



*Using an Integrated Systems Approach
to Personalize Medicine*

Joe Veltmann PhD FAAIM DCCN
Institute for Individualized Medicine
GENESIS Center for Integrative Medicine
2713 Nublado Court
Santa Fe, NM 87505

Course Objectives IHS 481

- Introduction to human and ecological systems response and recovery mechanisms from natural or anthropogenic stressors;
- in-depth exploration of physical, chemical and biological environmental stresses affecting human health;
- methods to assess risks to human health and to ecological receptors;
- detailed application of alternate methods for recognizing environmental stressors, and
- applications of recovery mechanisms for sustainable human health and ecosystem sustainability.

Outcomes

- Familiar with array of **complementary healthcare techniques** specifically those addressing **environmental toxins/allergens**.
- Knowledgeable of research and literature regarding **Integrative Healthcare**.
- Gain **marketable skills in Integrative Healthcare**
- Use **evidence-based critical thinking skills** to navigate the field of **integrative healthcare**.



Integrative Healthcare

Bridge between Western biological knowledge and those forms of healing that incorporate the mental, emotional and spiritual capacities of humans to heal.

Wisneski and Anderson. 2005

The Scientific Basis of Integrative Medicine. CRC Press

Five Evidenced-based Healing Therapies for Integrative Healthcare

- Mechanical Energy
 - Chiropractic, Cranial-sacral, Osteopathic
- Chemical Energy
 - Nutrients, Herbs, Phytochemicals
- Psychological Healing
 - Talk Therapy, Experiential, Art, Music, Horses
- Electromagnetic Energy
 - TENS, Pulsed Electromagnetic stimulation
- Energetic Healing

Integrative Healthcare versus Conventional Healthcare

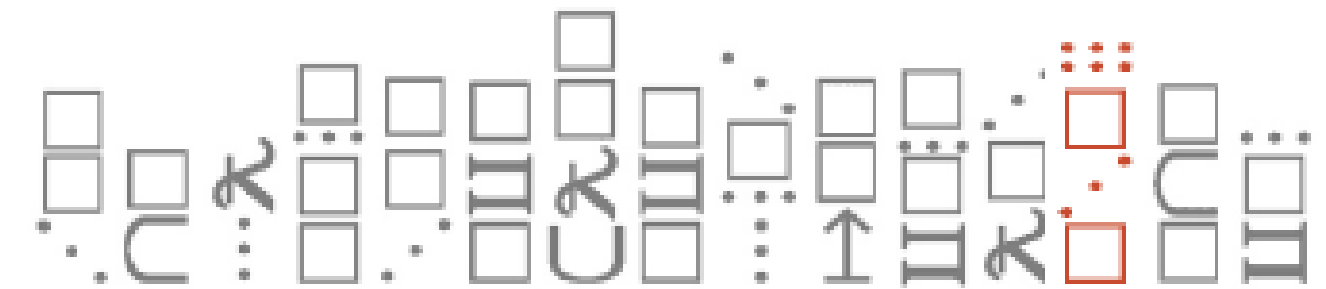
- Focus on the person versus the disease
- Preventive Strategies versus “reactive medicine”
- Patient centered
 - Communication tools
 - Listening skills
- Chronic disease as a multi-factorial condition versus one organism, one disease, one molecule to “kill or “treat” it and one method of the “proof of efficacy.”

Goals of Integrative Healthcare Practitioner

- Personalize, customize and individualize healing modalities, therapies and treatments based on the phenotypic and genotypic uniqueness of a particular patient.

Assessment of Genotype

- Intake Form
 - Family Disease History
 - Signs and Symptoms
- Blood Data correlated to S/S or Family History
- Complaints about a therapy, medication side effects or lack of response to botanical, drug or therapy.



GENESIS

M A T R I X

GENESIS Matrix

Variable	Genes	Environment	Nutrition	Emotions	Stress	Inflammation	Spirituality
GI Tract							
Allergies							
Endo- crine							
Cardio- Vascular							
Bones							
Brain &CNS							
Mood							
Glucose Balance							

Interactions Between and Among GENESIS Matrix Variables-Bone Health

Variable	Genes	Environment	Nutrition	Emotions	Stress	Inflammation	Spirituality
Bone Health	????	Amount and Type of Exercise	Calcium Mg Vit D Hydroxy appatite	????	???	????	???

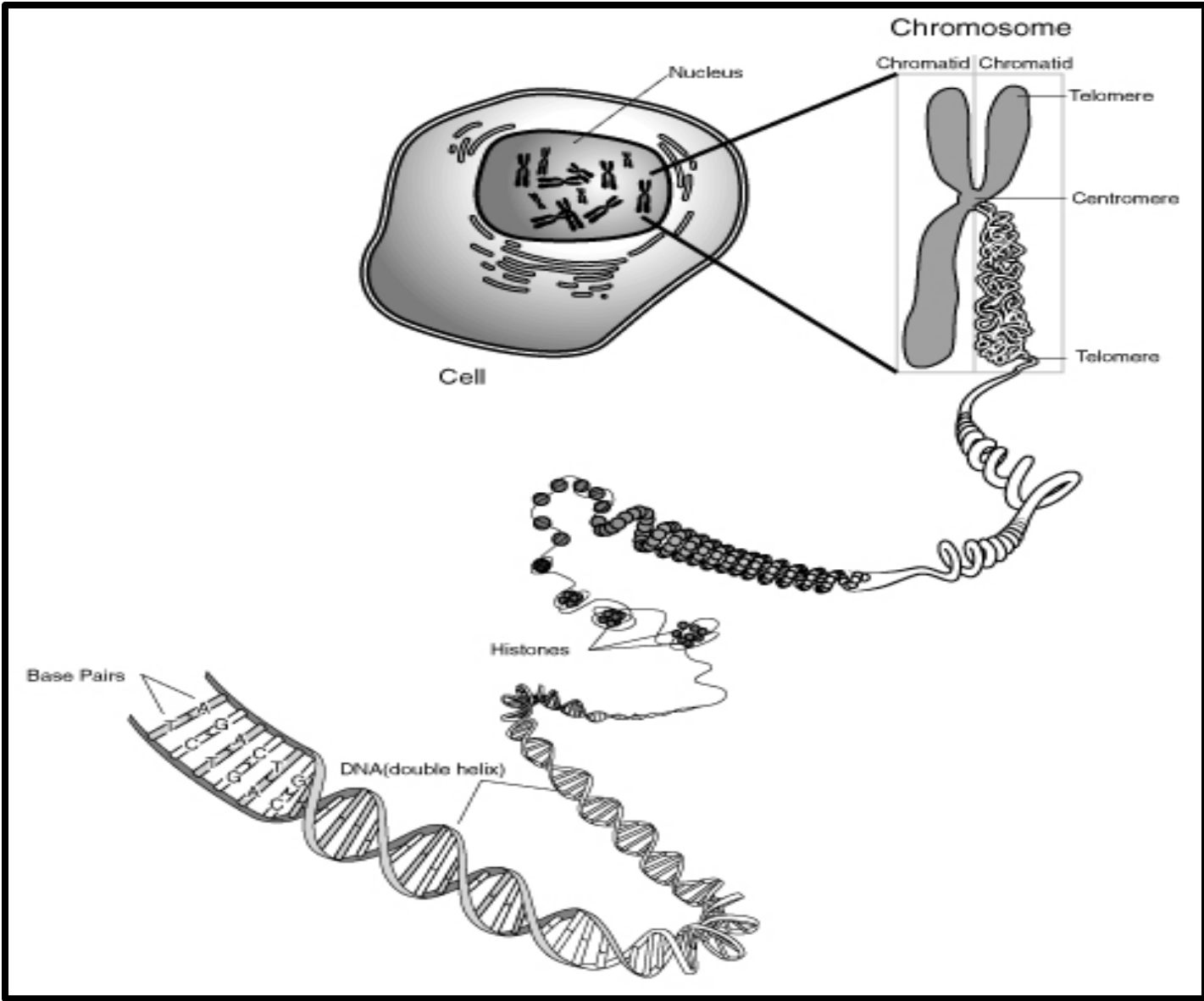
Human Genome Project

- Completed in 2003
- Identified between 30,000 and 40,000 genes
- Revealed the sequence of over 3.5 billion chemical base pairs (nucleotides) that make up human DNA

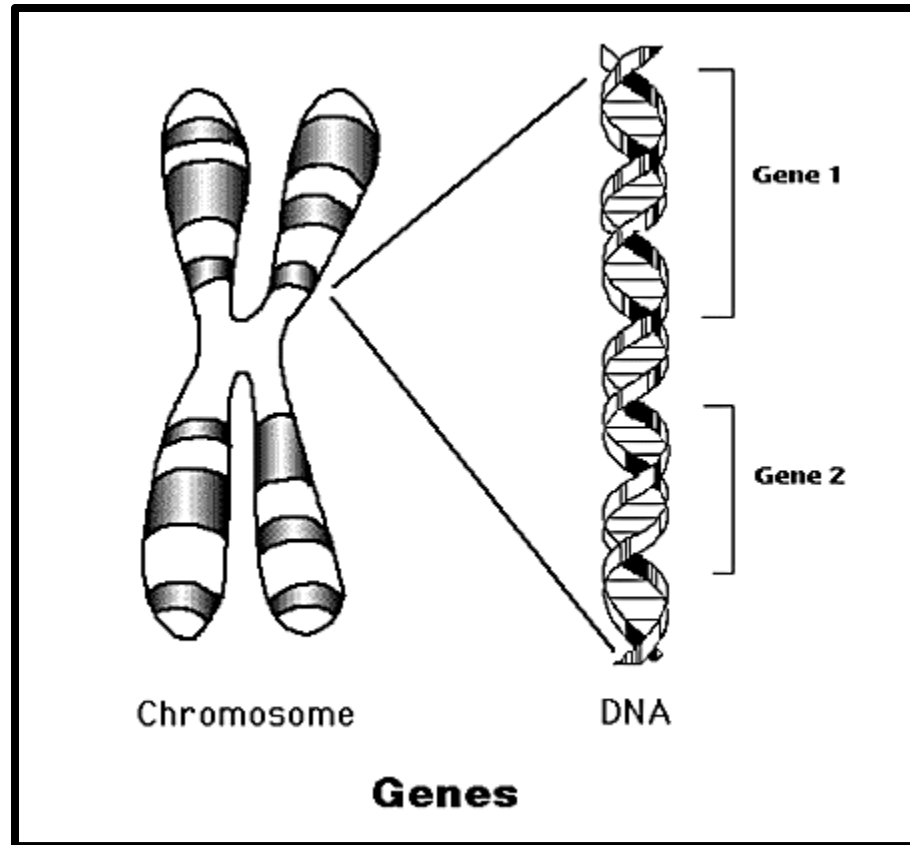
Autobiography of a Species

- The Human Genome is a book:
- Within this book, there are 23 chapters which we can call **CHROMOSOMES**;
- Each chapter (chromosome) contains several stories called **GENES**;
- Each story contains paragraphs or **EXONS**
- Words within each paragraph are called **CODONS**
- Words making up each paragraph are written in four letters (A, C, G, T)
- These four letters code for every protein and enzyme made by the body

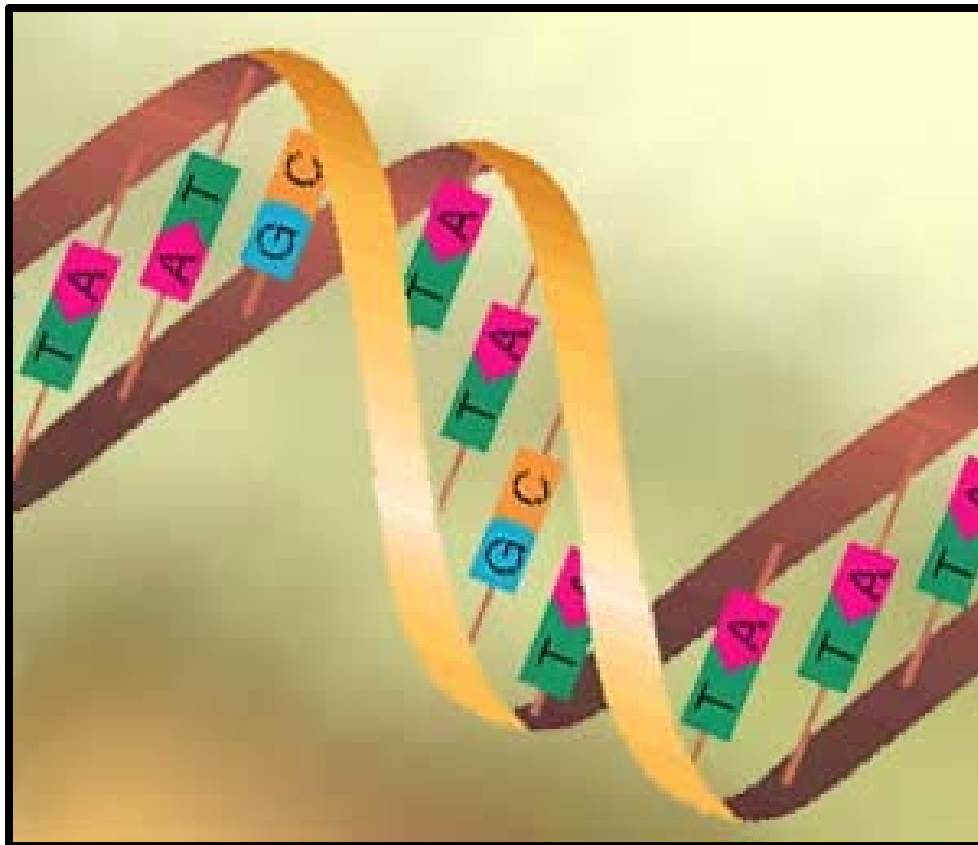
Matt Riley 2000. Autobiography of a Species in 23 Chapters



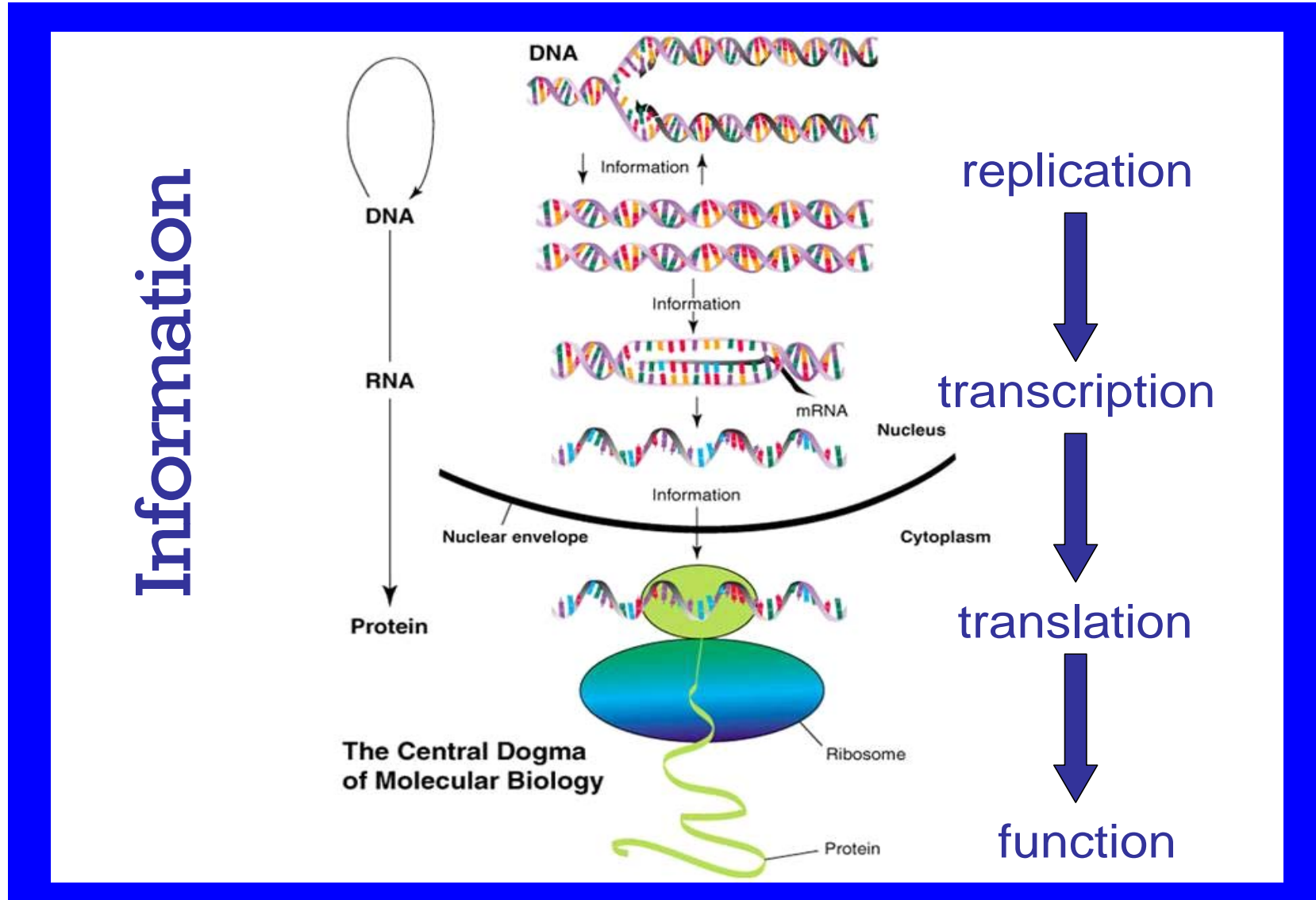
Relationship between Chromosome and Genes



Double Helix of DNA

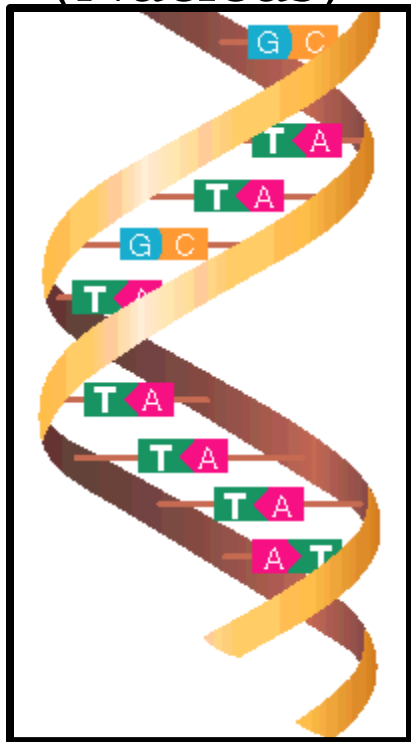


DNA Replication and Protein Synthesis

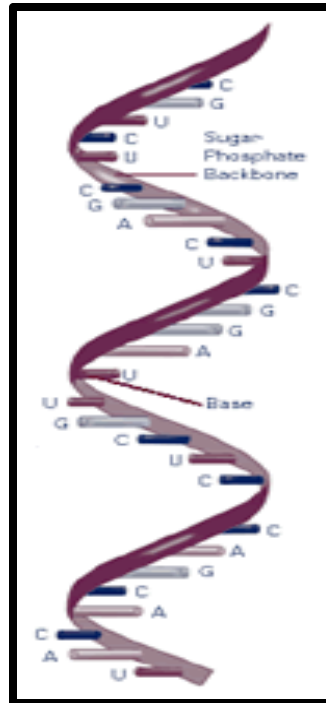


Genomics, Proteomics and Metabolomics

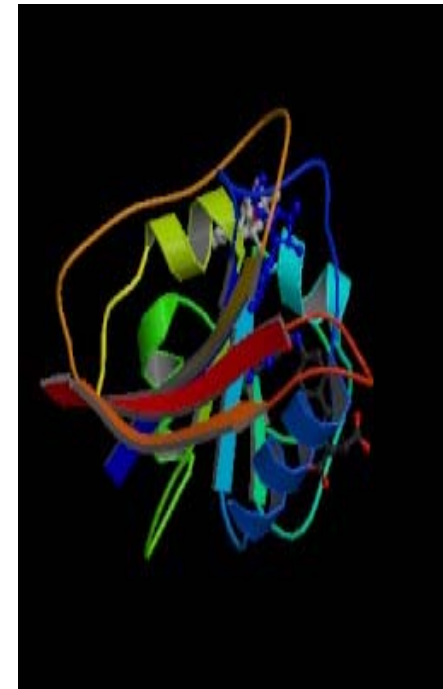
Genomics
(Nucleus)



Proteomics
(Cytoplasm)



Metabolomics
(Cell Function)



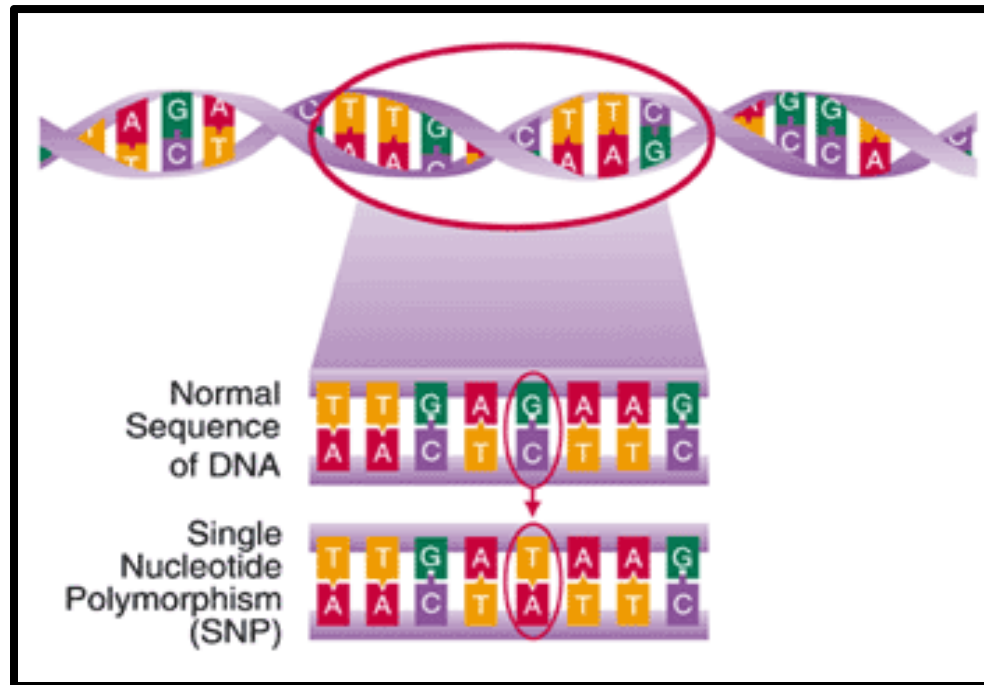
Mendelian Genetics

- Dominant versus Recessive
- Heterozygous versus Homozygous
- Allele versus Crossover
 - Leads to medical determinism
 - One bad gene leads to a disease
 - A genetic mutation confers a inborn error of metabolism

Single Nucleotide Polymorphism (SNP)

- Slight variations in an individual's genetic code associated with nucleotides, which has the potential to create a disease outcome.
- More than 30,000 genes but 2 million SNPs

Example of SNP



DNA Sequence Variation in a Gene Can Change the Protein Produced by the Genetic Code

Gene A from Person 1



Protein Products



Gene A from Person 2

Codon change made no difference in amino acid sequence



Gene A from Person 3

Codon change resulted in a different amino acid at position 2



OR



Predetermine vs Predispose

- Old paradigm: genes predetermine whether you get a disease.
 - Cystic fibrosis, Huntington's Disease, sickle cell anemia, or Tay Sachs.
- New paradigm: genes predispose an individual to a disease.

SNPs and Disease

- The vast majority of SNPs have the potential to cause health problems if exposed to the wrong mix of environmental, nutritional, and lifestyle choices over time.
- Especially true for chronic disease associated with aging
 - Heart disease
 - Osteoporosis
 - Cancer
 - Arthritis
 - Dementia
 - Alzheimer's

Functional Genomics

- Identify SNPs that exist in a person's genome before the advent of a chronic disease
 - Potentially decreases the risk of chronic disease
 - Empowers patient to take personal responsibility
 - Eliminates the “guess work” by health care professional about diet, supplements, lifestyle recommendations
 - Affirms Biochemical Individuality

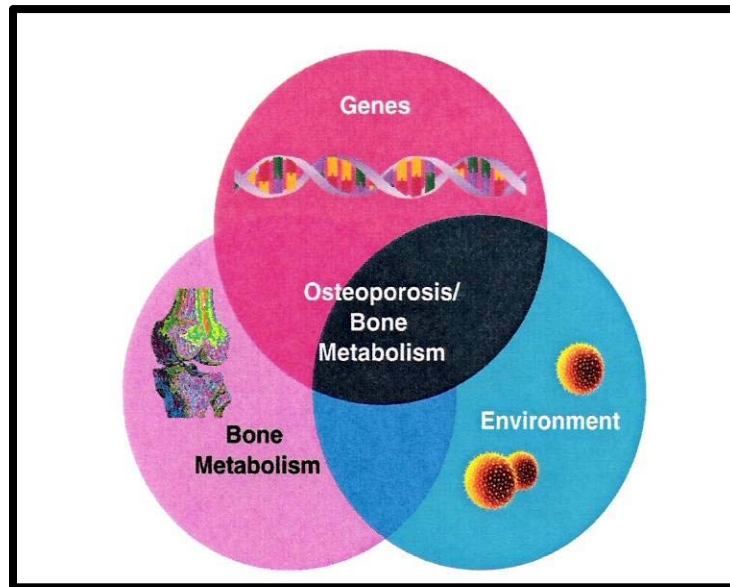
Potential for Clinical Benefit

- Pxs with a known family history of disease
- Challenging cases
- Adopted children
- Exposed to environmental toxins
- Personalize diet, nutritional supplements and/ or herbs and lifestyle to match DNA profile
 - Take the guess work out of supplements and herbs
- Drug-drug or drug-herb interactions
- Customize a disease prevention and/or treatment program unique as your DNA

Key Points about Human Diseases

- All human diseases occur from the interaction between a genetic predisposition and modifiable environmental, nutritional and/or lifestyle factors.
- Slight variations in DNA called SNPs are associated with almost all chronic diseases.

OsteoGenomic Overview



OsteoGenomic Platform






- Bone Formation

- COL1A1
- CALCR
- VDR

- Bone Resorption

- IL-6
- TNF-alpha

OsteoGenomic Results

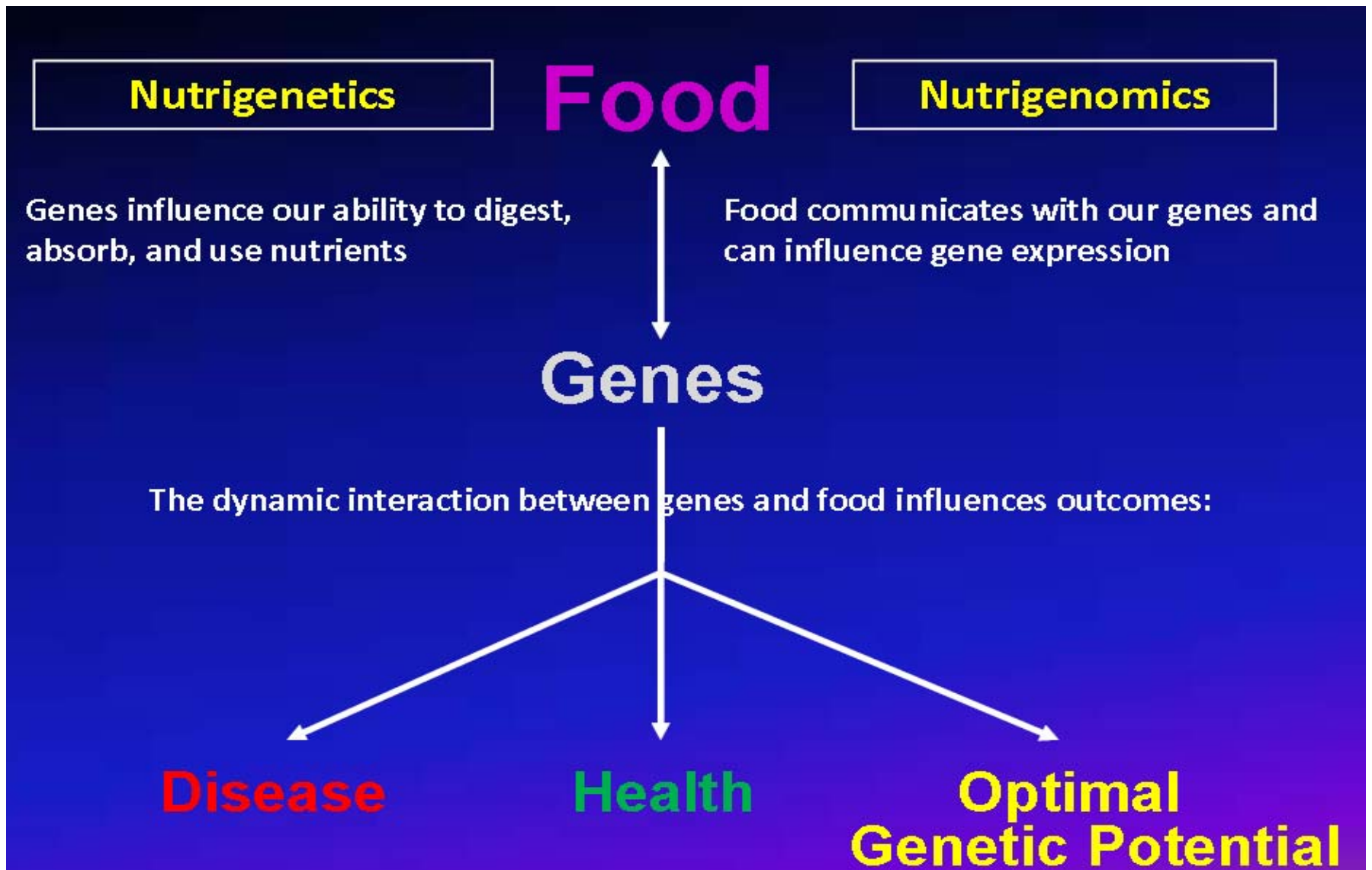
<i>Bone Markers</i>	
Bone Formation	
COL1A1	
CALCR	
VDR	
<hr/>	
Bone Resorption/Inflammation	
IL-6	
TNF-α	

Nutrigenomic Intervention: Bone Health

Variable	Genes	Environment	Nutrition	Emotions	Stress	Inflammation	Spirituality
Bone Health	COL1A1 CALCR IL-6	Amount and Type of Exercise	Calcium Mg Vit D Hydroxy- apatite Fish oils	Yes	Yes	Yes	Yes

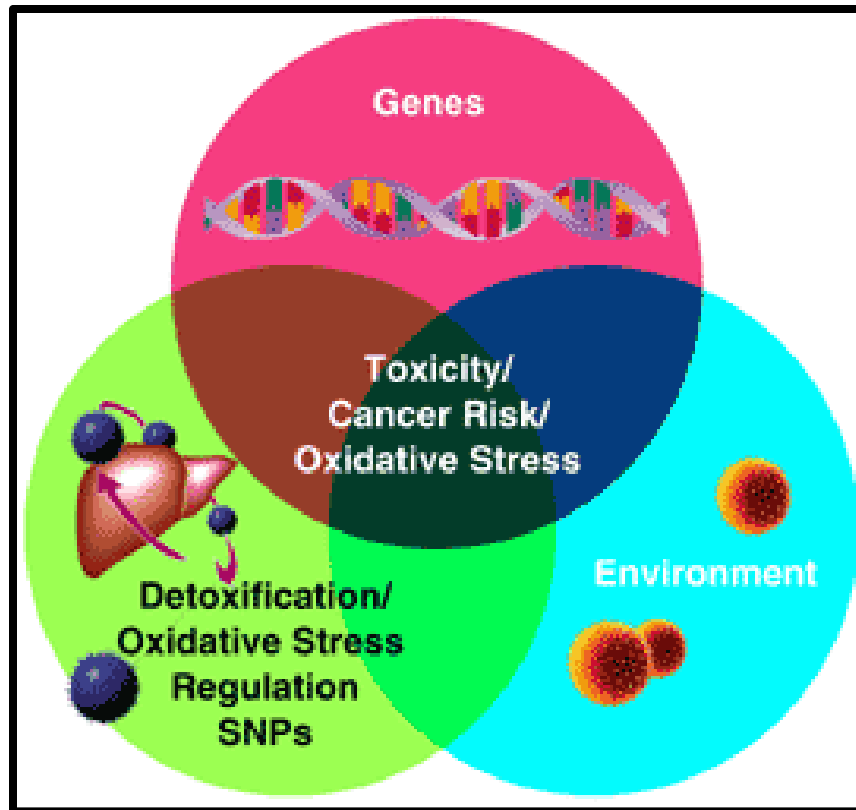
Nutrigenomics

- Nutrigenomics is the understanding that micronutrients and macronutrients can be potent dietary signals that influence the metabolic programming of cells and have an important role in the control of homeostasis
 - Muller and Kersten, Nutrigenomics goals and strategies, Nature Review 4: 315-322 (2003)



From Ruth DeBusk, Nutritional Genomics for the Clinical Dietitian, Tallahassee, FL

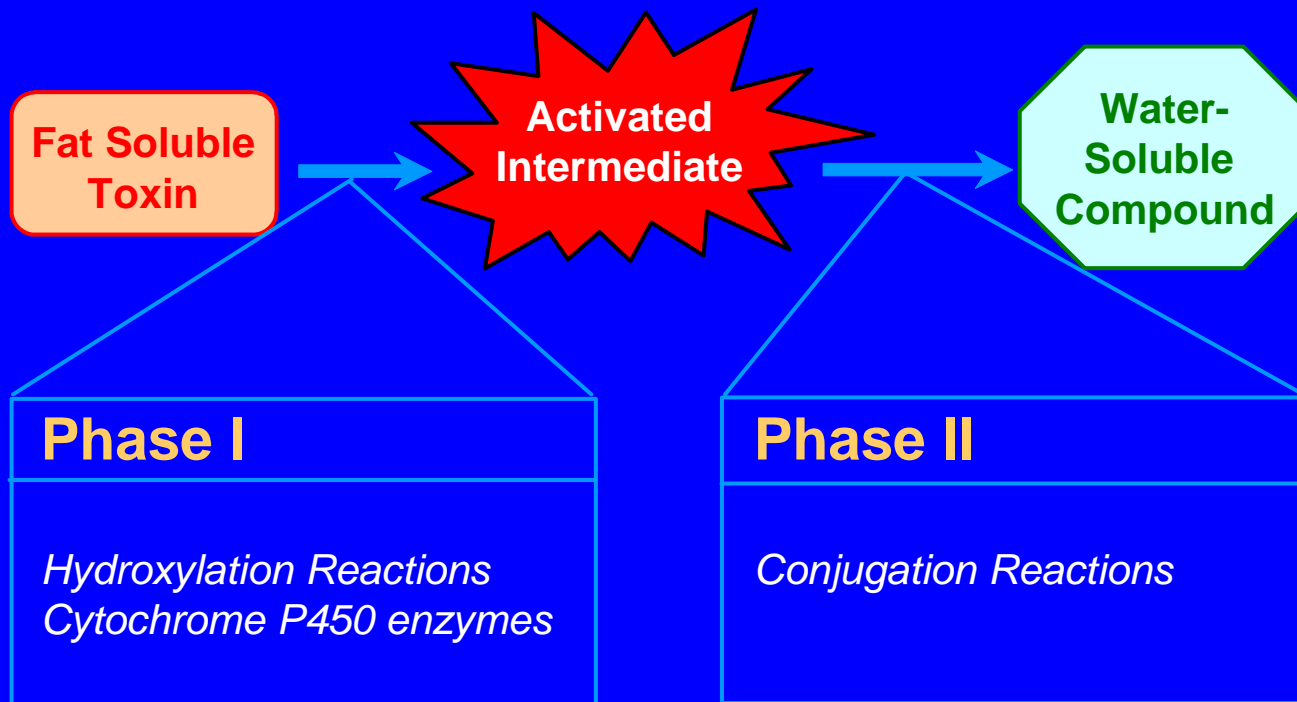
Detoxification Genomic Overview



Xenobiotics

- Chemical compounds foreign to the body
 - Natural food products
 - Drugs
 - Food Additives
 - Supplements
 - Pesticides, solvents, plastics, industrial products and by-products

Two Major Pathways of Hepatic Detoxification



Detoxification Genomic Panel Phase I

Cytochrome P₄₅₀ Enzymes



CYP 1A1 *

CYP 1B1 *

CYP 2A6

CYP 2C9 *

CYP 2C19 *

CYP 2D6

CYP2E1

CYP₃A₄ *

Detoxification Genomic Panel Phase II



Methylation
COMT

Acetylation
NAT₁, NAT₂

Glutathione S-transferase
GSTM₁
GSTP₁
GSTT₁

Superoxide dismutase
SOD (extracellular)
SOD (mitochondrial)

Biotransformation Differences

- Genetic Polymorphisms (Phase 1 and Phase 2)
- Nutrient Deficiencies (Mg, Se, vitamin B-6)
- High sugar, low protein diet
- Stress, emotional stuffing, trauma
- Heavy metal exposure (Hg, Cd, Pb)
- Environmental exposure to toxins (Uranium, Radon)
- Pharmaceutical drugs, OTC medications, herbs

GST Polymorphism

<i>Glutathione Conjugation (Glutathione s-transferase)</i>				
Result	Gene	Location	Internet Information	Affects
NULL	GSTM1	1p13.3	www.genovations.com/gdgstm1	Liver/Kidney
--	GSTP1	I104V	www.genovations.com/gdgstp1	Brain/Skin
--	GSTP1	A113V	www.genovations.com/gda113v	Brain/Skin

GSTP1 Polymorphism

- Higher rates of:
 - Testicular cancer
 - Oral cancer
 - Pharyngeal cancer
 - Bladder cancer

Dietary Modulators of Detoxification

- Cruciferous vegetables
- Epigallocatechingallate (EGCG)
- Isoflavones
- Ellagic Acid
- Antioxidants Associated with the Antioxidant Cascade
 - NAC
 - Vitamin A, Carotenoids
 - Vitamin C
 - Vitamin E
 - Selenium
 - Glutathione

Pharmacogenomics

- The study of genetic variability and its relationship to an individual's response to pharmaceutical drugs, non-prescription drugs and OTC medications.
 - Goal: use the right drug for the right person at the right time.

Pharmacogenomics and Adverse Drug Reactions (ADRs)

- Less than 50 % of patients experience the intended benefit of most drugs, despite taking them as directed.
- Most drugs have side-effects

ADRs in 2004

FDA drug complaints surge: report

A reported rise in complaints coincides with increased use of prescription drugs.

March 14, 2005: 9:27 AM EST

NEW YORK (CNN/Money) - Complaints to the Food and Drug Administration regarding drug side effects and other related health problems reached an all-time high in 2004, according to a published report.

The federal agency received about 422,500 adverse-event reports from pharmaceutical companies, health professionals and patients, up nearly 14 percent from the 370,887 reports filed in 2003, reported *USA Today*. A final 2004 total is expected later this year, but FDA officials don't expect it to vary significantly from the estimate.

The 2004 increase occurred during a year that saw rising questions about prescription drug safety. However, a top FDA official said the rise reflects a surge in prescription drug use, not an increase in health risk.

Genetic SNPs and Drug Dosage

Getting Exactly What You Need

A gene variant can influence tolerance for a drug commonly used to treat acute lymphoblastic leukemia in children:

90

percent of kids have two normal copies of the gene and can tolerate a full dose of mercaptopurine

10

percent have only one normal copy of the gene and should receive only 50 percent of the standard dose

.03

percent have two defective copies and should receive just 5 to 10 percent of a normal dose

Newsweek Summer 2005

Genes and Depression

Mind Matters

Researchers are now decoding depression at the molecular level. Some new tools:

G1463A

A variation at this point in your DNA sequence causes low levels of serotonin, making you less responsive to drugs like Prozac.

The Stress Gene

People with a particular mutation in the serotonin transporter gene are more likely to become depressed in response to stress.

Beta-Arrestin-1

Depressed patients have unusually low levels of this protein. Measuring it may enable doctors to monitor the effects of treatment.



The government may soon approve a treatment intended specifically for blacks. Would that be progress, or a setback? BY JENNIFER BARRETT

A Race-Based Heart Remedy

Medicine Tailored Just for You

Genetic tests will tell you which lifestyle changes are crucial for you, and which drugs might work best for your disease—with the fewest side effects.

BY ANNE UNDERWOOD
AND KAREN SPRINGEN

Nutrient-Gene Interaction: Breast Cancer Risk

Prospective study of grapefruit intake and risk of breast cancer in postmenopausal women: the Multiethnic Cohort Study

KR Monroe^{*,1}, SP Murphy², LN Kolonel² and MC Pike¹

¹Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089-9175, USA; ²Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI 96813, USA

Grapefruit intake was significantly associated with increased risk of breast cancer (RR= 1.30) for post menopausal women consuming $\frac{1}{4}$ grapefruit or more per day compared to controls whether they were on HRT or not. **NET RESULT:** FDA mandated labeling of menopausal HT products that grapefruit juice may increase plasma concentration of estrogens. *Cancer Res.* (2007) 97:440-445.

Naringenin: CYP 3A4 Inhibitor

- Naringenin found in grapefruit inhibits the enzyme activity of CYP 3A4.
 - CYP 3A4 converts estrone to 16 α -OH estrone
 - Inhibiting CYP 3A4 pathway increases plasma estrogen concentrations;
 - Breast cancer risk expected to increase if a woman has SNP at CYP1A1 and/or CYP1B1 because of unwanted estrogen metabolites
 - (Monroe et al. 2007 Nutr. Cancer 58: 1-10.)

Physical & Psychological Concerns of Breast and Prostate Cancer Patients

- Likelihood of recurrence
- Co-morbidities
- Toxicities associated with chemotherapy
- Fear, Anxiety, Anger, Depression, Sadness, Hurt, Resentment, Hostility
 - Will I see my son/daughter graduate from college?
 - Will I live long enough to be a grandmother?
 - Can the chemo and/or radiation kill me?

Pharmaceutical Drugs in Breast Cancer and their Detoxification Pathways

<u>Drug</u>	<u>Phase I</u>	<u>Phase II</u>
Cytoxan	3A4, 2C19	
Doxorubicin	3A4	
Myleran		Glutathione
Taxol	3A4	
Zofran	3A4, 2D6, 1A1	Glucuronidation
Tamoxifen	2D6	
Arimidex		Glucuronidation

Tamoxifen and CYP2D6 SNPs

- Tamoxifen's bio-conversion to endoxifen is handled by CYP2D6 enzyme
- Women with CYP2D6 genetic SNP have lower concentrations of endoxifen:
 - Heterozygous 2 x less than wild type
 - Homozygous 4 x less than wild type
 - Clinical implications ? Breast cancer patients taking Tamoxifen survived longer if they had wild type CYP2D6 genotype.

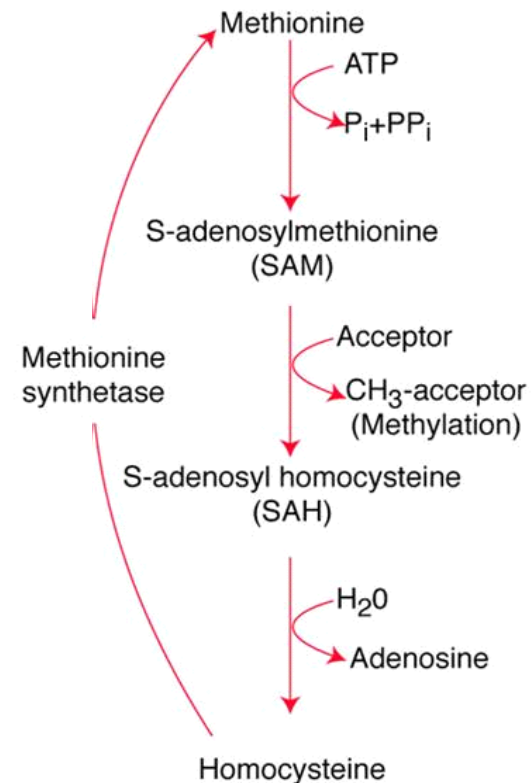
Jin, Y., et al., 2005. J. Natl. Cancer Institute. 97 (1); 30-39

Methylenetetrahydrofolate Reductase

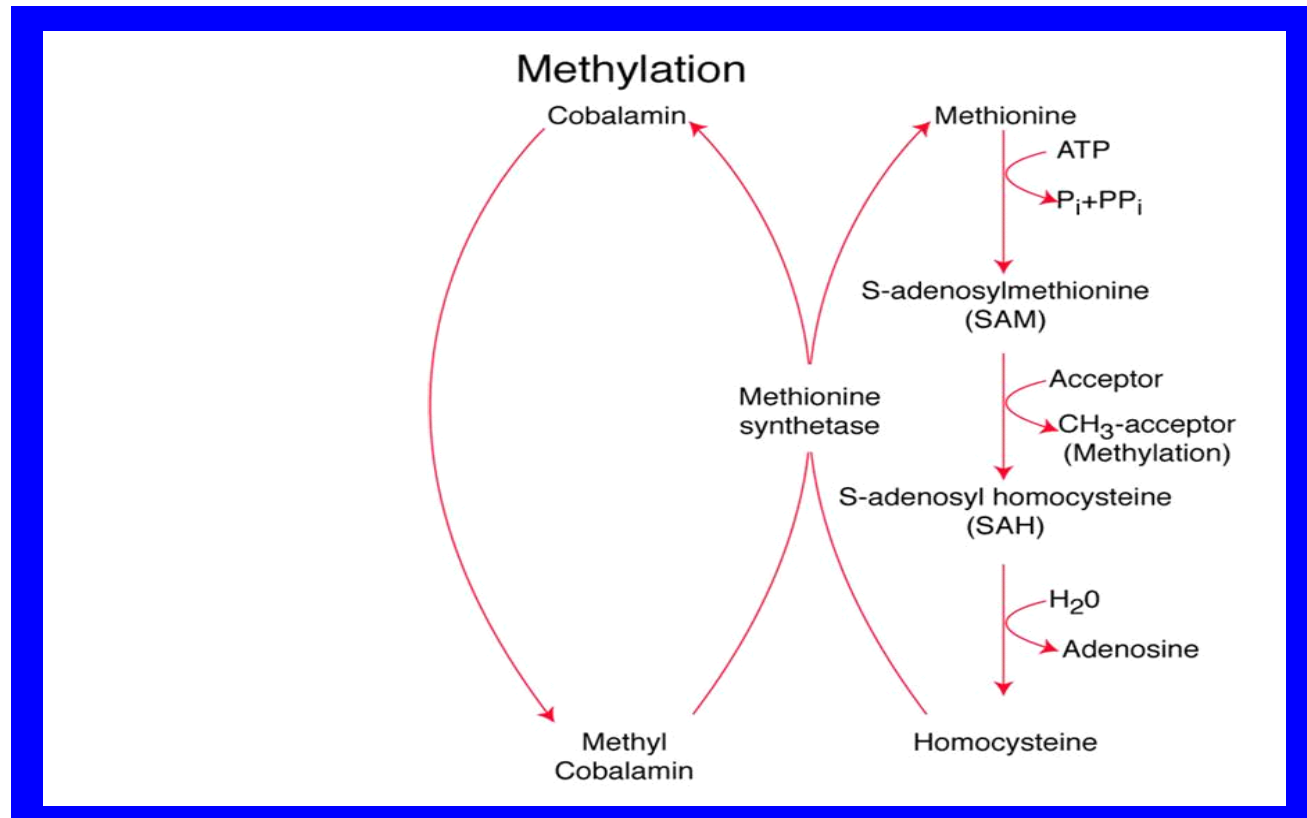
- Critical enzyme under genetic control in folate metabolism
 - SNPs lead to elevated homocysteine levels and defective methylation capacity
 - Atherosclerosis
 - Stroke
 - Cervical Dysplasia
 - Cognitive Impairment
 - Senility
- Coronary Heart Disease
Deep Vein Thrombosis
Cervical Cancer
ALZ Disease
Neural Tube Defect

Methylation (Step 1)

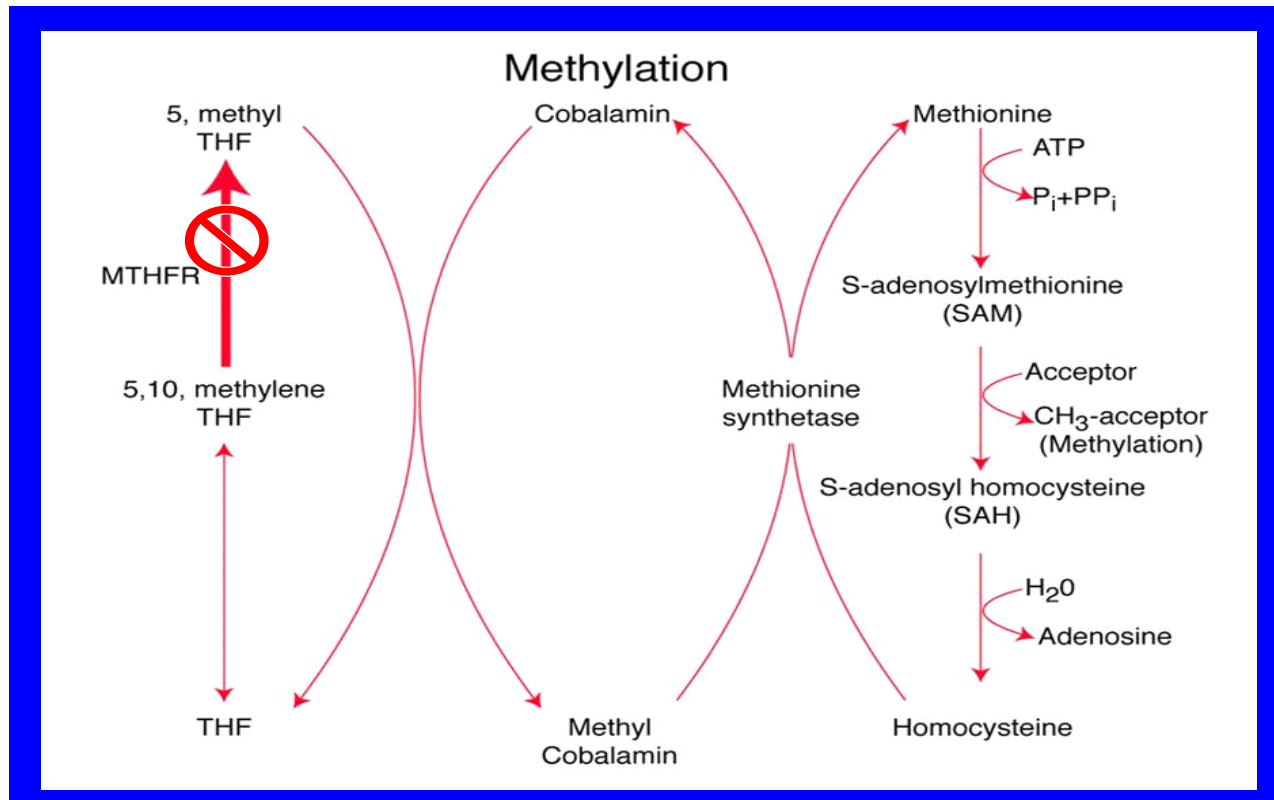
Methylation



Methylation (Step 2)



Methylation (Step 3)

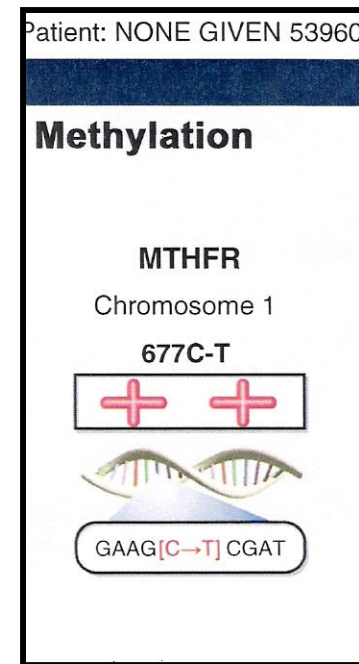


Prevalence of MTHFR 677C-T Single Nucleotide Polymorphism

- Approximately 50 % of all Caucasians and Asians are heterozygous for the 677C-T
- Approximately 12 % are homozygous with severely impaired methylation capacity
- Approximately 28 % of patients with elevated homocysteine levels and 677C-T SNP did not respond to folic acid, B-6 and B-12 supplementation
 - Am. J. Human Genetics 56: 142-150 (1995)

Nutrigenomic Intervention for MTHFR SNP

- Folic Acid
- 5-methyl and 5-formyl THF
- Betaine/ Trimethylglycine
- Methylcobalamin (B-12)
- Pyridoxal-5-phosphate
- Riboflavin (B-2)



Welcome to Personalized Medicine



Personalized medicine is redefining the health industry and disrupting existing business models.

PriceWaterhouseCoopers' Health Research Institute.