

The GENE Model

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Objectives

- Explore how the GENE model delivers individualized and personalized medicine within a benefit plan design;
- Illustrate through case histories how the GENE model was used with a diverse population of men, women and children;
- Demonstrate cost savings to the members and Plan using functional genomic testing.

Traditional Wellness Program

Predict what pre-disease risk burden and lifestyle factors exist within a distinct population (gender, age group)

Software calculates frequency and severity of pre-disease risk before and after exercise, nutrition, and/or lifestyle intervention(s)

Reduction of health plan costs by 10 %

- Pre-disease risk patterns (family history) are based genetic variants that are inherited, which only account for 5 to 10 % of the incidence of chronic diseases.

AMO Medical Plan: Overview

- 4,000 Members 12,000 covered lives
- Budget: 35 million dollars per annum
- Demographics:
 - Mean age 48 (male)
 - Licensed and trained Captains and Engineers
- Location: International
- **Unique Differences**

Self-insured fund, self-administered, medical benefits designed around industry; comprehensive in-house case management

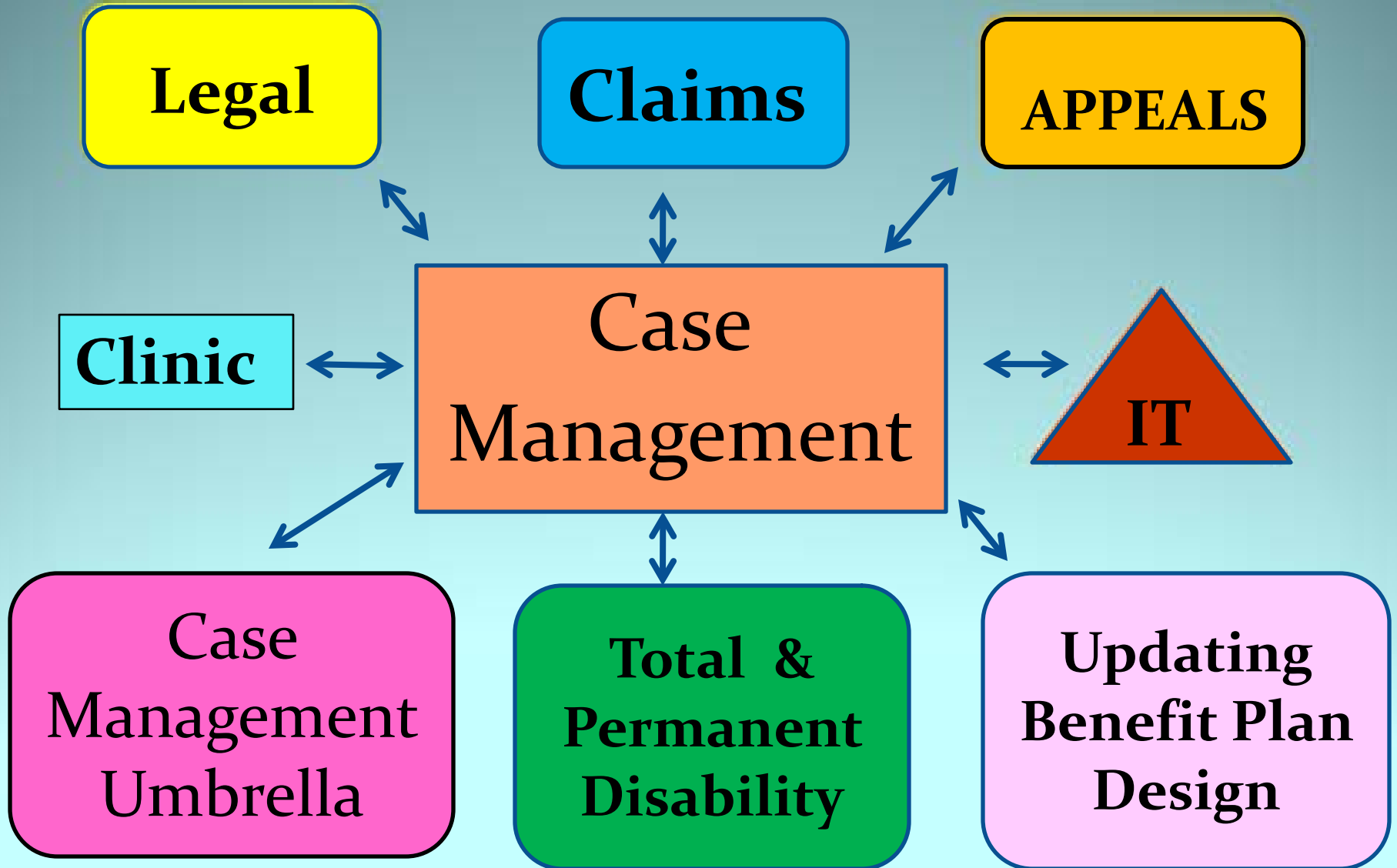
AMO: Custom Benefit Design

- Group funded plan: employers pay per man day
- “Cadillac” Benefits until 2000; industry standards applied
- New Plan Design implemented in 2004 cuts \$\$\$
 - Negotiated medicals costs for out-of-network providers
 - Individualized and Personalized Reviews of Each Case including Claims
 - **Integrated Case Management Model**

Case Management Umbrella

- At Home Interventions
- Oxygen Therapy
- Nutritional Supplements
- Psychological Intensives
- Detoxification Colonics and Cleanses
- Fit-4-Duty 2-week Weight Reduction Program

Case Management Integration



The GENE Model: Integrative Case Management (ICM)

- Functional Genomic Testing was added in 2006 to the existing model with the intent of further reducing costs.

- Genomics
- Environment
- Nutrition
- Exercise

GENE Model



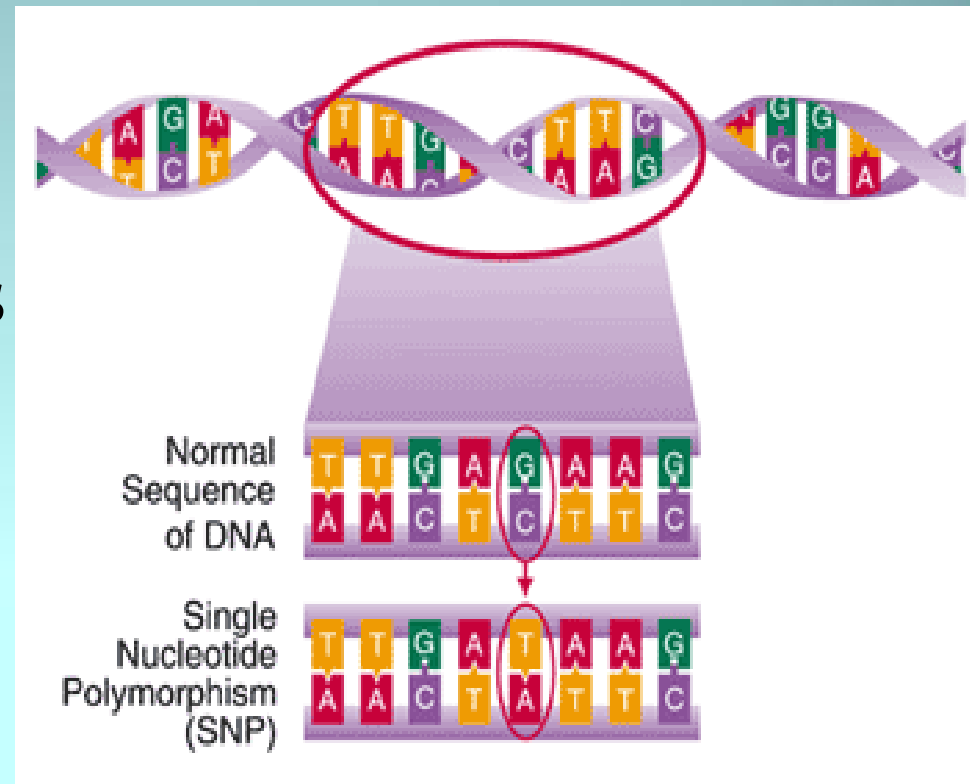
Functional Genomics Testing

- Evaluates a carefully selected group of genetic variants in a person's genome;
- Provides an unseen “glimpse” into his/her potential health future; and
- Reduces the potential risk of disease without waiting for signs or symptoms to appear

Genetic Variants: Single Nucleotide Polymorphism (SNPs)

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



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

Gene A from Person 1

GCA AGA GAT AAT TGT... Protein Products

Ala Arg Asp Asn Cys ...

1 2 3 4 5



Gene A from Person 2

Codon change made no difference in amino acid sequence

GCG AGA GAT AAT TGT...

Ala Arg Asp Asn Cys ...

1 2 3 4 5

Gene A from Person 3

Codon change resulted in a different amino acid at position 2

GCA AAA GAT AAT TGT... OR

Ala Lys Asp Asn Cys ...

1 2 3 4 5



SNPs and the Disease Process

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 diseases associated with aging:

Heart Disease

Cancer

Dementia

Osteoporosis

Arthritis

Alzheimer's

Case Histories

Osteoporosis

Prevention & Treatment

Breast Cancer

Recurrence prevention

Multiple Drugs for Migraines

Cost Benefit Analysis

Case History: Osteoporosis

- 60-year old Caucasian man
- Signs and Symptoms: Elevated PSA
 - Health History: 1983-1984 Cancer (Hodgkin's Disease); radiation therapy
 - 1990's Atrial Fibrillation
 - 1995 Elevated PSA, Enlarged Prostate, BPH
- Medications: None
- Supplements/Botanicals: Presurre-Lo (Blood Pressure)
- Functional Genomic Test:
 - OsteoGenomic

Prostate Cancer & Vitamin D receptor SNP

OPEN ACCESS Freely available online

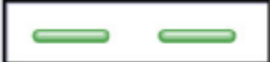




PLOS MEDICINE

A Prospective Study of Plasma Vitamin D Metabolites, Vitamin D Receptor Polymorphisms, and Prostate Cancer

Haojie Li^{1*}, Meir J. Stampfer^{1,2,3,4,5}, J. Bruce W. Hollis⁶, Lorelei A. Mucci¹, J. Michael Gaziano^{4,5}, David Hunter^{1,2,3},

Data suggest that a large proportion of US men have suboptimal Vitamin D status (especially during the winter/spring season) as measured by plasma 25(OH)D. Men with less functional VDR polymorphism are more susceptible to prostate cancer in the presence of low 25 (OH) D status. PLoS Medicine (2007) 4:562-570.

OsteoGenomic Results

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

Bone Mineral Density

Jul 2007	Mean BMD	g/cm ²	T-Score
Baseline	Neck (Femur)	0.768	-2.3
	Spine (Total)	1.021	-1.7

Nutrigenomic and Pharmacogological Intervention:

Mar 2008	Neck (Femur)	0.768	-2.3
	Spine (Total)	1.107	-1.1

Projected Savings to Plan: \$243,000.00

Case History: Osteopenia



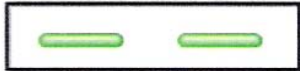


66 year old white, post menopausal woman

- Diagnosed in 2006 with osteopenia

<u>BMD</u>	<u>g/cm²</u>	<u>T score</u>
Neck (Femur)	0.735	-1.09
Spine (Total)	0.911	-1.24

- Supplements: Ca, Mg, Vitamin D
- Exercise: aerobic and weight bearing
- Medications: None

OsteoGenomic Results

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

Osteopenia Treatment

- **Nutrigenomic Interventions:**
 - **Supplements: Ca, Mg, Vitamin D, Hydroxyapatite and Sterol 117 (Beta-sitosterol); aerobic exercise; weights**
 - **3 months of Calcitonin Nasal Spray:**

BMD	g/cm ²	T score	% Change
Neck	0.903	-0.64	22
Spine	1.106	-0.79	18

Projected savings to Plan: \$5,000 per year

Case History: Breast Cancer ER +

- White, 54 year old woman
- Heavy, debilitating menstrual period (2002)
 - 3 months Provera
- Lump found in left breast (March 2007)
- Biopsy of mass in left and right breast (Sept. 2007)
- Bilateral Mastectomy + reconstruction (Nov. 2007)
- Pathology:
 - ER + tumor
 - OncotypeDx ordered

Actual Case Costs:

\$174,000

Phase 1 DetoxGenomic Profile: ER + Breast Cancer Patient

Cytochrome P-450

Result	Gene	internet information
✓	CYP1A1 *	www.genovations.com/gdgen01
●	CYP1B1 *	www.genovations.com/gdgen02
✓	CYP2A6	www.genovations.com/gdgen10
●	CYP2C9 *	www.genovations.com/gdgen05
✓	CYP2C19 *	www.genovations.com/gdgen06
✓	CYP2D6	www.genovations.com/gdgen03
✓	CYP2E1	www.genovations.com/gdgen04
✓	CYP3A4 *	www.genovations.com/gdgen07

Phase II Detoxification Profile: ER+ Breast Cancer Patient

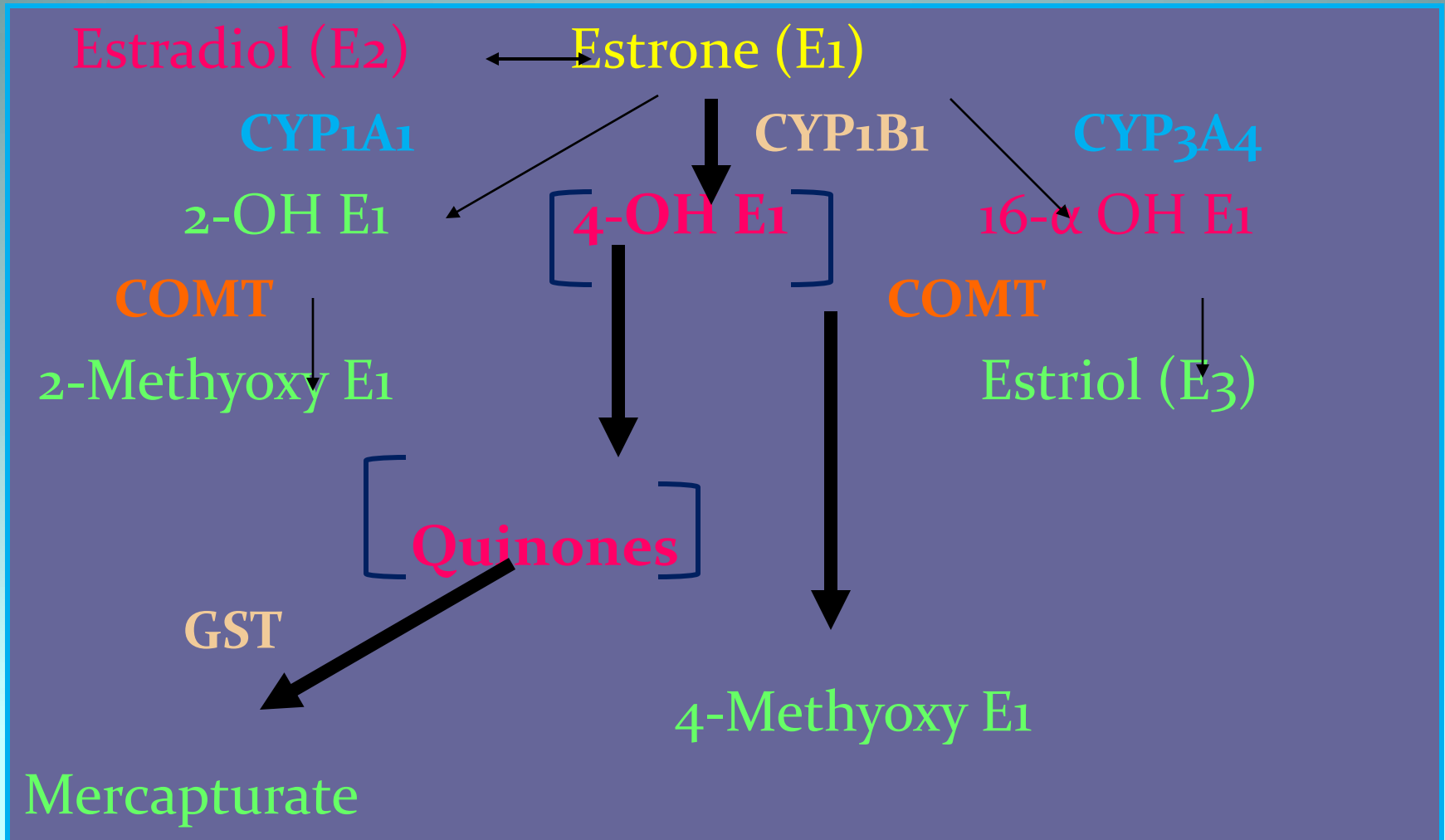
Methylation

Result	Gene	SNP Location	Internet Information	Affects
— —	COMT	V158M	www.genovations.com/gdv158m	Liver/Gut

Glutathione Conjugation (Glutathione s-transferase)

Result	Gene	Location	Internet Information	Affects
PRESENT	GSTM1	1p13.3	www.genovations.com/gdgstm1	Liver/Kidney
+ —	GSTP1	I105V	www.genovations.com/gdgstp1	Brain/Skin
— —	GSTP1	A114V	www.genovations.com/gda114v	Brain/Skin

Estrogen Metabolism: Breast Cancer ER + (Phase I and II Detoxification Enzymes)



Estradiol and Estrogen Metabolites (Urine): ER+ Breast Cancer Patient Prior to Nutrigenomic Intervention

Estrone (24hr urine)	2.87
Estradiol (24hr urine)	<dl
Estriol (24hr urine)	<dl

2-Hydroxyestrone (24hr urine)	1.15	0.26-13.68 mcg/24 hr
2-Methoxyestrone (24hr urine)	2.12	0.34-9.03 mcg/24 hr
16 α -Hydroxyestrone (24hr urine)	<dl	0.25-7.89 mcg/24 hr
4-Hydroxyestrone (24hr urine)	2.72	0.33-1.98 mcg/24 hr
4-Methoxyestrone (24hr urine)	<dl	0.20-1.60 mcg/24 hr
2-Hydroxyestrone/16 α -Hydroxyestrone Ratio (24hr urine)	>2.35	0.94-1.56
2-Methoxyestrone/2-Hydroxyestrone Ratio (24hr urine)	1.84	0.11-4.00
4-Methoxyestrone/4-Hydroxyestrone Ratio (24hr urine)	<dl	0.18-3.60

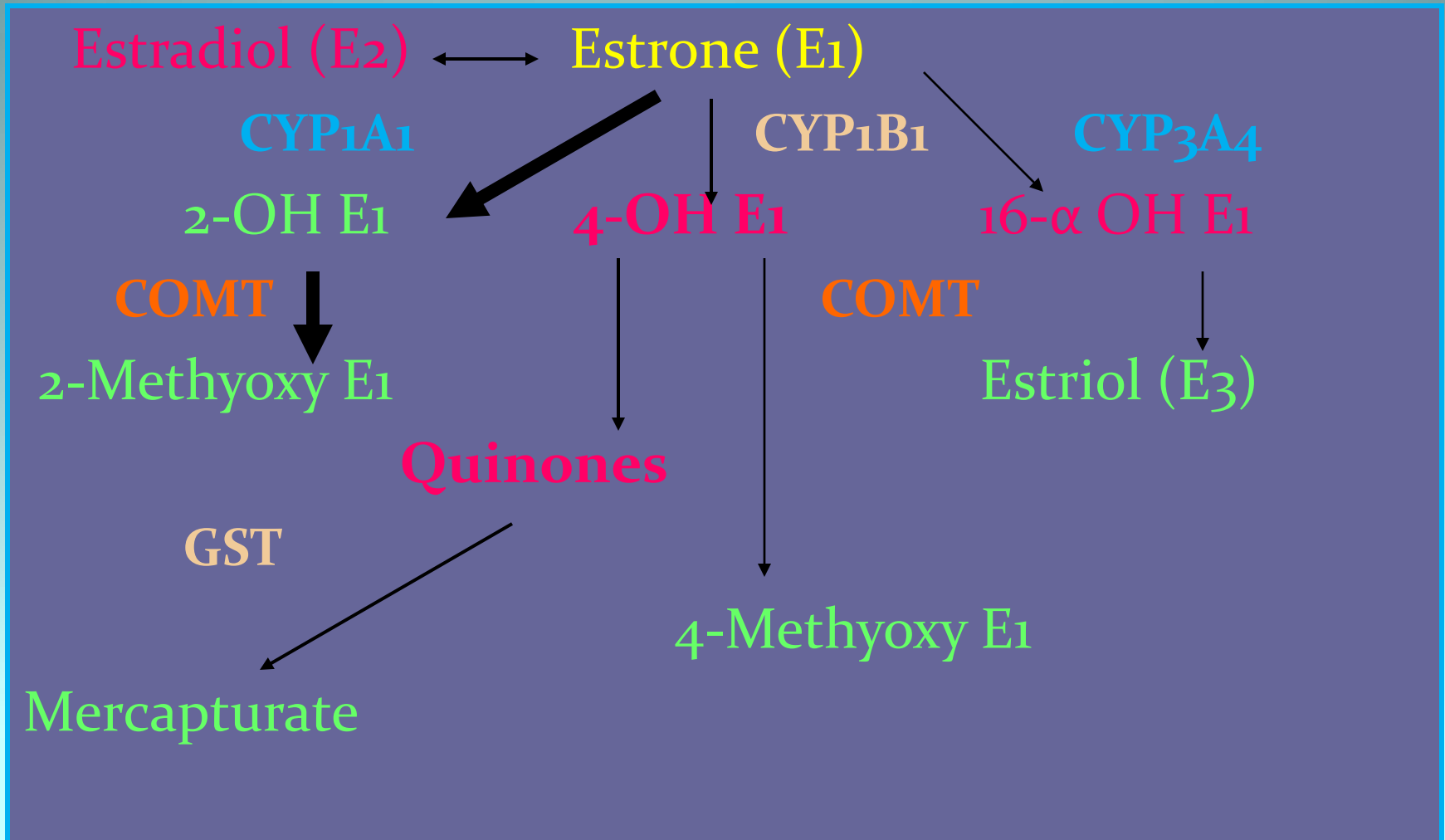
Nutrigenomic Interventions

- **Up-regulators of CYP_{1A1}**
 - DIM Pro Plus (75 mg per day)
 - EPA/DHA (640 mg/ 320 mg) 2 x per day
- **Antioxidants**
 - Vitamin C (500 mg) 2 x per day
 - Mixed Tocopherols (400 IU per day)
 - Vitamin A (7,500 IU retinyl palmitate, 7500 IU Beta Carotene)
 - N-acetyl-cysteine (500 mg) 3 x per day

Estradiol and Estrogen Metabolites (Urine): ER+ Breast Cancer Patient After Nutrigenomic Intervention

Estrone (24hr urine)	20.04
Estradiol (24hr urine)	5.15
Estriol (24hr urine)	0.34
2-Hydroxyestrone (24hr urine)	2.95
2-Methoxyestrone (24hr urine)	1.34
16 α -Hydroxyestrone (24hr urine)	2.53
4-Hydroxyestrone (24hr urine)	0.70
4-Methoxyestrone (24hr urine)	0.79
2-Hydroxyestrone/16 α -Hydroxyestrone Ratio (24hr urine)	1.17
2-Methoxyestrone/2-Hydroxyestrone Ratio (24hr urine)	0.45
4-Methoxyestrone/4-Hydroxyestrone Ratio (24hr urine)	1.13

Estrogen Metabolism: Breast Cancer ER + (Phase I and II Detoxification Enzymes)



Endogenous Hormone Levels in Premenopausal Women Tied to Breast Cancer

- High plasma levels of total and free estradiol in early follicular phase (3 to 5 days of menstrual cycle)
- High total and free testosterone in luteal (7 to 9 days before anticipated start of menstrual cycle) and follicular phases
- Associations strongest with women with invasive breast cancer or ER +/-PR + tumors
 - Eliassen, A. H. (2006). Endogenous Steroid Hormone Concentrations and Risk of Breast Cancer among Premenopausal Women. *J. Natl. Cancer Institute.* 98: 1406-1415

Decreasing the Risk of Breast Cancer Recurrence

- Physiological data to quantify estrogen levels and its metabolites (Urine, Saliva, Blood);
- Genomic data to evaluate how estrogen and its metabolites are bio-transformed (detoxified);
- Diet, nutritional supplements and/or botanicals to up-regulate enzymes involved in estrogen metabolism (Phase I) and facilitate removal of estrogen metabolites (Phase II).

One drug, One symptom yields multiple drug cocktail

- 51 year old, white, post menopausal woman who had serious ADR to Premarin and Provera

- **Health issues**

Mood swings

Migraines

Heart Health

Hypothyroid

Medications

Wellbutrin XL (300 mg)

Inderal LA (120 mg)

Elavil (50 mg)


Replax (40 mg)

Asprin (80 mg)

Armour (90 mg)

Phase I and Phase II Detoxification SNPS

Cytochrome P-450

Result	Gene	internet information
	CYP1A1 ≠	www.genovations.com/gdgen01
	CYP1B1 ≠	www.genovations.com/gdgen02

Glutathione Conjugation (Glutathione s-transferase)

Result	Gene	Location	Internet Information	Affects
ABSENT	GSTM1	1p13.3	www.genovations.com/gdgstm1	Liver/Kidney
+ -	GSTP1	I105V	www.genovations.com/gdgstp1	Brain/Skin
- -	GSTP1	A114V	www.genovations.com/gda114v	Brain/Skin

Pharmacogenomics of Medications

Drug	Phase I	Phase II
Wellbutrin	CYP ₂ B6	
Inderal	CYP ₂ D6, ₁ A ₂	Glucuronidation
Elavil	Not clearly defined	
Replax	CYP ₃ A ₄	

Insights from DetoxGenomics

- CYP1B1 SNP: Explains why patient complained that HRT prescribed years ago for menopausal symptoms resulted in toxic effects.
- SNPs in Phase I and Phase II did not impact the drugs prescribed by her MD.
- Patient was able to use bio-identical hormones (troches) to ameliorate all menopausal symptoms; patient off all medications for migraines, mood swings and hot flashes, resulting in significant cost reduction.
- Projected savings to plan: \$20,000 to \$30,000/yr

Conclusions:

- Functional genomic testing enhanced AMO's health and wellness program by individualizing prevention and treatment;
- The GENE model is credited with helping the AMO Medical Plan keep costs contained below the national average;
- Furthermore, the GENE model has empowered members to take responsibility for their daily health, well-being and the members report that "they just feel better."

Are You Frustrated?

