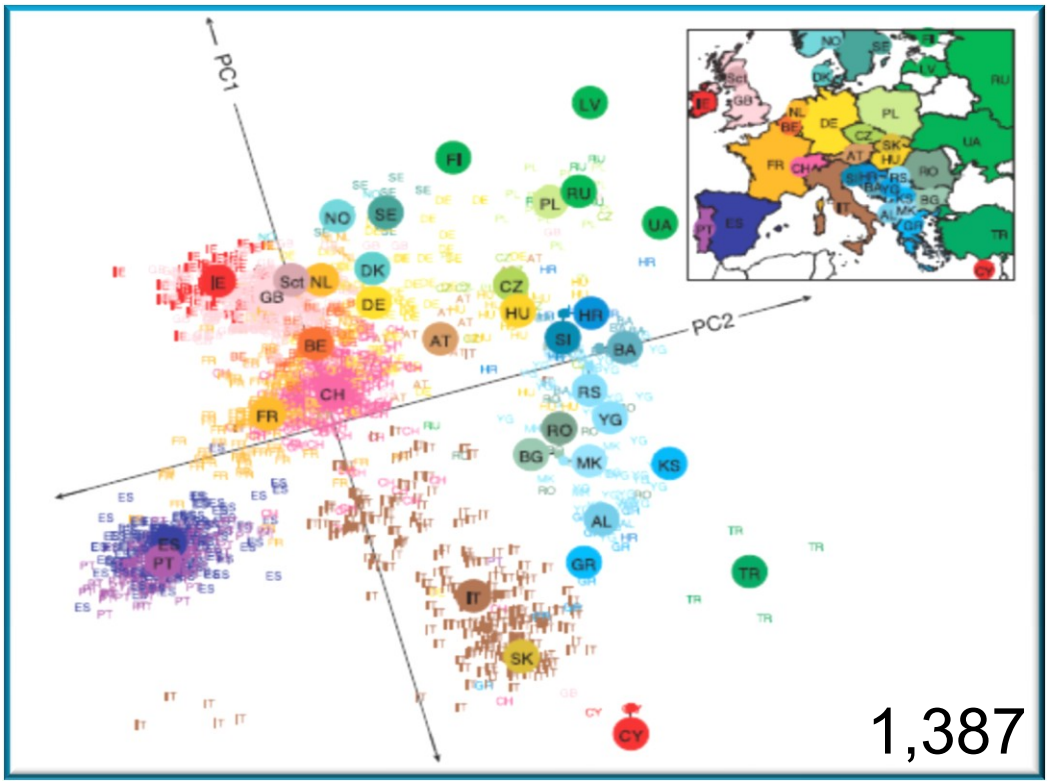
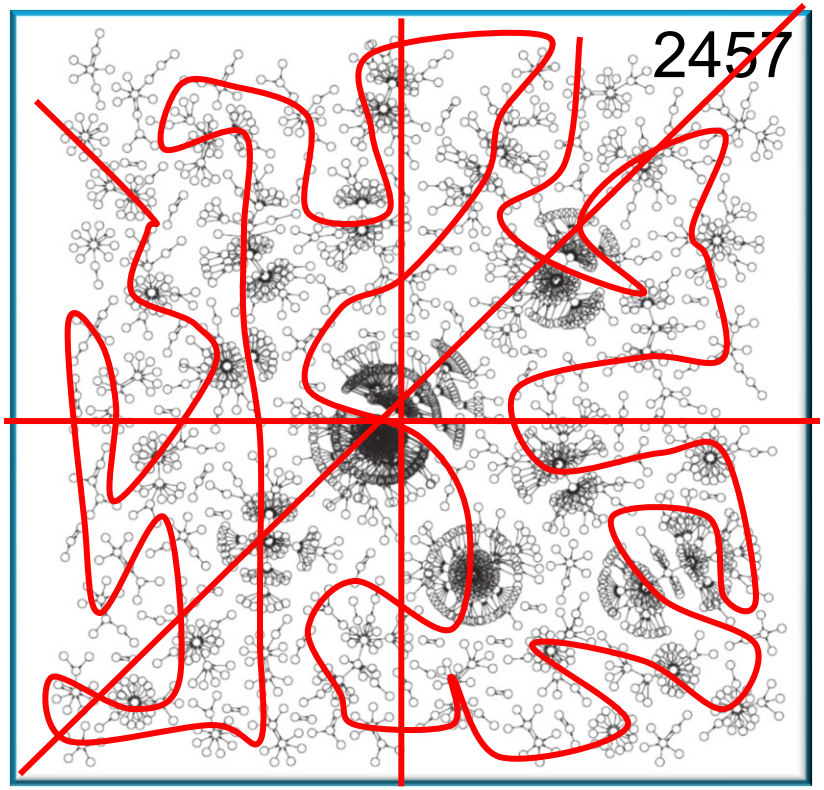
Facts & Challenges Genetic Diversity



Novembre et al *Nature* 456, 98 (2008)



Lu et al *EJHG* 17, 967 (2009)

1000Genomes: 300 – 400 variants affecting 250 – 300 genes resulting in loss of function (LOF) *per person*

Projects Global Initiatives

Connect genomics to nutrigenomics

Connect lifestyle to genomics

SPECIAL ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS

Human Mutation 30, 496 – 510 (2009)

Planning the Human Variome Project: The Spain Report*

Genetic variation linked to phenotype

Yoon Shin Cho,[24] Yeun-Jun Chung,[25] Mireille Claustres,[26] Garry Cutting,[27] Raymond Dalgleish,[28] Johan T. den Dunnen,[29] Carlos Díaz,[30] Steven Dobrowolski,[31] M. Rosário N. dos Santos,[32] Rosemary Ekong,[33] Simon B. Flanagan,[34] Paul Flicek,[35] Yoichi Furukawa,[36] Maurizio Genuardi,[37] Ho Ghang,[13] Maria V. Golubenko,[38] Marc S. Greenblatt,[39] Ada Hamosh,[40]

Chinese government committed to $300 million to the HVP over 10 years to curate 5000 genes

Variome Project Planning Meeting

Genes Nutr (2010) 5:275–283

Proposing to HVP 10% of these genes be involved in nutrient metabolism

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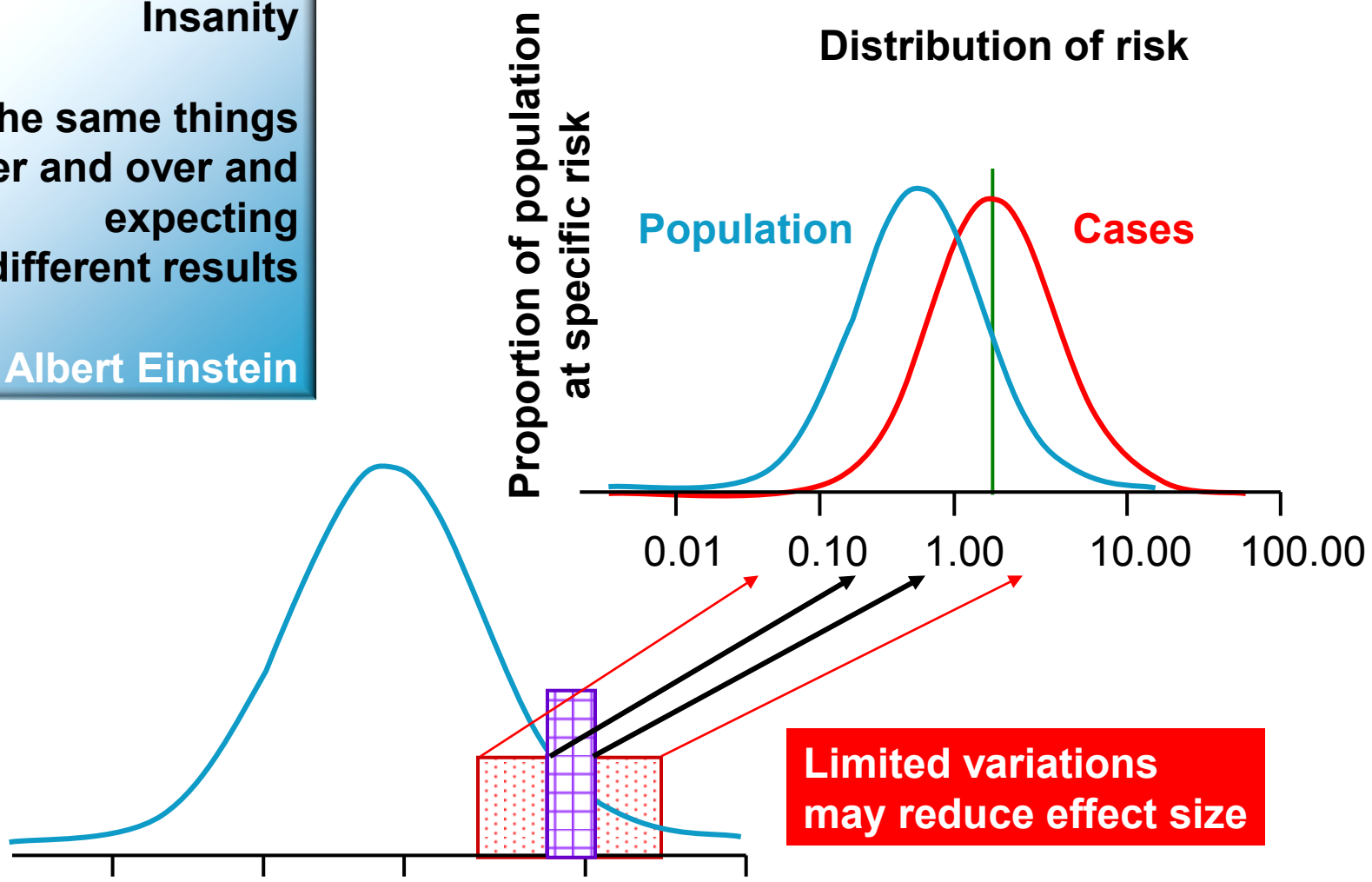
8 – 12 December 2011 in Beijing

Facts & Challenges 20th Century Logic

Insanity

Doing the same things over and over and expecting different results

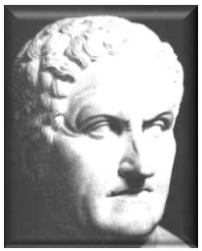
Albert Einstein



Human genetic, nutritional, physiological variations

…food be your medicine

…aptitude of the body



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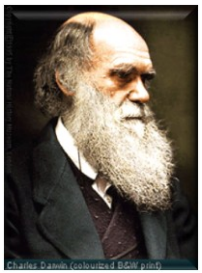

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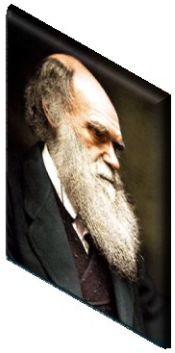
Strategies: Conceptual Basis

A different effect of a *genotype* on disease in persons with different *environmental* exposures

Genotype X Environment Interactions



A different effect of an *environmental* exposure on disease risk in persons with different *genotypes*

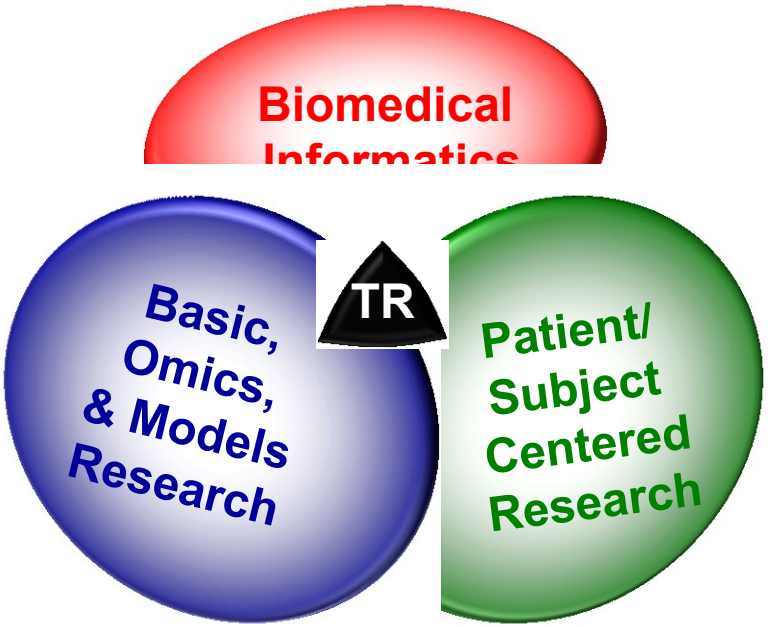
Ottman, *Prev. Med* 25, 764 (1996)

Statistical Parlance

The *main effect(s)* may be *genotype x environment interaction(s)* for chronic diseases and modifying effects

Design Translational Research Strategies

Follow patients/subjects over time – evaluate



Homeostatic assessments
(clinical + omic)

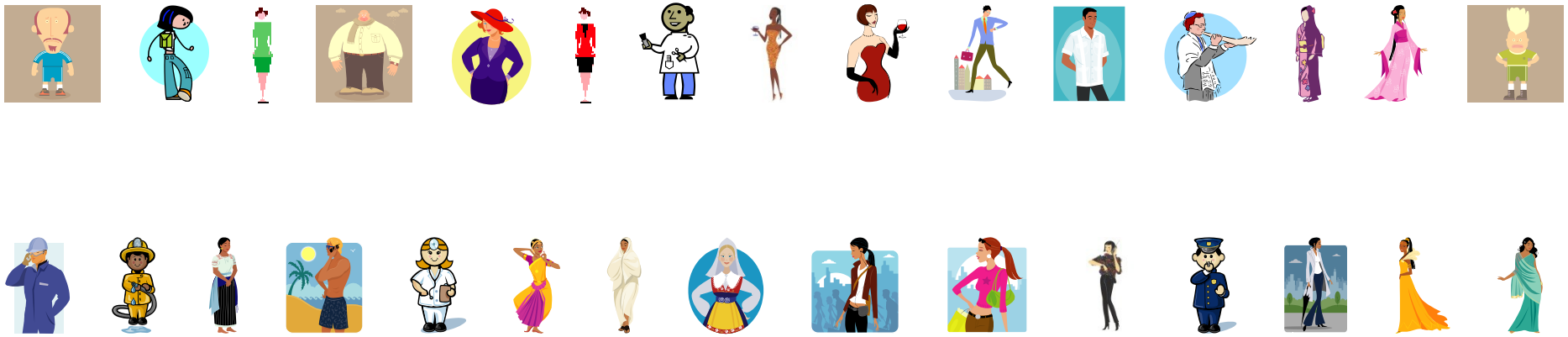
Lifestyle assessments
(food intake + activity)

Changes in biomarkers due to medical or lifestyle interventions

Genomic (once) & Epigenomic

Associate changes/outcome in quantitative assessments in the context of individual genomes

Strategies: Human Study – Analyses



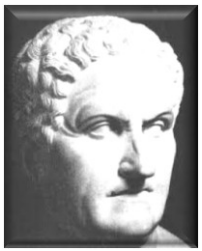
?? Dimensionality reduction + classification algorithms ??

New: A_N1_N, B_N1_N, B_N2_N, C_N1_N, C_N2_N = Genotype X Environment Interactions

Old: A, B, C = single genes or GWA, no environment (1,2)

…food be your medicine

…aptitude of the body



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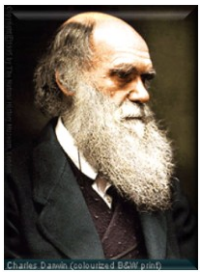

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Strategies: Human Study 1 – Homeostatic Challenges

Challenge homeostatic systems

- Functional challenge
- Nutrient challenge

Examples
Oral glucose tolerance
Lipid challenge
Activity challenge
Oxidative stress challenge
OTC Drug challenge

Dose, kinetics, and relevant physiological measures

- Deep genotyping and deep phenotyping

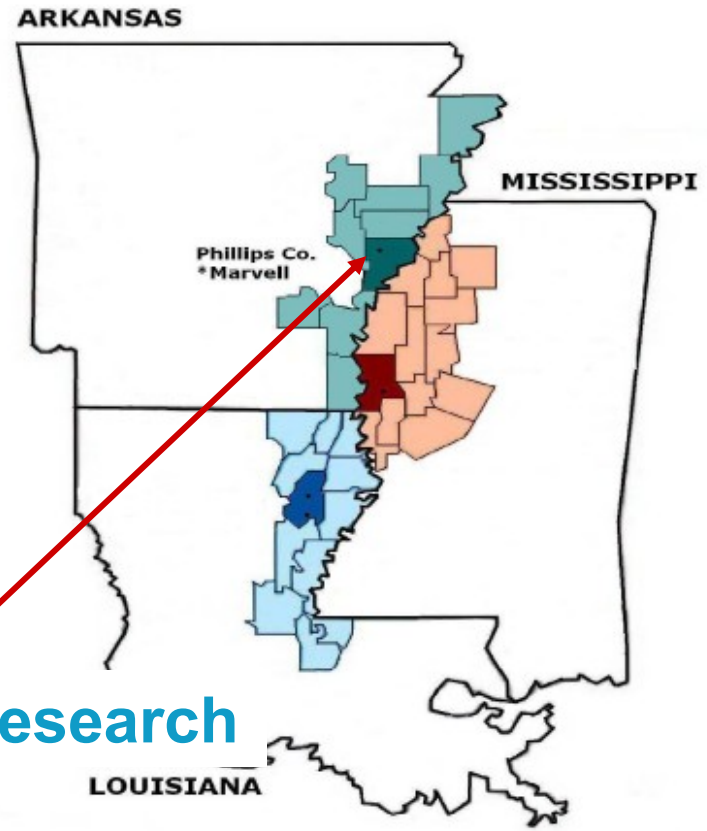
No reference population for health

- Compare responses in differing genetic make-ups & cultures

Define health and biomarkers

Van Ommen, Keipper, Heil, Kaput (2009) Molecular Foods Nutrition 53, 795

Strategies: Human Study 2 – CBPR Translational Research



Community Based Participatory Research

With USDA – ARS in Little Rock

Track individuals' nutrition, health, genetics, economics

Interventions to improve nutrition & health

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McCabe-Sellers et al. Omics 12, 263 (2008)

Strategy CBPR Long-term Intervention

Metabolites in blood @ **pre**, **end**, **post-intervention**

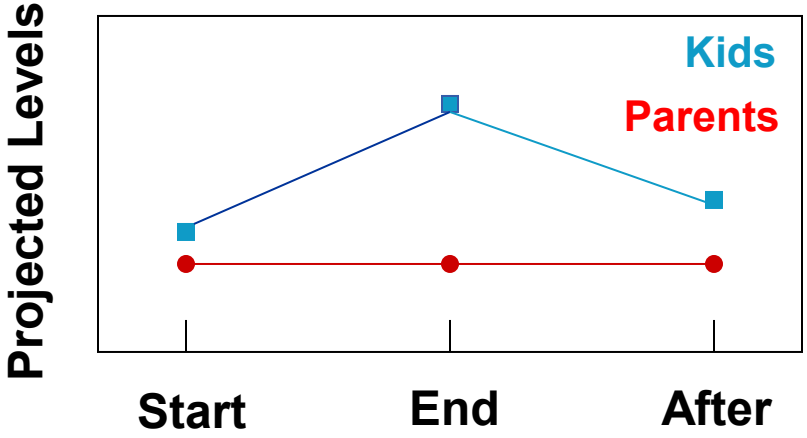
Genomics, DNA methylation

Sequence genes micronutrient metabolism genes

Diet Intakes – 24 hr **Activity** – Body Bugg **Skin tone** – Dermometer

Correlate Δ metabolite(s) to an individual's genotype

In kids and parents



Quantitative assessment of efficacy *per individual*

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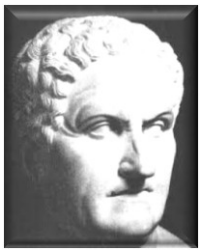

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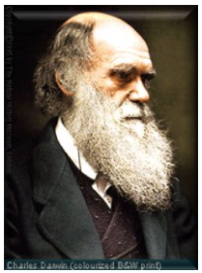

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Rationale Harmonized Protocol

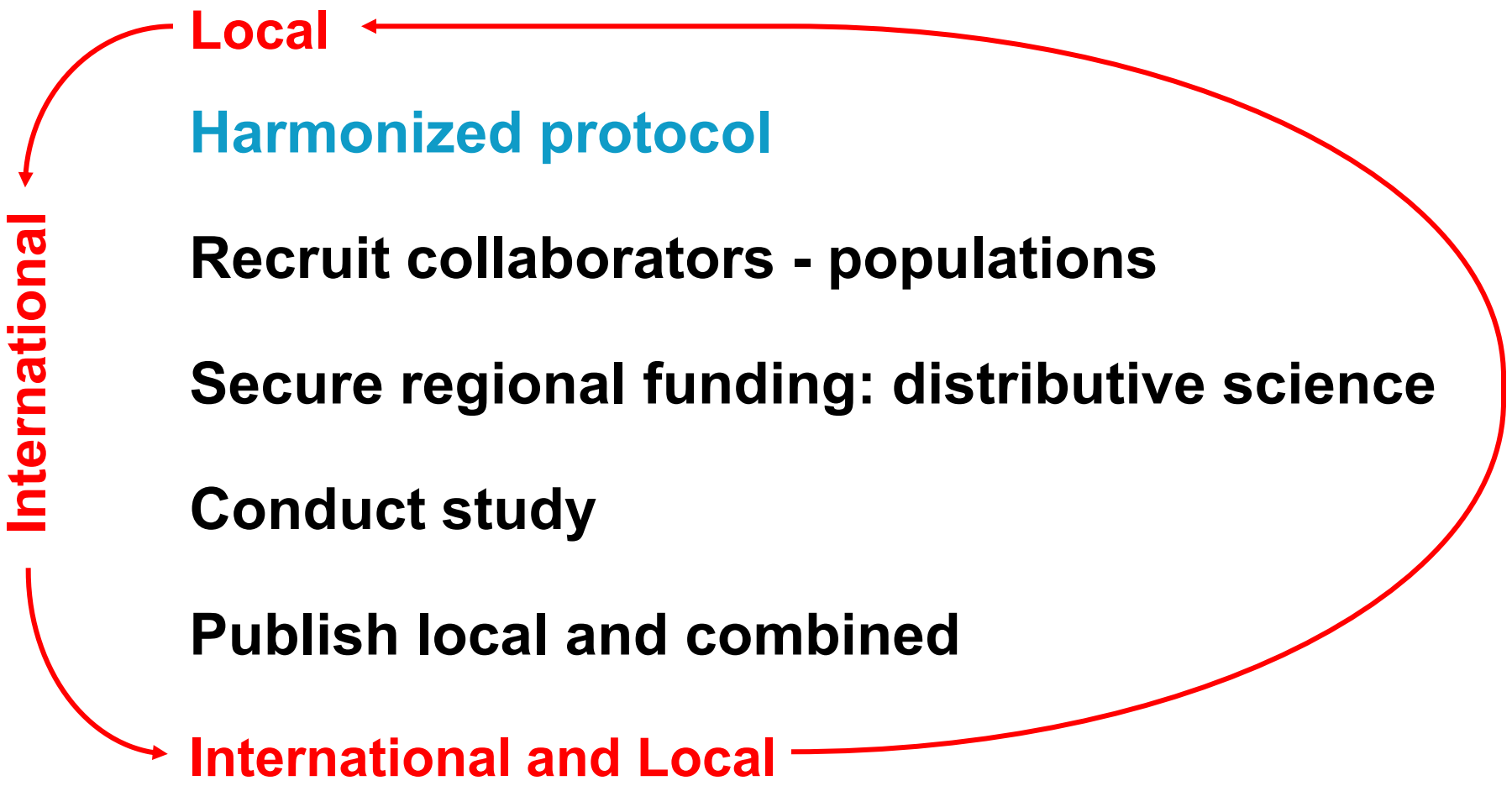
The range of micronutrient needs to maintain human health is not known

Genetic variation in metabolism genes is known but the full range has not been analyzed

Small studies and different designs, interventions, and assessments have not created knowledge to optimize or maintain health.

(Note: obesity, T2DM epidemics)

Projects Global Initiatives Process



Micronutrients = 2012

T2DM = 2012

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Thank You and Input

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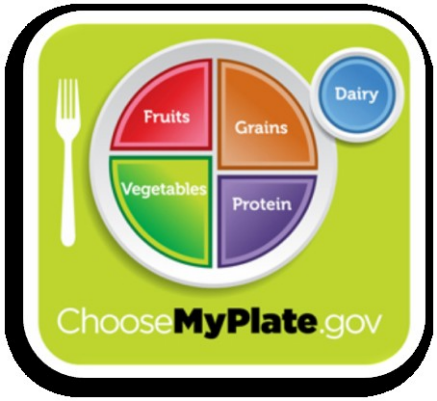
Move more

Choose ancestors wisely



Eat less