



Biomarkers and Surrogate Endpoints for Evaluating Health Benefits of Food Components: Promises and Perils

J. A. Milner

milnerj@mail.nih.gov

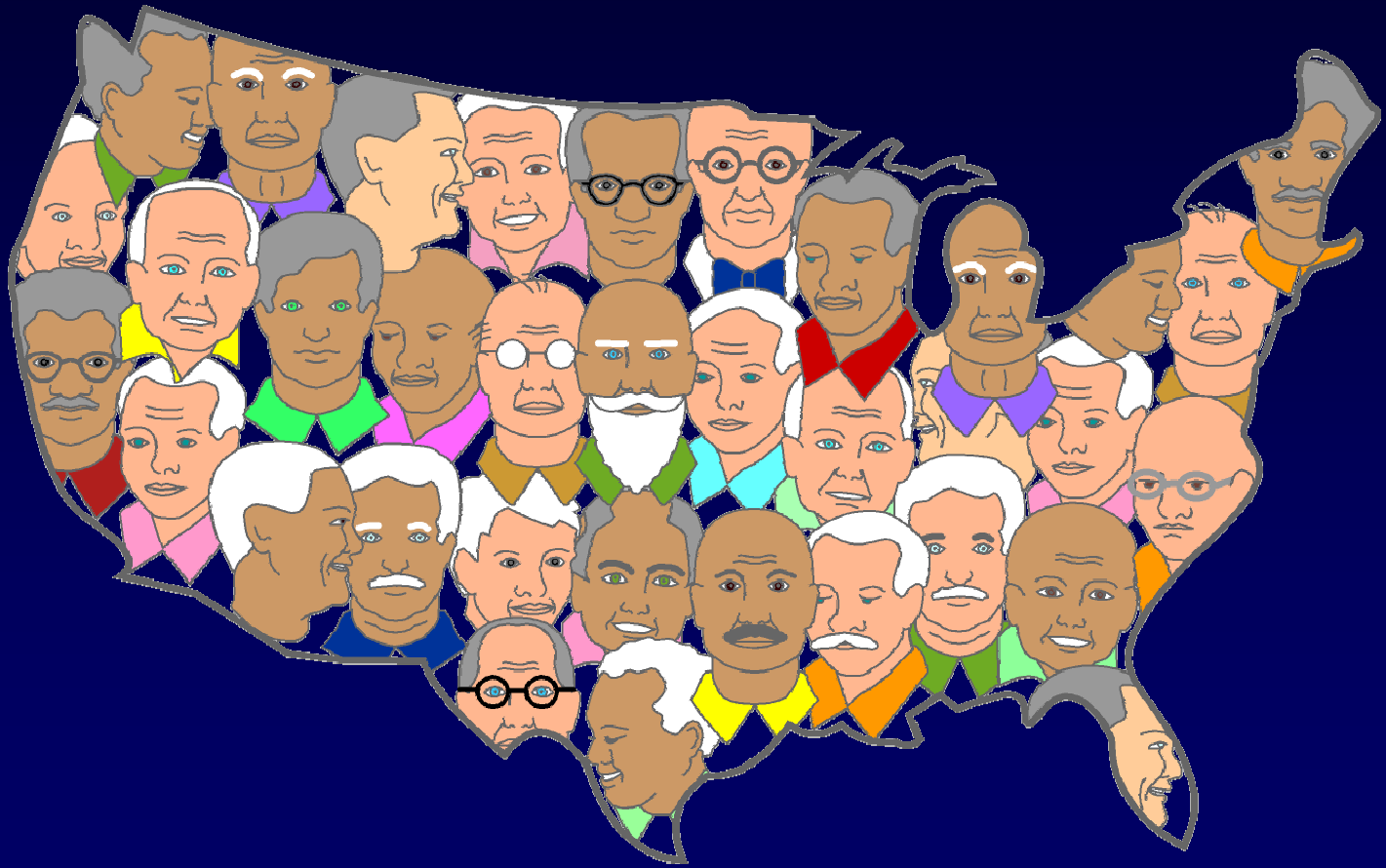
**Nutrition Science Research Group
Division of Cancer Prevention
National Cancer Institute
Bethesda, MD 20892**





Unprecedented opportunities exist for the expanded use of foods and components to achieve genetic potential, increase productivity and reduce the risk of disease

5 of the Top 10 Causes of Death of Americans Relate to Dietary Habits



Cancer and Heart Disease Battle for Top Position

DEFINITION

Clinical Endpoint - A characteristic or variable that reflects how a patient feels, functions or survives.

Surrogate Endpoint - a biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

Source: Biomarkers Definition Working Group -1998

Surrogate marker

Is a response variable for which a test of the null hypothesis on no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint.

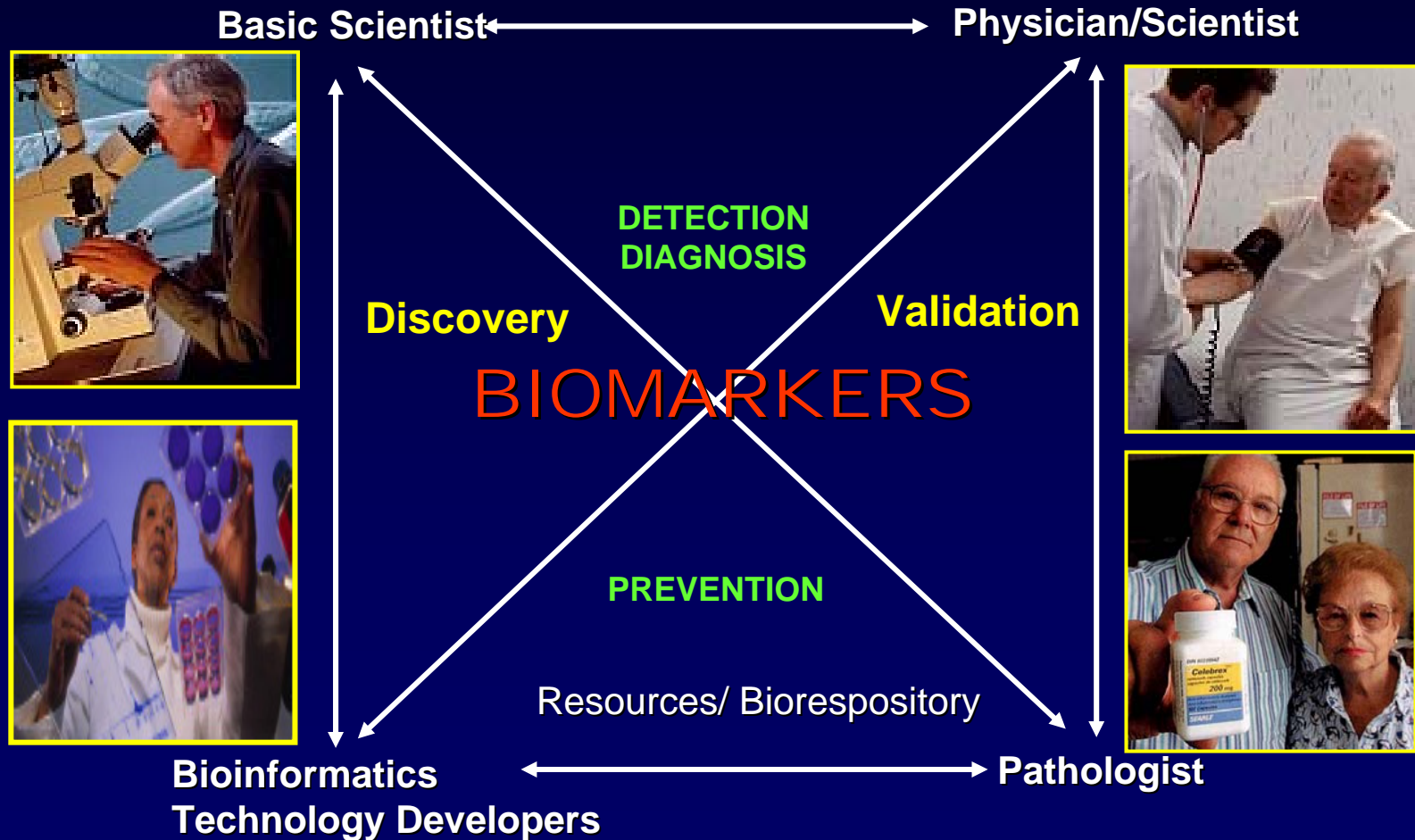
Prentice, Stat. Med., 1989

i.e. A laboratory or physical sign that is used in studies as a substitute for a clinically meaningful endpoint such as pain or death.

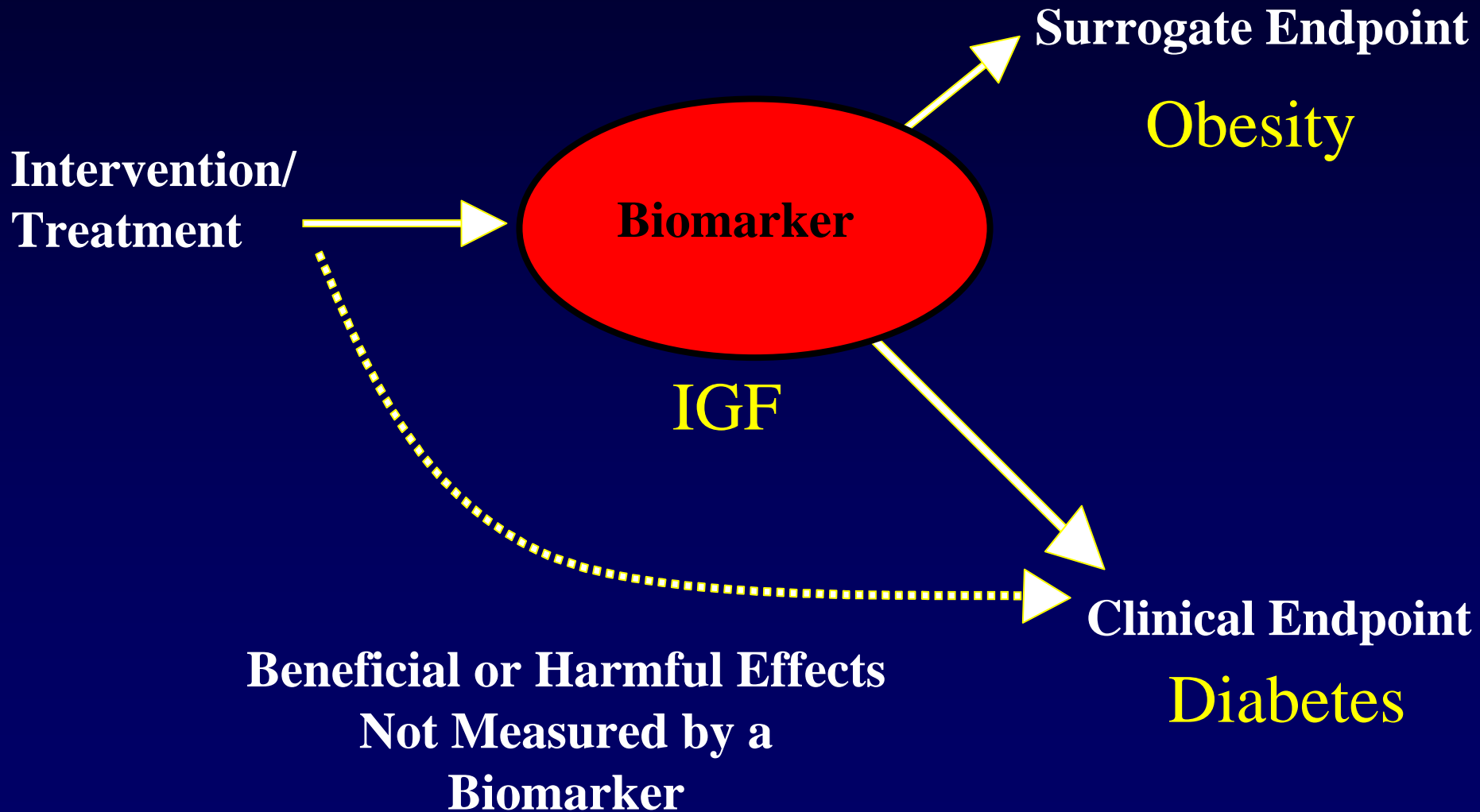
Biomarker (Biological Marker)

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

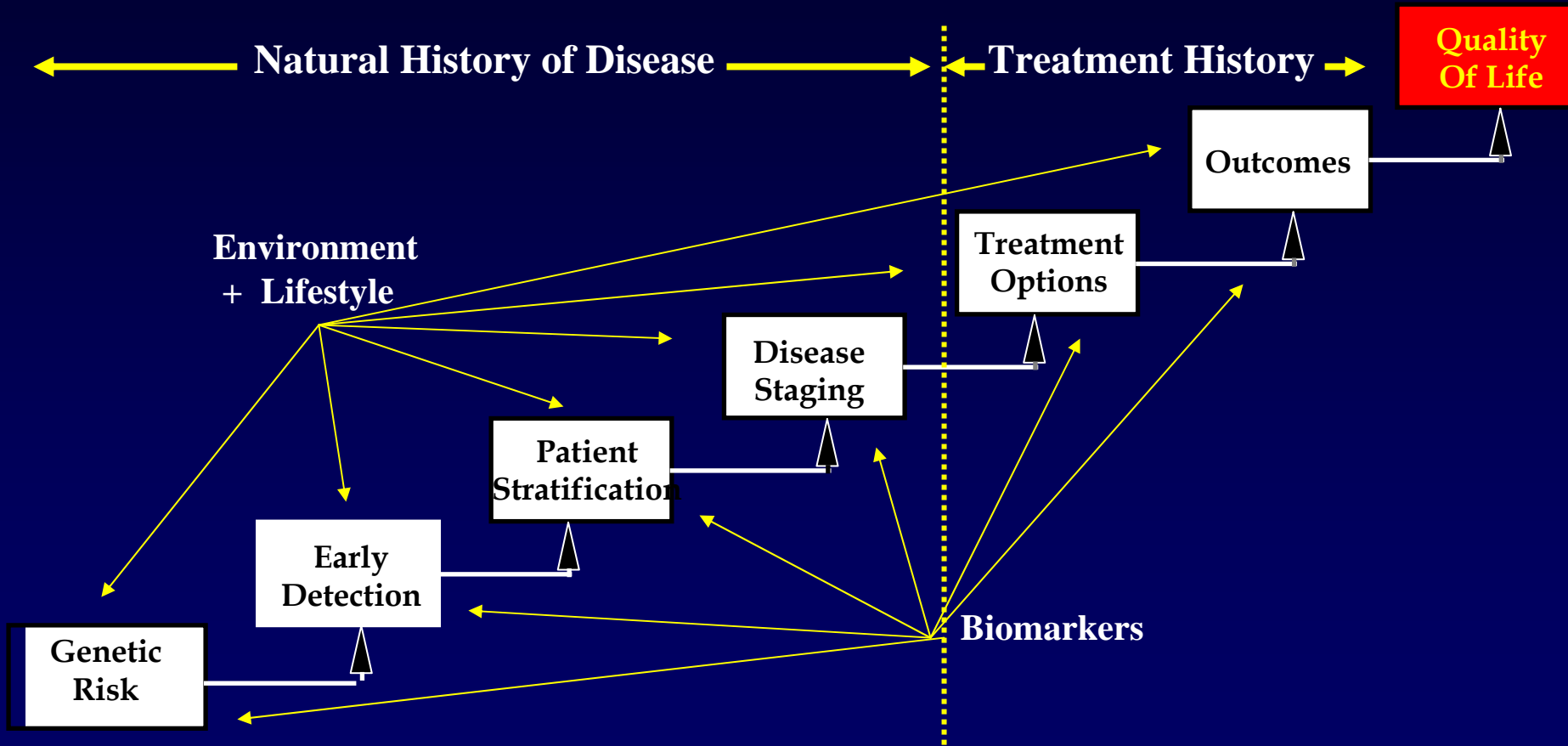
SYSYEMS BIOLOGY APPROACH TO BIOMARKERS RESEARCH



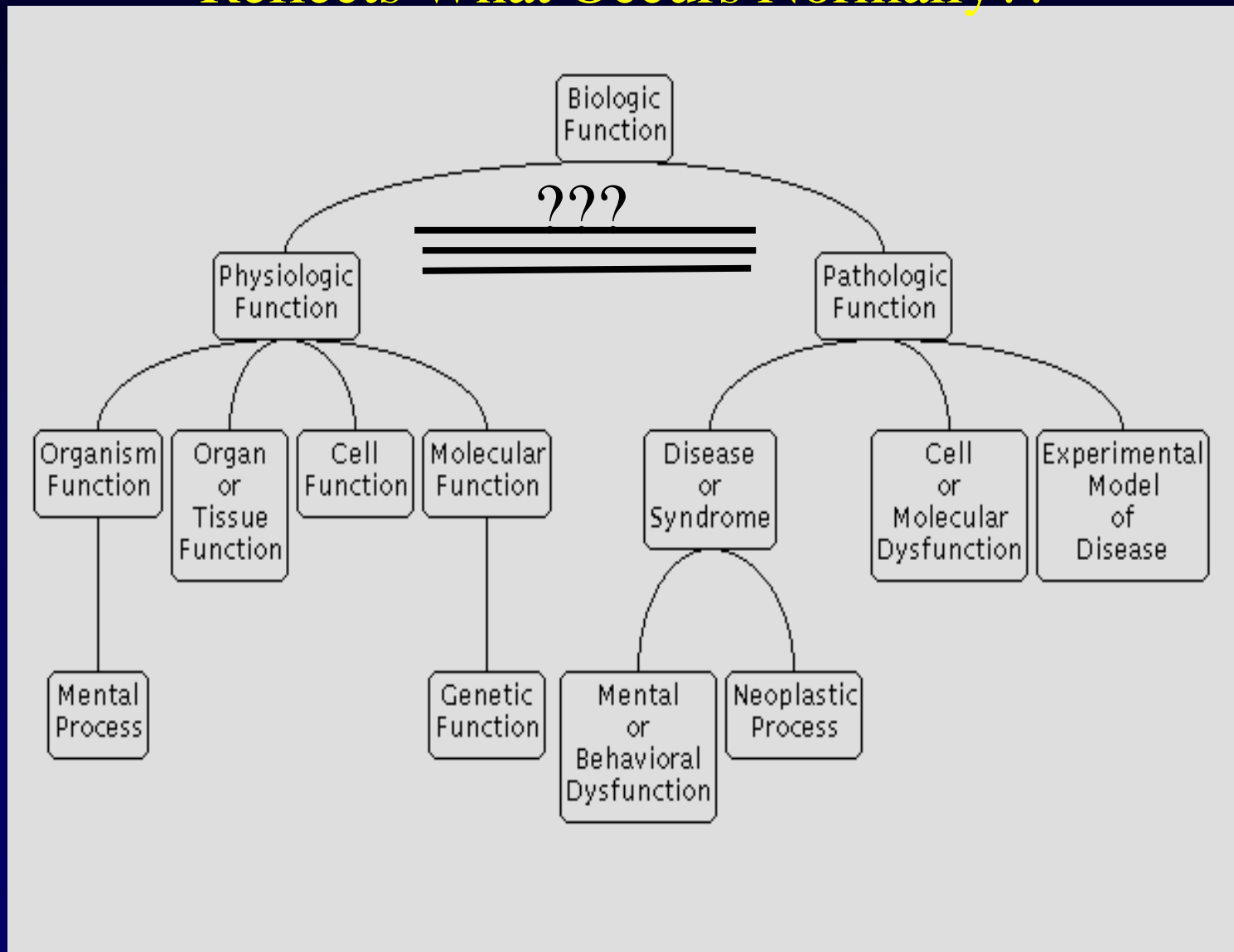
Capturing the Response



Pathway of Disease



Fundamental Question Remains if Pathologic Evaluations Reflects What Occurs Normally??



Biomarkers and Other Intermediate Endpoints

Ideal Qualities:

- Readily accessible
- Easily & reliably assayed
- Differentially expressed
- Directly associated with disease progression
- Modulable
- *Predictive*

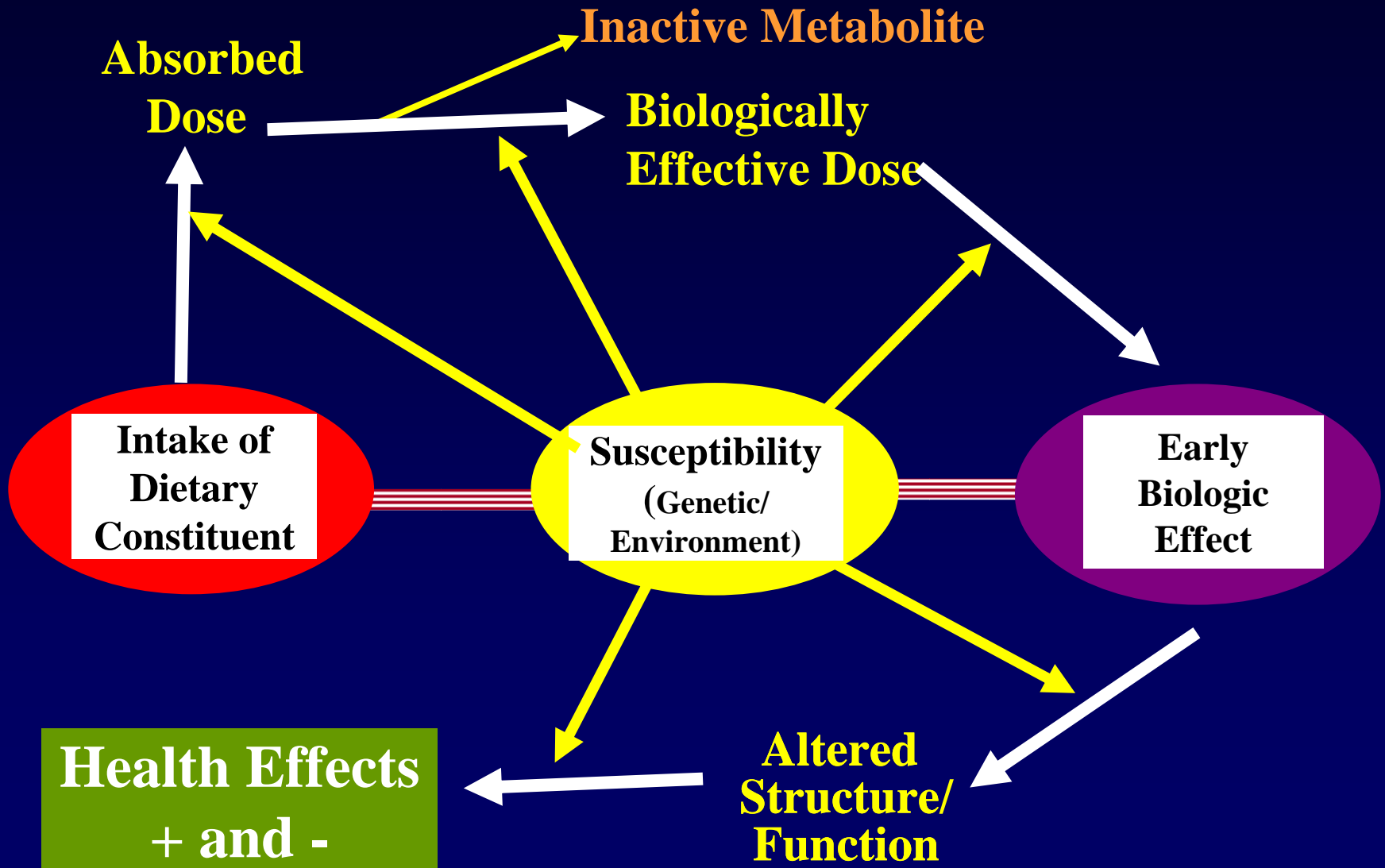


Multiple Promises and Perils

- Many putative biomarkers
 - few validated
 - lack of criteria for validation
 - more clinical studies needed

Thus biomarkers for disease assessment and early detection are woefully inadequate

Three Types Biomarkers Needed Exposure, Effect, Susceptibility



Numerous Dietary Components May Influence Health

■ Essential Nutrients- Ca, Zn, Se, Folate, C, E

■ Non-Essential

Phytochemicals- Carotenoids, Flavonoids, Indoles, Isothiocyanates, Allyl Sulfur

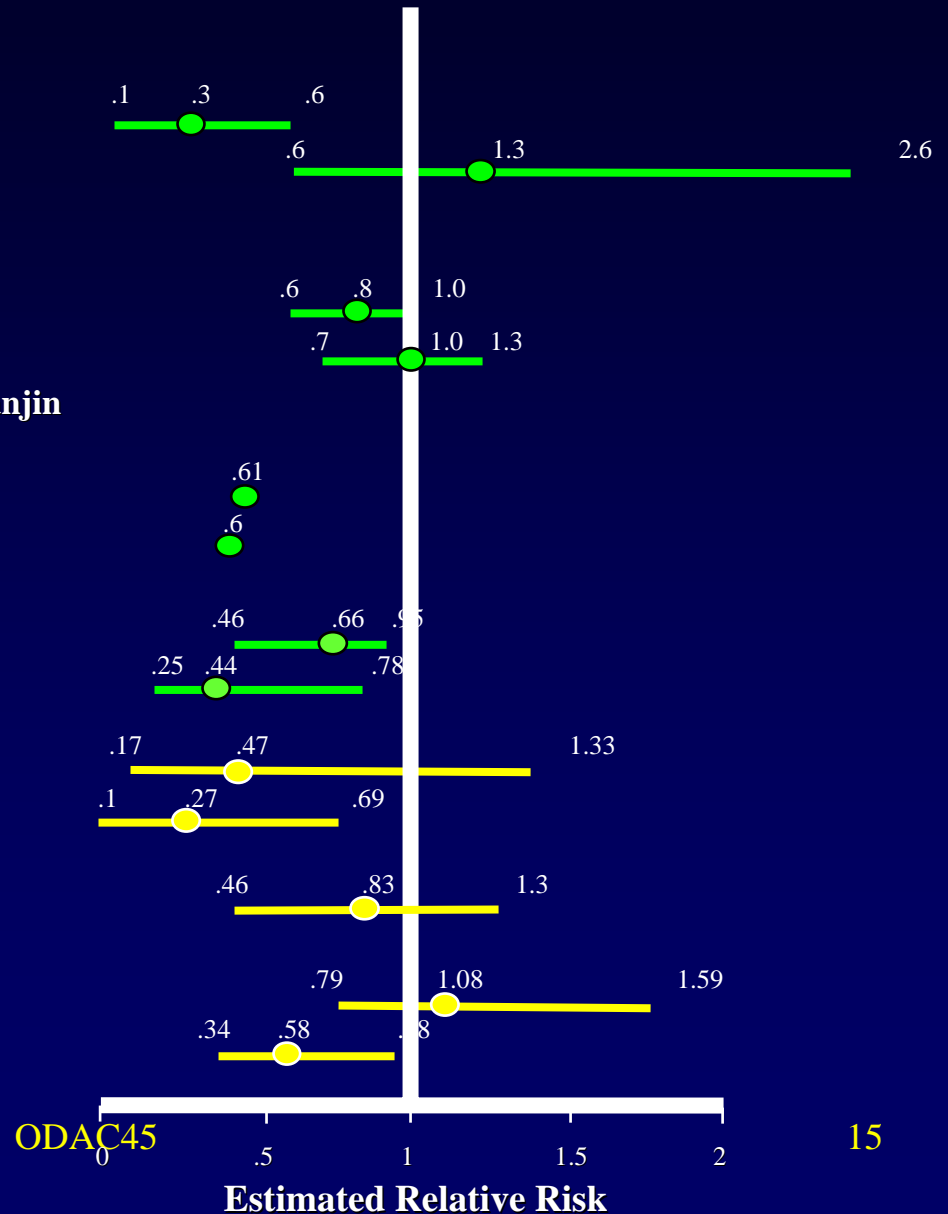
Zoochemicals - Conjugated linoleic acid, n-3 fatty acids

Fungochemicals - Several compounds in mushrooms

Bacteriochemical - Those formed from food fermentations and those resulting from intestinal flora

Epidemiologic Studies of Soy Components in Diet: Breast Cancer Risk Reduction

- Asian**
- Lee '92 (total soy protein)**
p < 0.001 Premenopausal
NS Postmenopausal
 - Hirose '95 (beancurd, miso)**
 - Yuan '95 (tofu, soymilk)**
NS Premenopausal
NS Postmenopausal
NS p = 0.44–0.79 Shanghai, Tianjin
 - Wu '96 (tofu)**
p < 0.01 Premenopausal
p < 0.05 Postmenopausal
 - Dai '01 (soy)**
NS All Breast Cancer
S Just ER+/PR+
- Western**
- Ingram '97 (urinary isoflavones)**
NS Diadzein
p = 0.009 Equol
 - den Tonkelaar '01 (urinary phytoestrogens)**
NS Postmenopausal
 - Keinan-Boker '02 (food content)**
NS Isoflavones
S Lignans



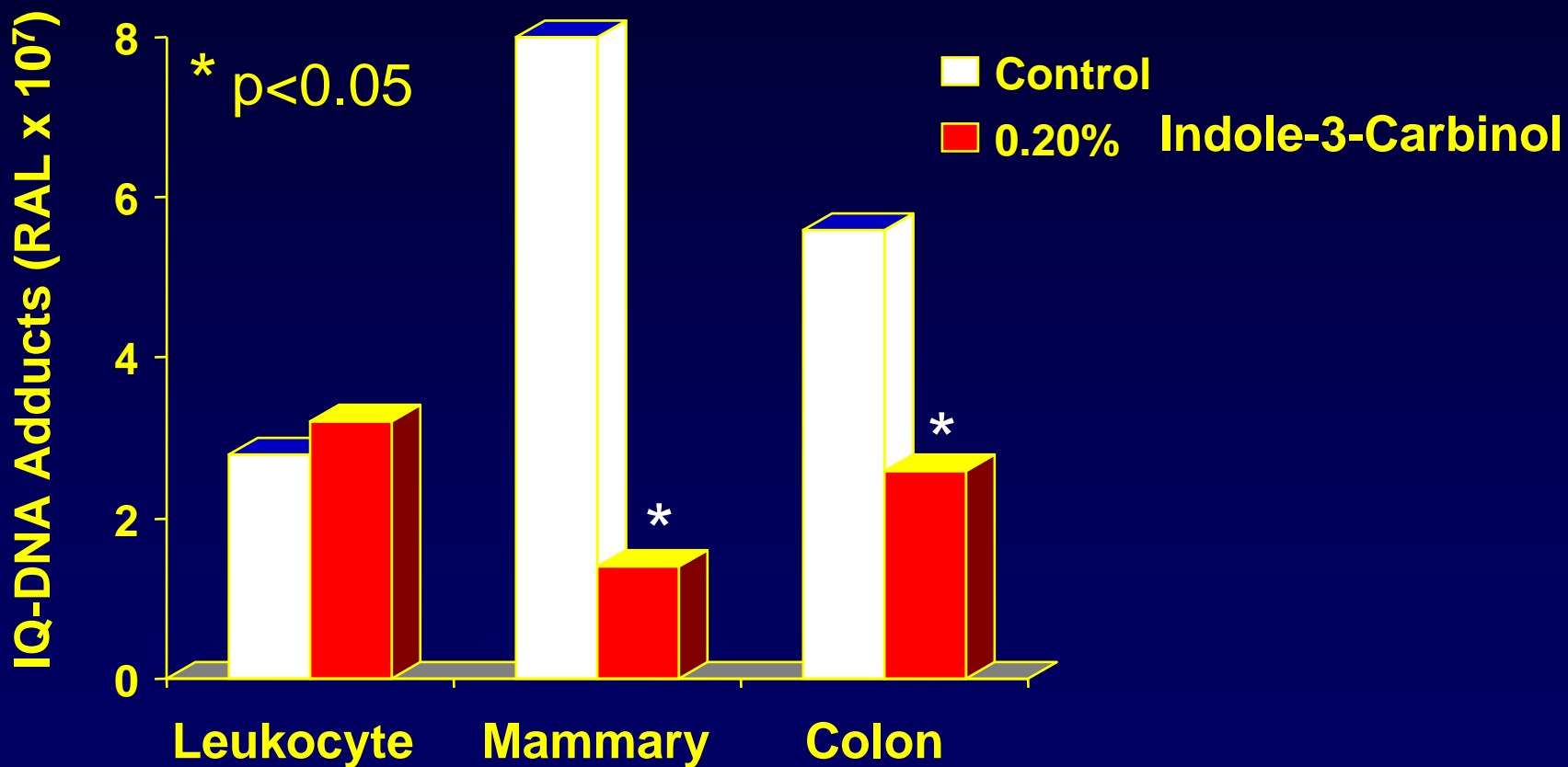
Promises and Perils for Diet Biomarkers

Undeniable limitation in evaluation of eating behaviors

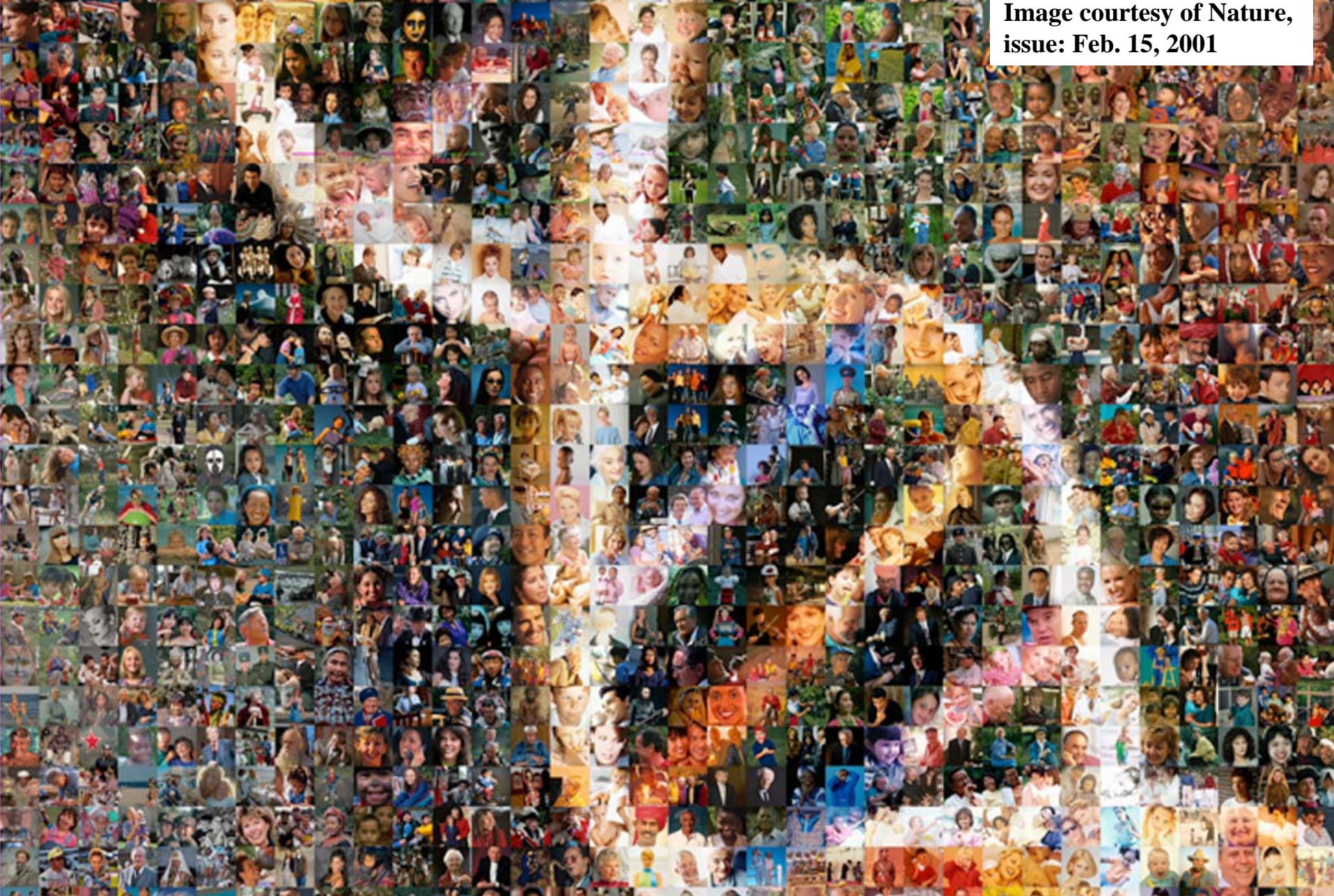
Unclear if markers should focus on nutritional status or dietary intake



Tissue and Leukocyte IQ-DNA Adducts

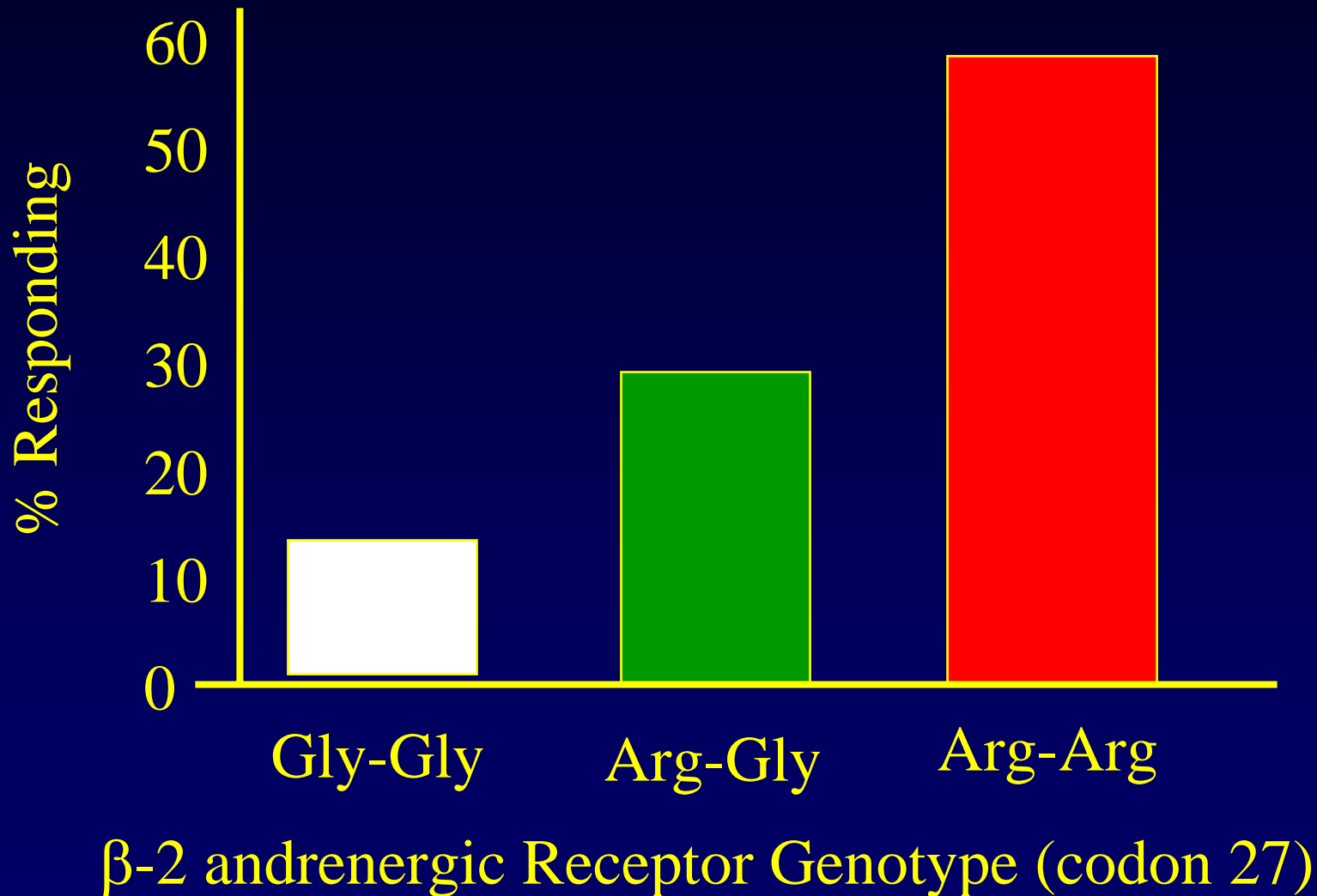


IQ= 2-amino-3-methylimidazo[4,5-*f*]quinoline

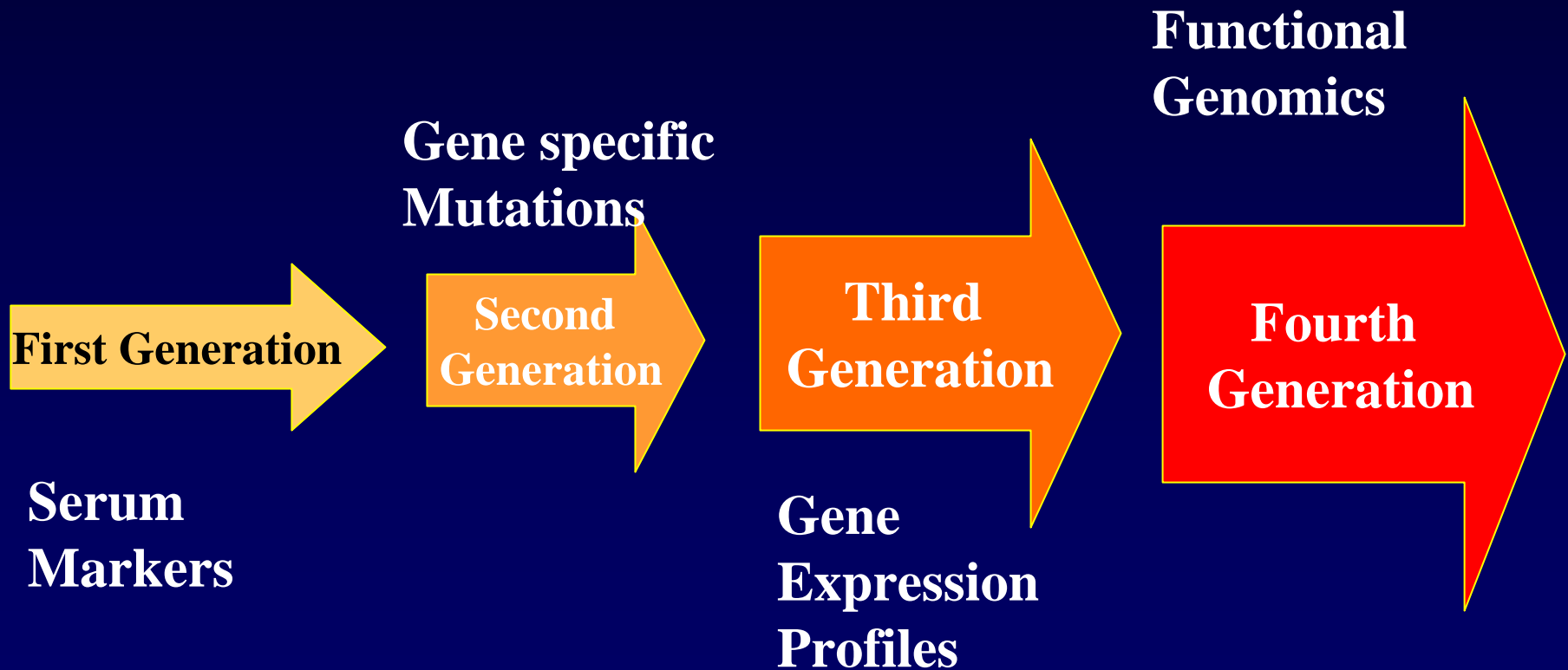


Advances in Genomics Are Significantly Changing Views and Strategies for Health Promotion and should help identify responders and non-responders

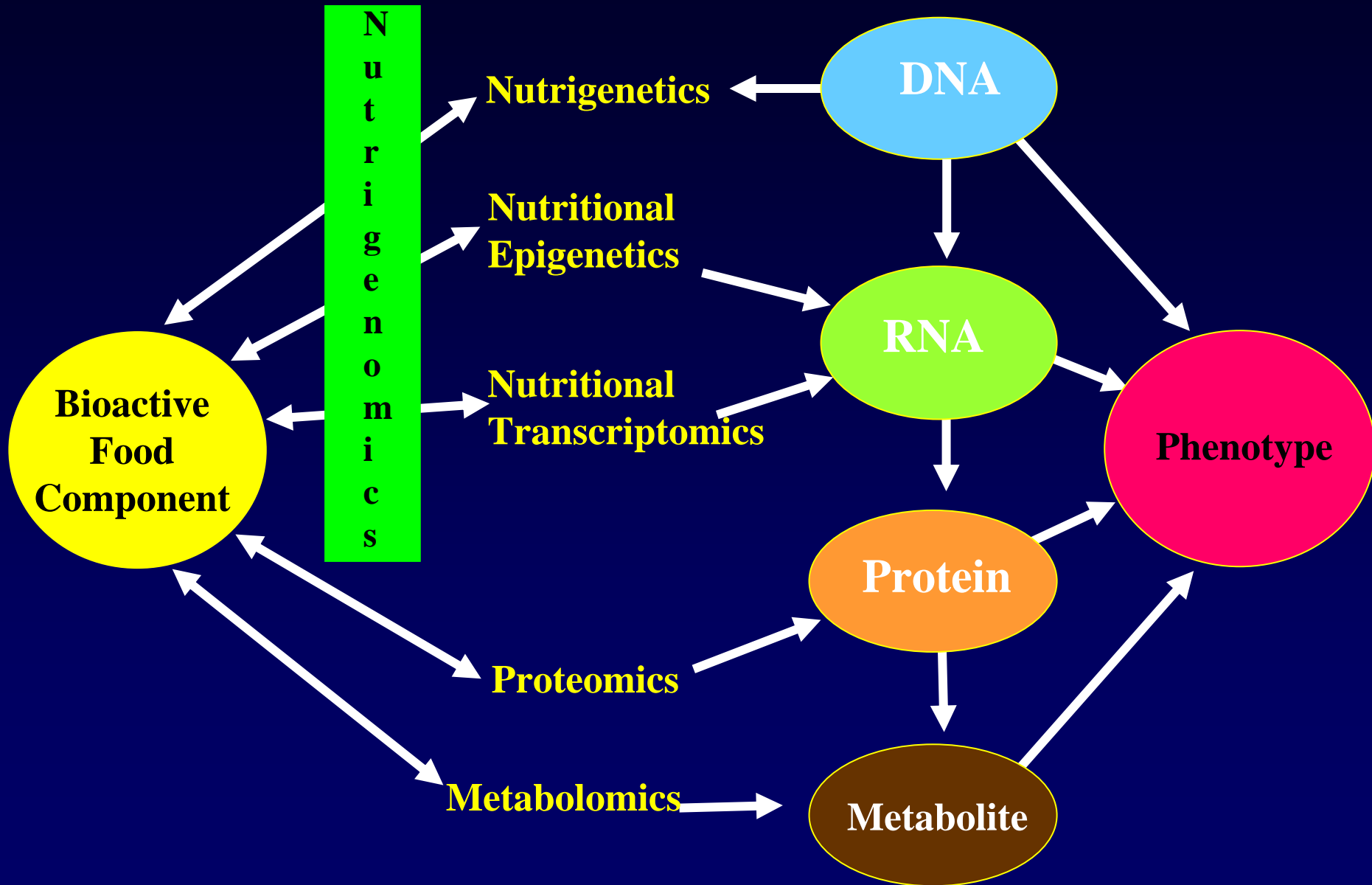
Bronchodilator Response to Albuterol



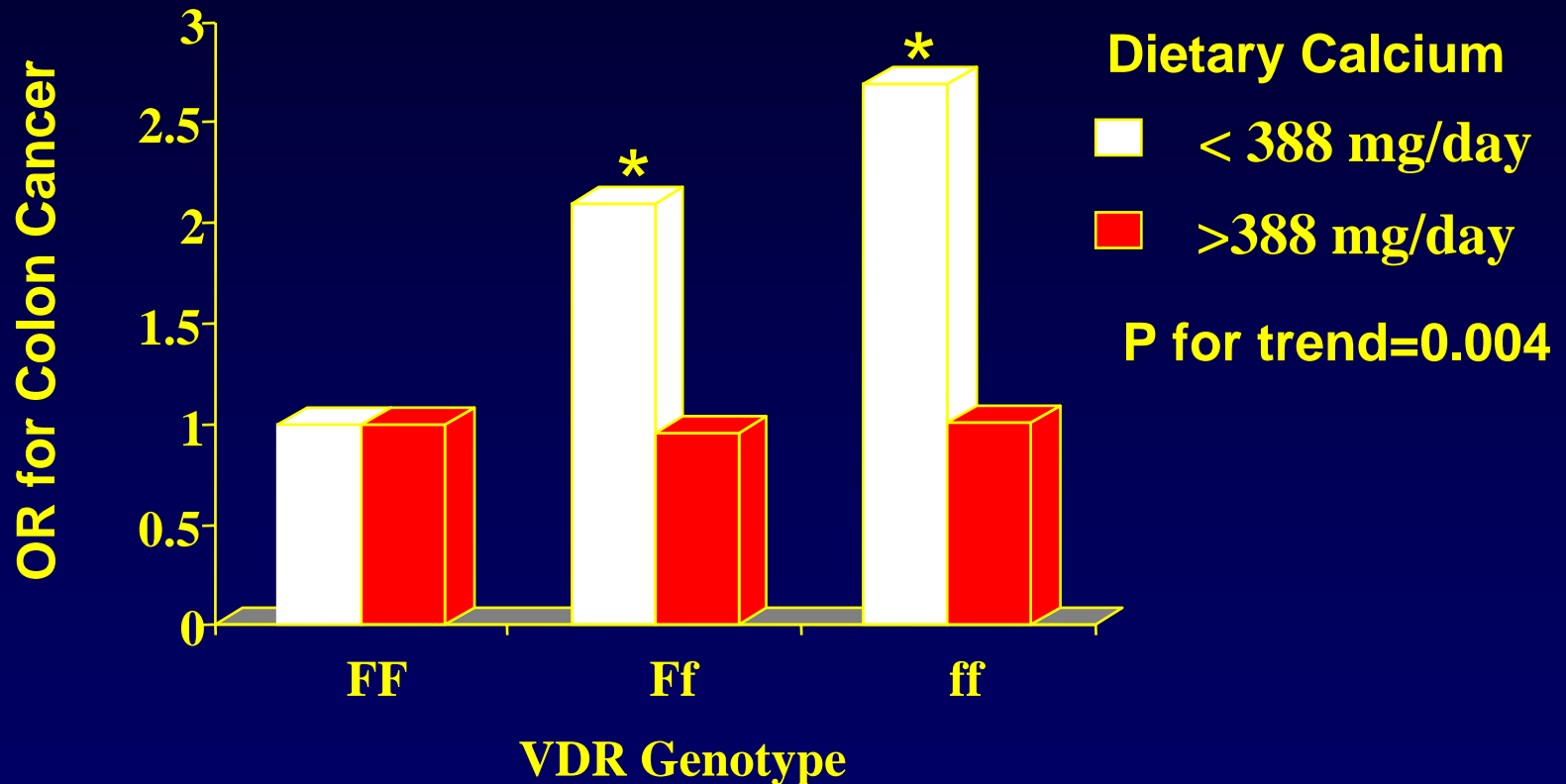
The Evolution of Biomarkers ??



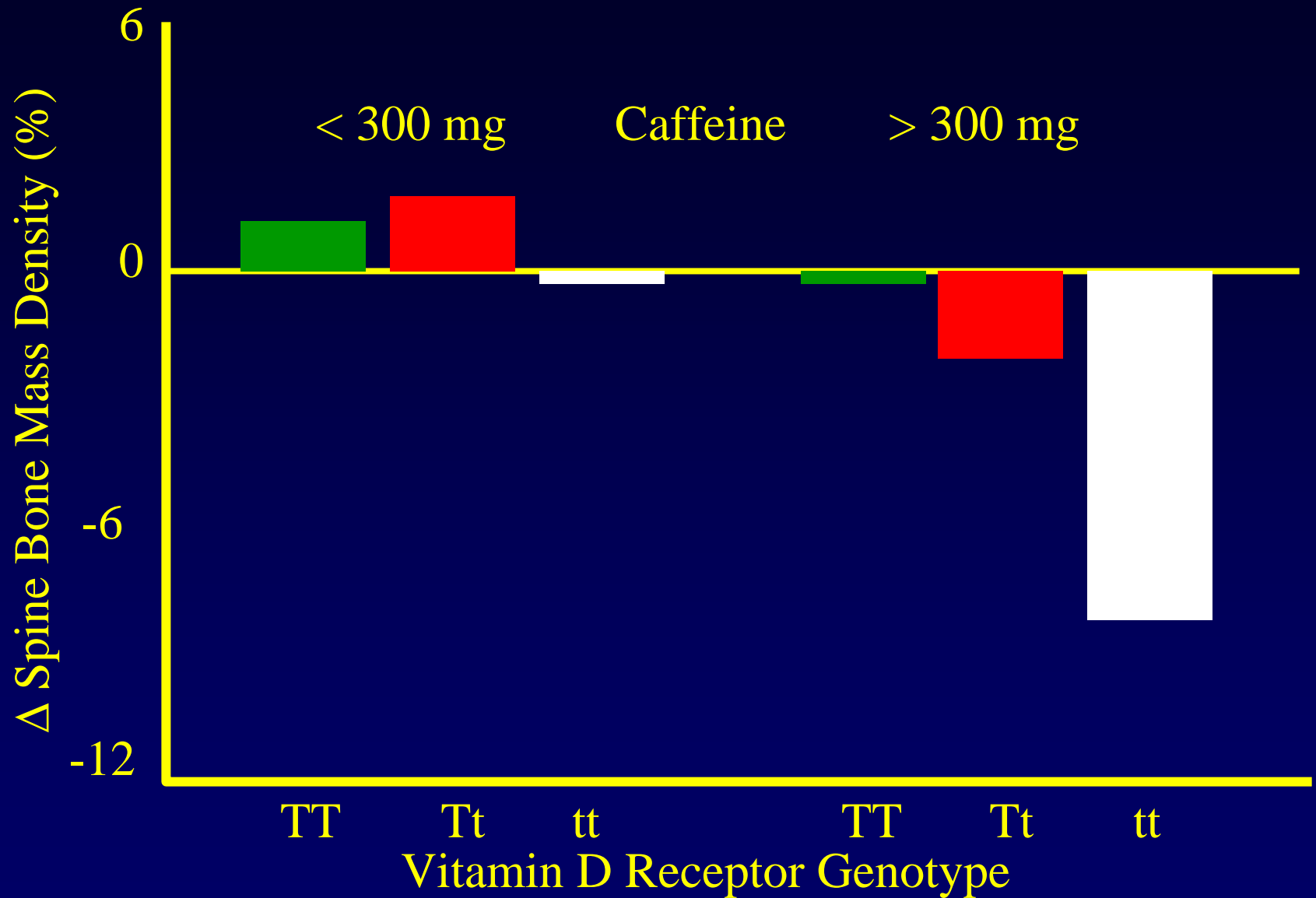
The “Omics” of Nutrition and Effect Biomarkers



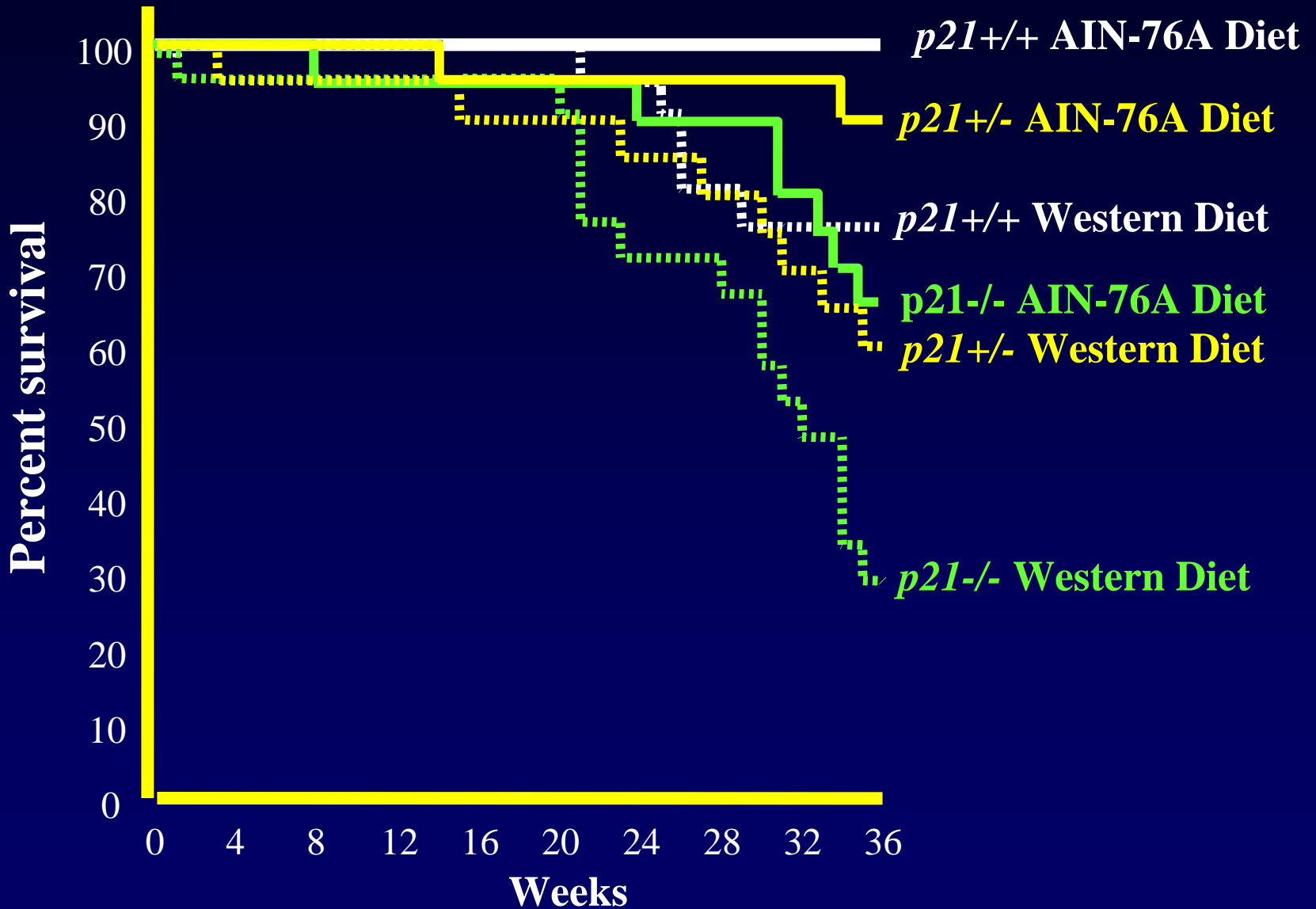
Dietary Calcium, VDR *FokI* Genotype and Colon Cancer Risk



Influence of Caffeine on Bone Mass May Depend on Genes



Diet-Gene Interactions in Colon Cancer

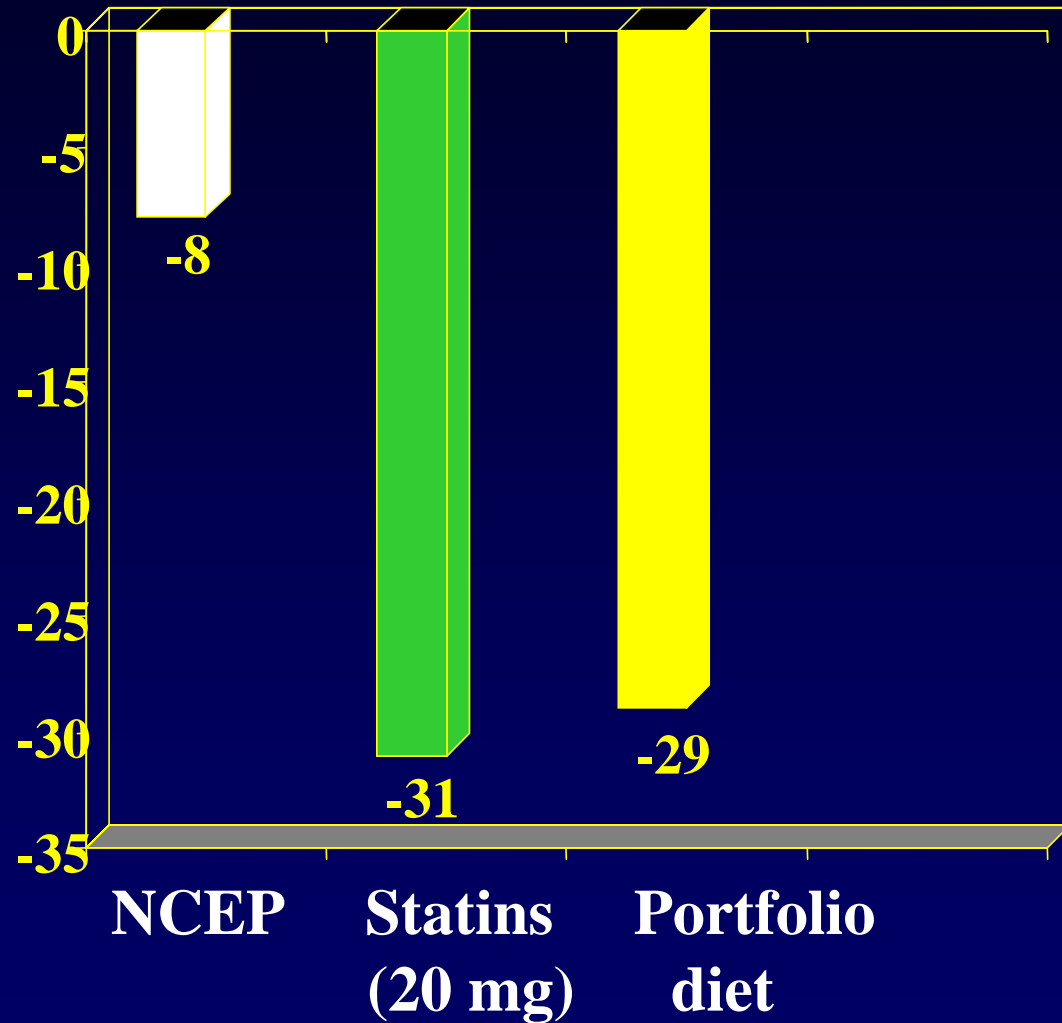


Nutrigenomics today!

- **Commercial Nutrition-Gene Test**
 - Genelex Sciona 19 genes including MTHFR \$395
 - Gene Care CVD nutritional genetic test (South Africa) MTHFR (Hcyst), apoA1 (HDL) +9 others \$400
- **About 30, 000 Genes, 5-8 Million SNPs**

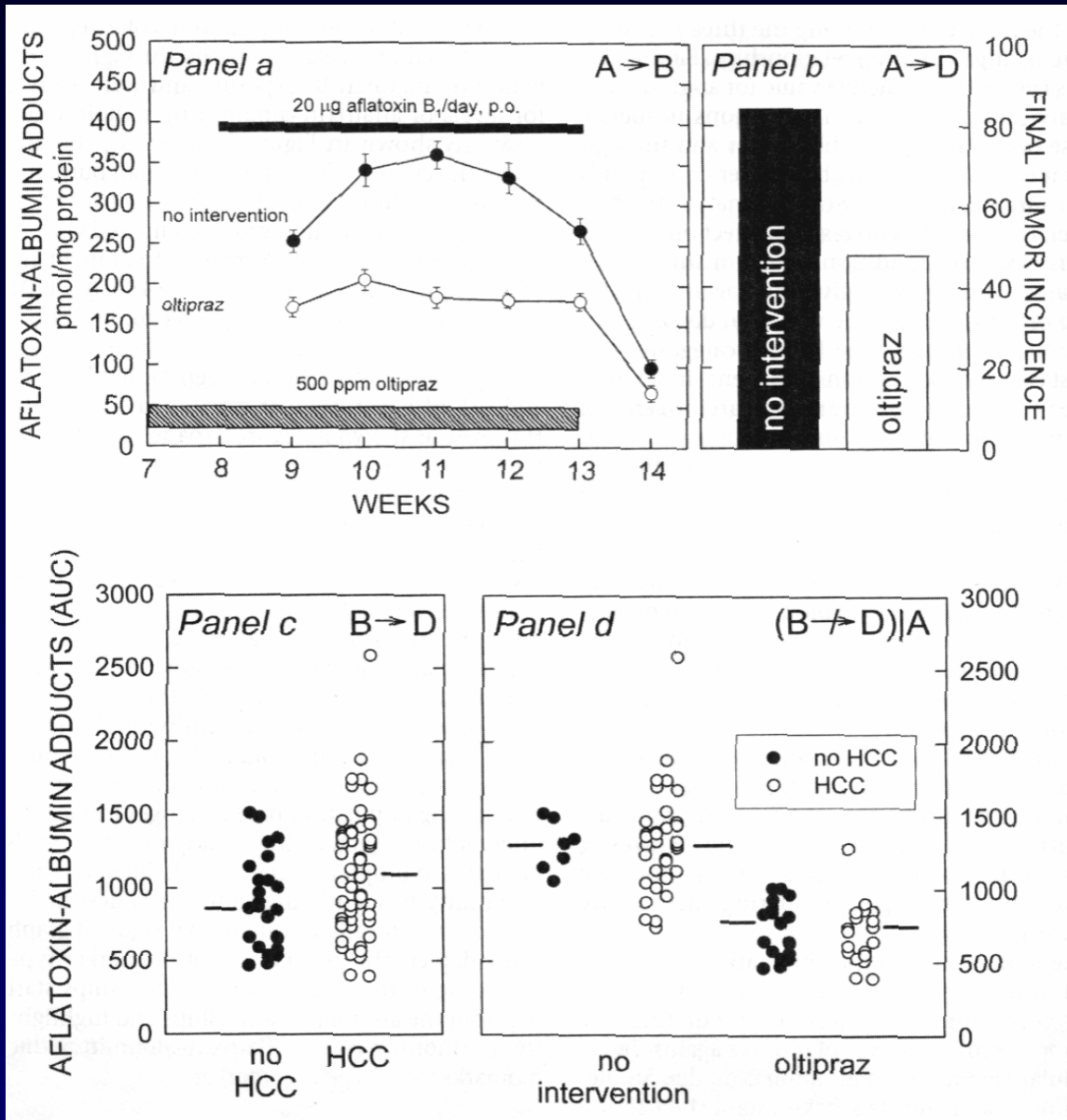
% Reduction in LDL Cholesterol as an Effect Biomarker

- **Jenkins *et al.*, JAMA 290: 502-510, 2003**
- **4 weeks**
- **Statins vs. NCEP Step 2 diet vs. a Portfolio eating plan:**
 - ◆ plant sterols (1g/1000 kcal)
 - ◆ almonds (14 g/1000 kcal)
 - ◆ viscous fiber (9.8 g/1000 kcal)
 - ◆ soy protein (21.4 g/1000 kcal)



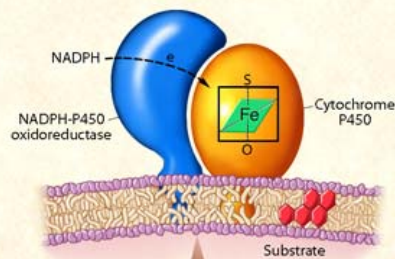
Dietary can lower cholesterol as much as cholesterol-lowering drugs

Do Not Over Interpret Biomarkers

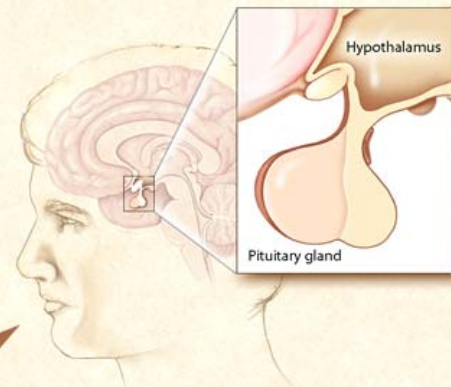


*Biomarkers and Surrogacy: Relevance to Chemoprevention. 2001.
Kensler, T.W., Davidson, N.E., Groopman, J.D., and A. Muñoz.*

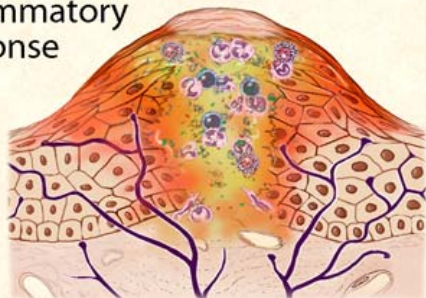
Carcinogen metabolism



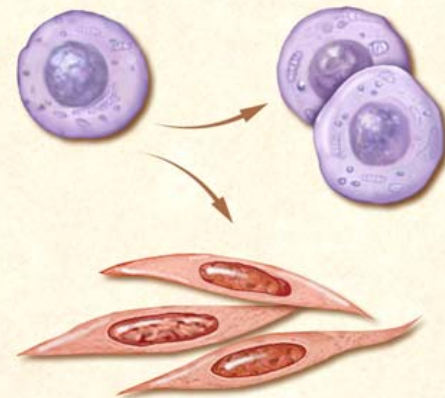
Hormone regulation



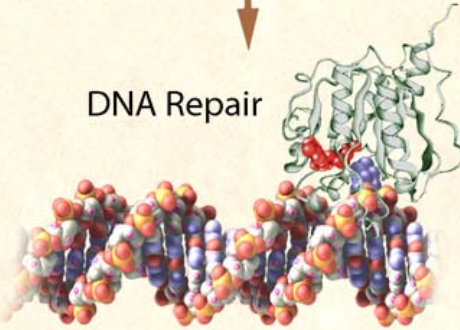
Inflammatory response



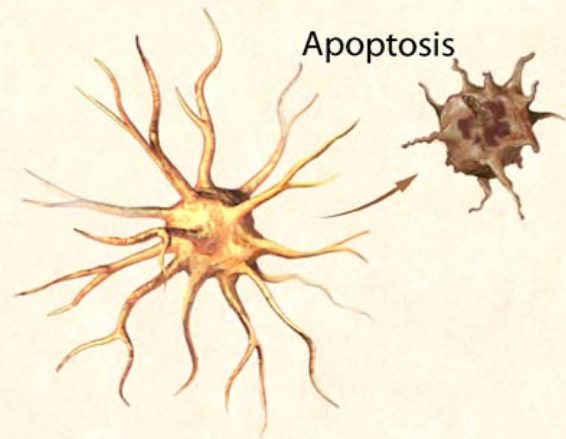
Cell differentiation



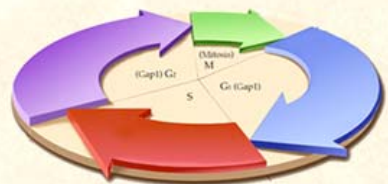
DNA Repair



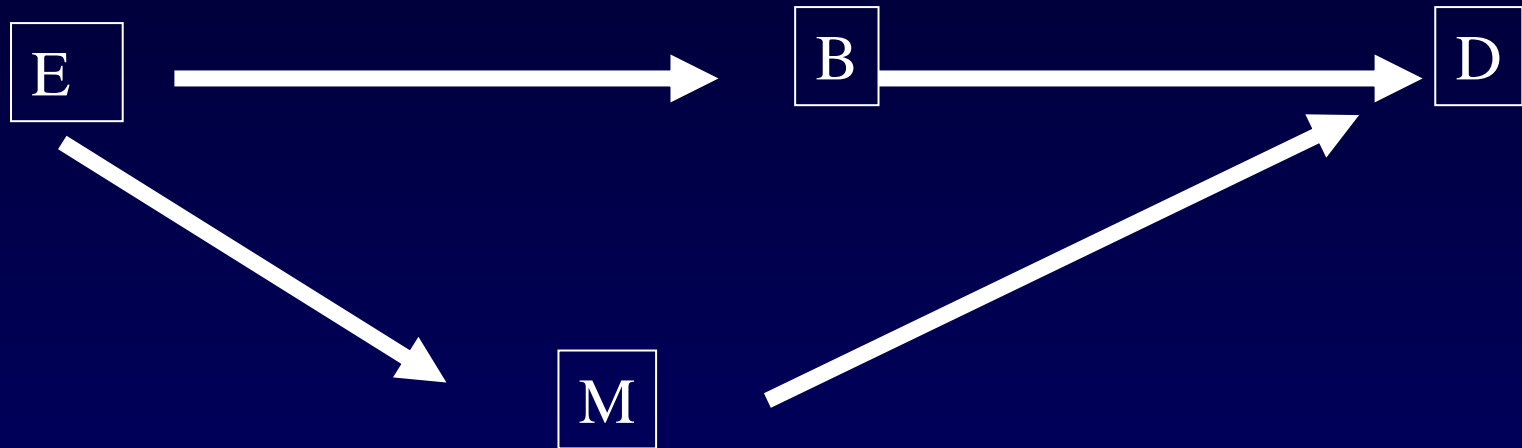
Apoptosis



Cell growth cycle



MULTIPLE PATHWAYS

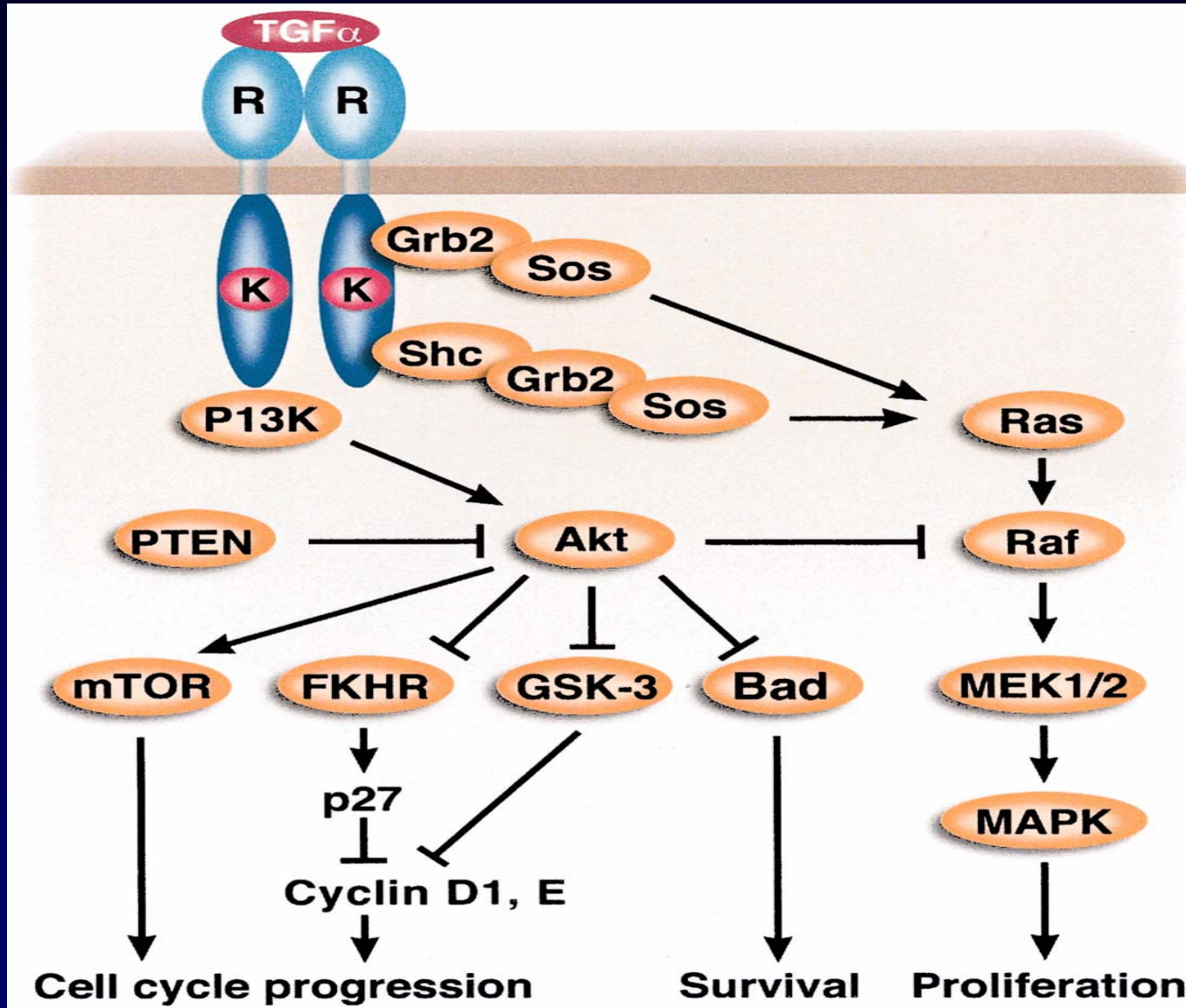


One Pathway: Attributable Proportion (AP) equals 1

Two Pathways: Attributable Proportion equals less than 1

$$AP = S (1 - 1/R)$$

MAPPING PATHWAYS AND NETWORKS





- Tomatoes
- Spinach
- Broccoli
- Garlic
- Nuts
- Salmon
- Oats
- Blueberries
- Green tea
- Red wine

Time Magazine: January 21, 2002

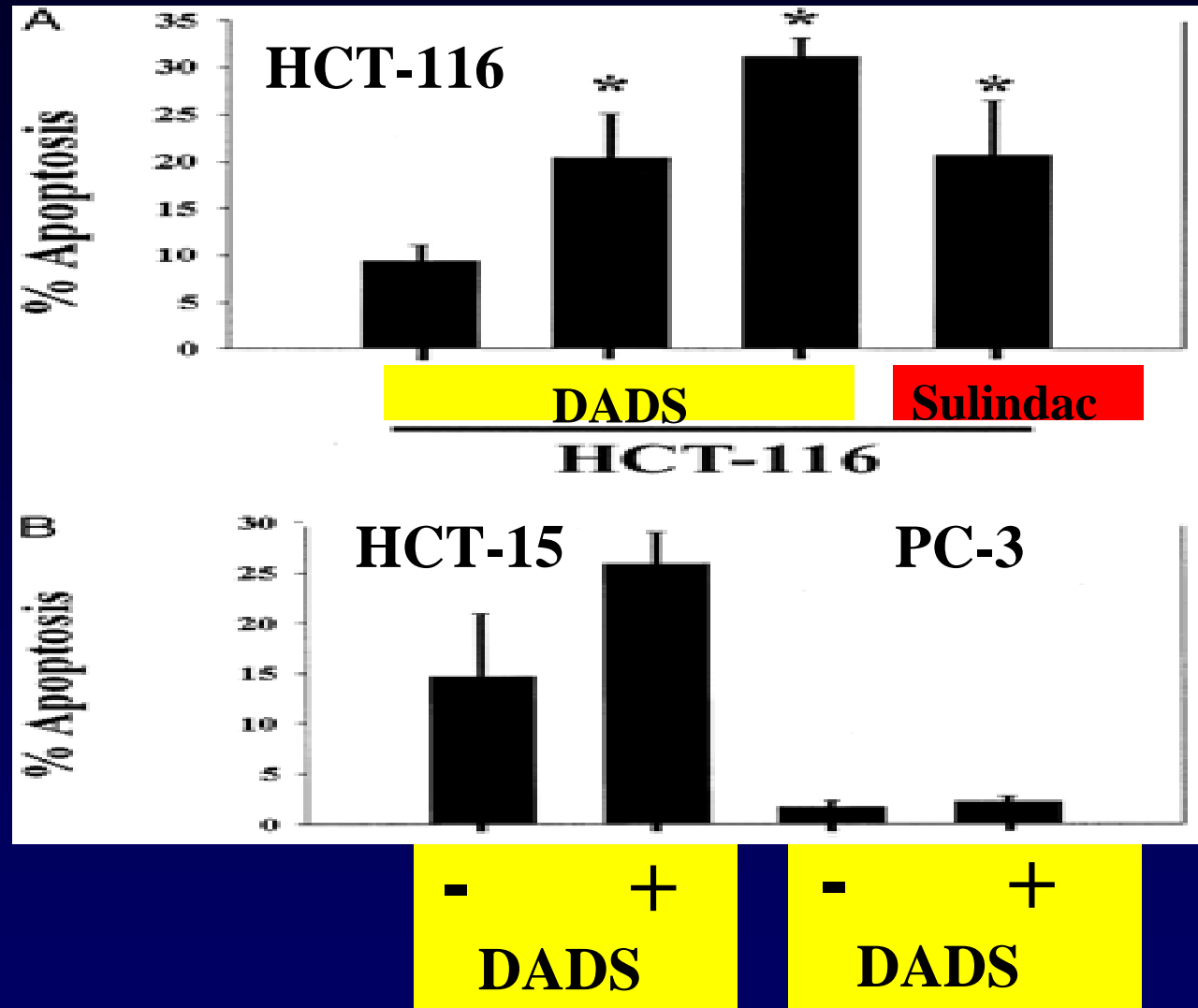
A Polymeal For Reducing Cardiovascular Disease Risk

Ingredient	Amount	Possible %Reduction
Wine	150 ml	32
Fish	114g 4X wk	14
Dark Chocolate	100g/d	21
Fruit/Veg	400g/d	21
Garlic	2.7g/d	25
Almonds	68g/d	12.5
Combined effects		76

Components are “complex mixtures” - act synergistically



“Caution: This tomato soup combined with our chicken noodle soup can form a lethal nerve gas.”

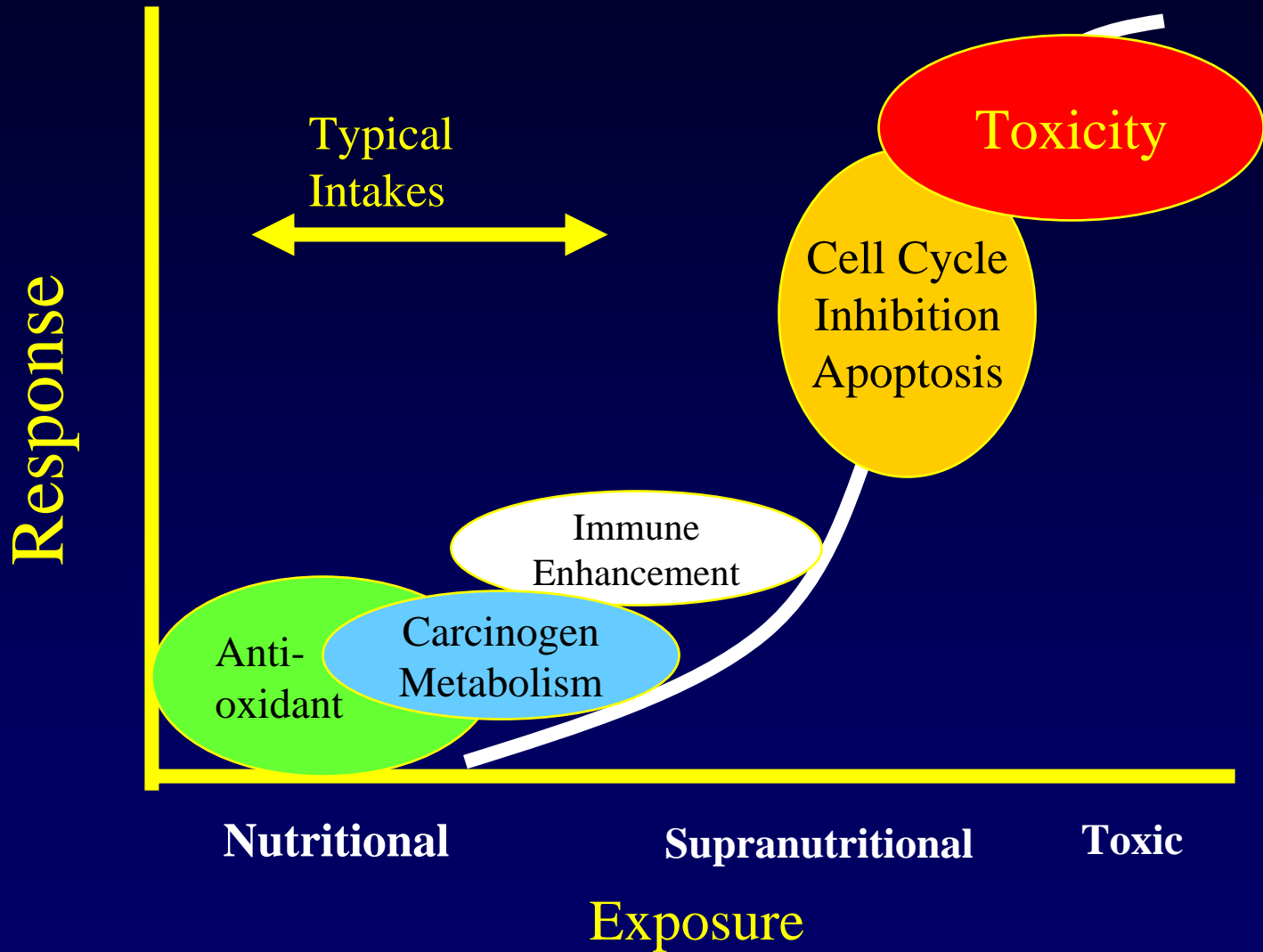


Bottone et al. (2002) J Nutr. 132(4):773-8.



**Similar to Drugs One Size Does Not Fit All for the
Effects of Diet on Cancer Prevention!**

**Identifying Responders from Non-responders to Bioactive Food
Components is the Challenge!**



Modified from Combs and Gray, *Pharmacol. Ther.* 79: 179-192, 1998.

Life Style Issues



- What are appropriate assessment at various stages in time?
- What time is most relevant?
- How does diet interact with other lifestyle factors including exercise?

No Perfect Diet Exists That is:

-Desired by everyone

-Ideal for everyone healthwise

Nutritional Preemption

(A Strategy for Health Promotion)

Concept that bioactive food components can be introduced at points of initiation & progression for pathway leading to an unhealthy or lethal phenotype

**When I knew all of life's answers,
they changed all the questions!**



Success Will Rest With the ability to:

- Identify and validate nutrigenetic, nutritional epigenetic & transcriptomic, proteomic and metabolomic biomarkers of effect and susceptibility**
- Communicate effectively its values to the health care community and consumers**
- Ensure a responsible bioethical framework**