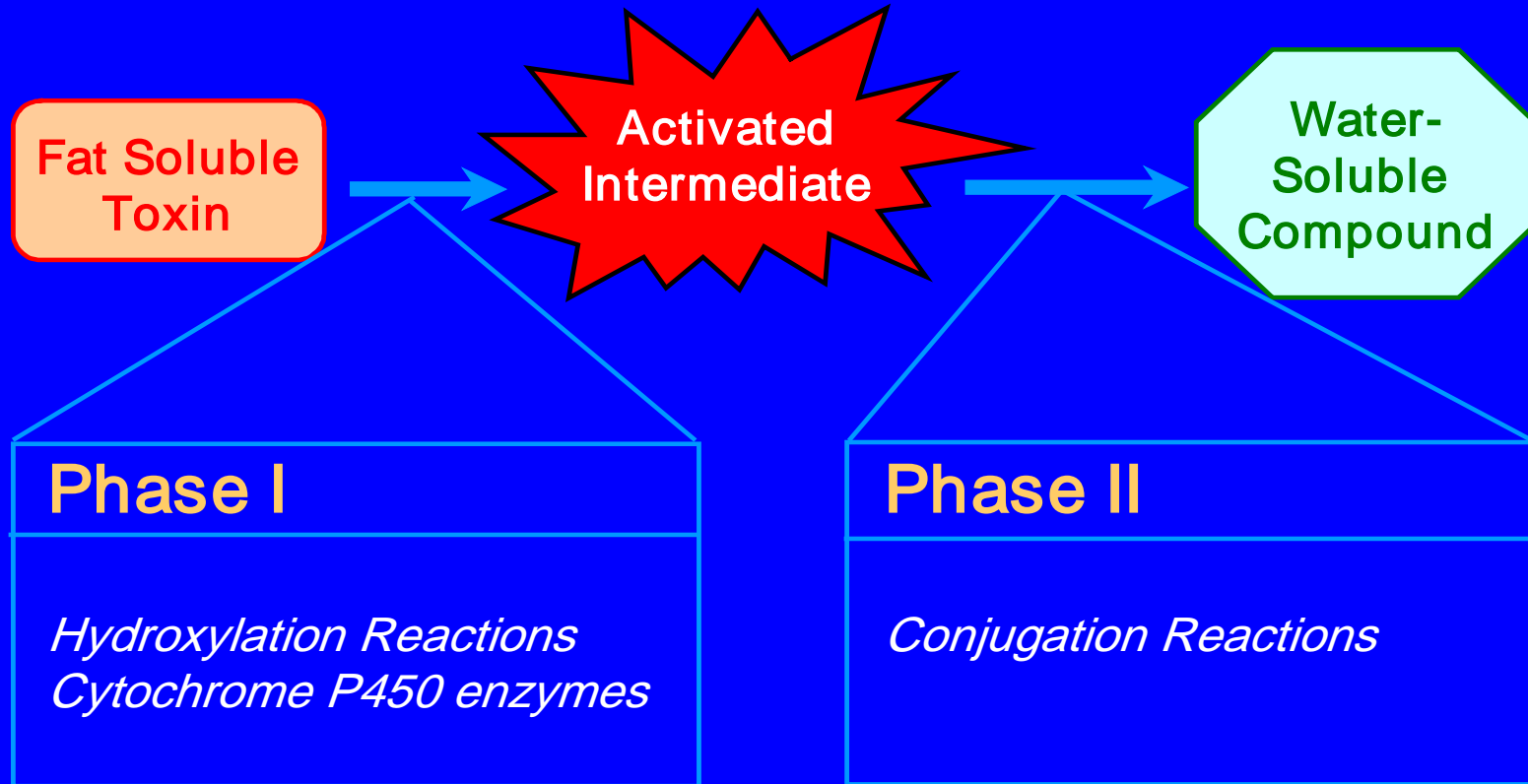


Pharmacogenomics

The study of genetic variability and its relationship to an individual's response to pharmaceutical drugs, prescription drugs and OTC medications.

- Goal: use the right drug for the right person at the right time.
- Identify potential drug-drug and drug-botanical interactions

Two Major Pathways of Hepatic Detoxification



Pharmacogenomics and in a Clinical Setting

- ⦿ Prior to surgery
- ⦿ Drug-drug interactions
- ⦿ Drug-botanical interaction
- ⦿ Drugs used in treatment of chronic diseases
 - Heart Disease
 - Hypertension
 - Breast Cancer
 - Hormone Replacement Therapy

Pharmacogenomics: One drug, One symptom yields multiple drug cocktail

- 51 year old, white, post menopausal woman

- **Health issues**

Medications

Mood swings

Wellbutrin XI (300 mg)

Migraines

Inderal LA (120 mg)

Elavil (50 mg)

Replax (40 mg)

Heart Health

Asprin (80 mg)

Hypothyroid


Armour (90 mg)

Pharmacogenomics of Medications

Drug	Phase I	Phase II
Wellbutrin	CYP2B6	
Inderal	CYP2D6, 1A2	Glucuronidation
Elavil	Not clearly defined	
Replax	CYP3A4	

Phase I and Phase II Detoxification SNPS

Cytochrome P-450

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

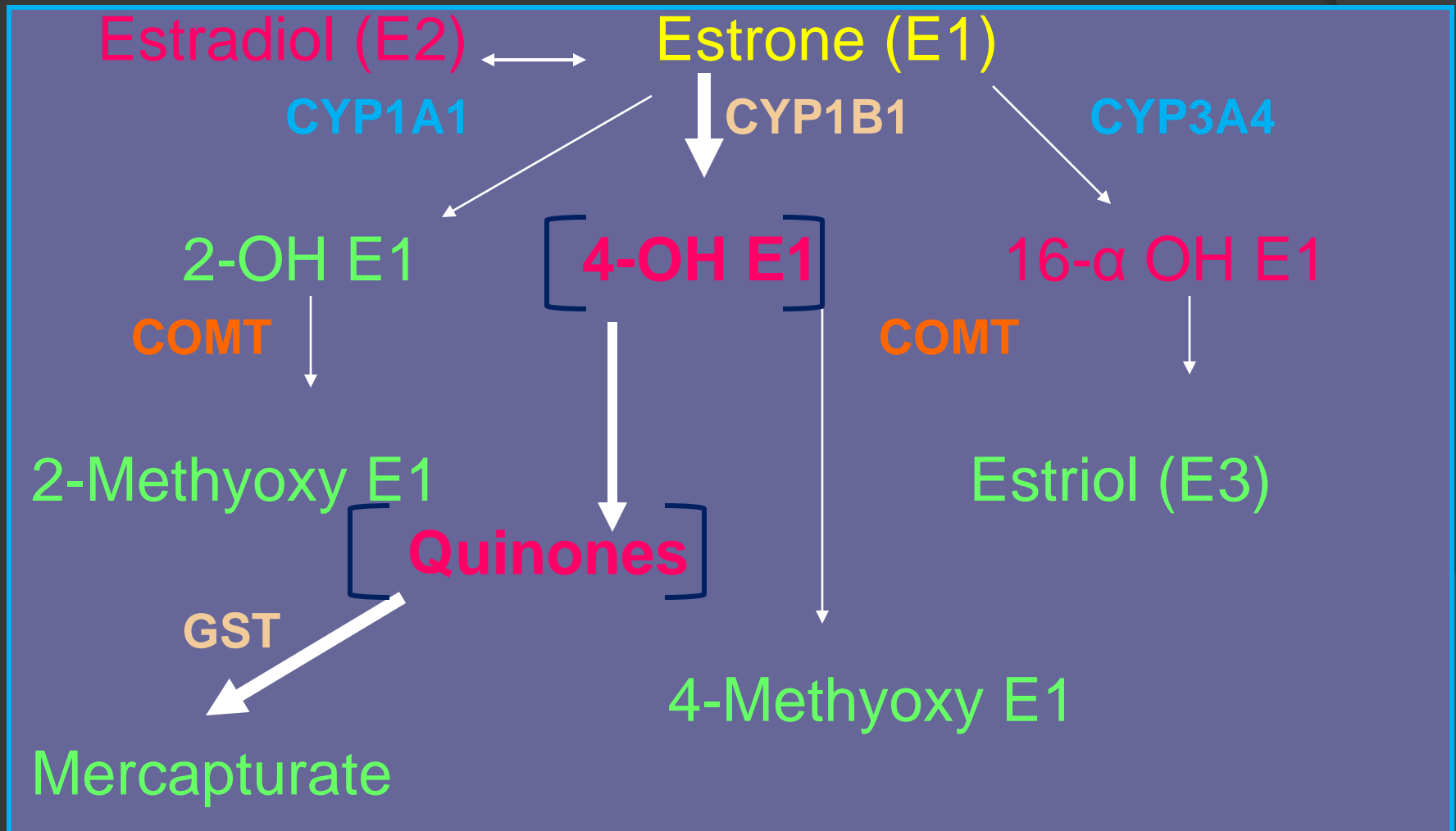
Glutathione Conjugation (Glutathione s-transferase)

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

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 influence the drugs prescribed by her MD.
- Patient was able to use bio-identical hormones (troches) to ameliorate all menopausal symptoms and now is off all medications for migraines, mood swings and hot flashes, resulting in significant cost savings to plan.

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



Decreasing the Risk of Breast Cancer

- 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) and genes associated with inflammation
- Diet, nutritional supplements and/or botanicals to up-regulate enzymes involved in estrogen metabolism (Phase I) and facilitate removal of estrogen metabolites (Phase II).

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

Tumor Genes Evaluated by OncotypeDX

Proliferation

Ki-67, STK15,
Survivin, Cyclin B1,
MYBL2

Estrogen

ER, PR,
Bcl2,SCMBE2

Her2

GRB7, Her2

Invasion

Stromelysin 3,
Cathepsin L2

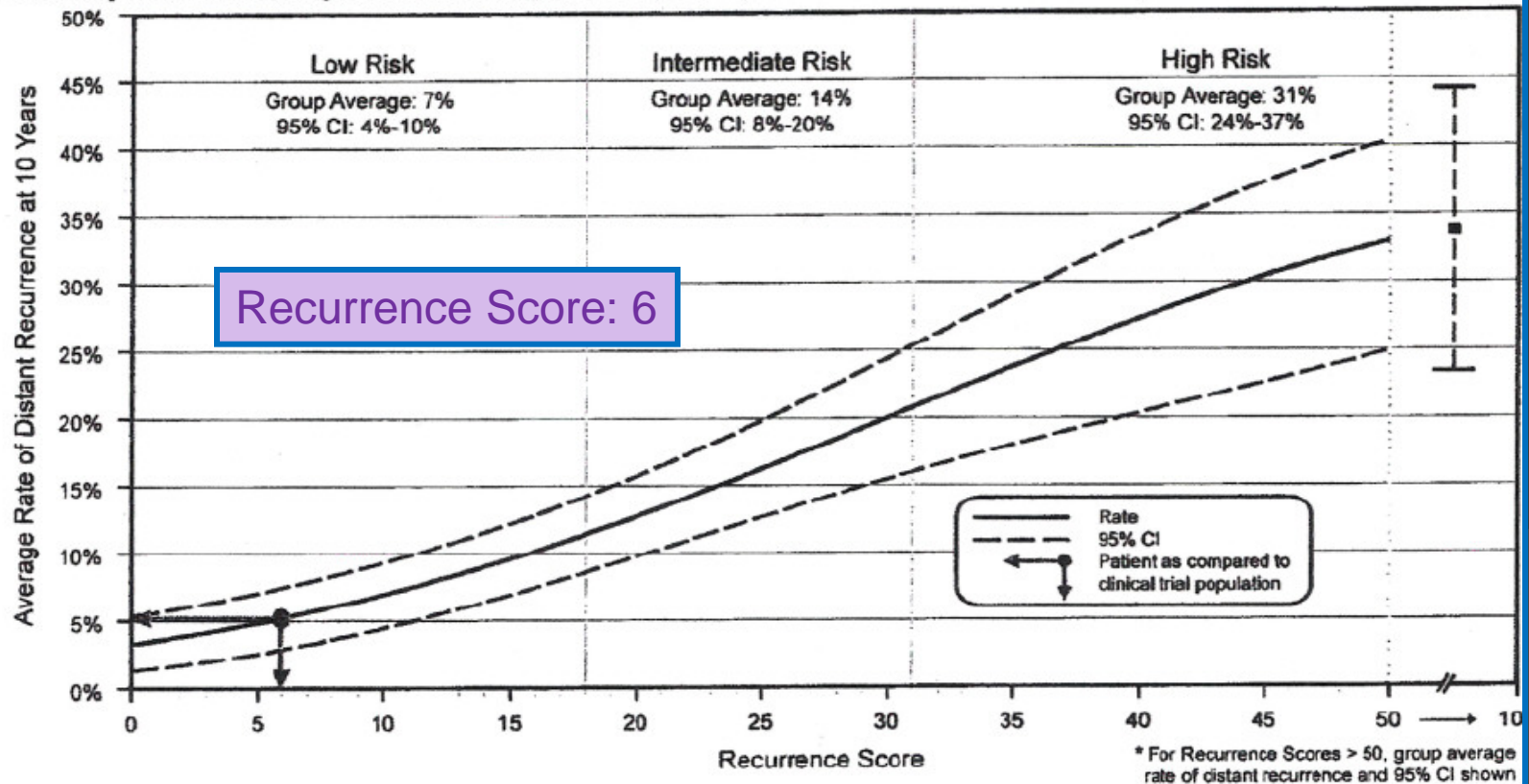
Others

GSTM1, CD68,
BAG1

Recurrence Score for Patient Diagnosed with Estrogen Receptor + Breast Cancer

Patients with a Recurrence Score of 6 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **5% (95% CI: 3%-7%)**

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive, and treated with tamoxifen. *N Engl J Med* 2004; 351: 2817-26.



Upside : Downside of Oncotype DX

- **Upside:** Identify the chemotherapeutic agent specific for a person's tumor;
- Psychological boost when recurrence score is low
- Aggressive therapies when recurrence score is high

- **Downside:** Does not evaluate the pharmacogenomics of the patient only the oncogenomics of the tumor
- Px can misinterpret probability of recurrence

Pharmaceutical Drugs and their Detox Pathways

Drug	Phase I	Phase II
Cytoxan	3A4, 2C19	
Doxorubicin	3A4	
Myleran		Glutathione
Taxol	3A4	
Zofran	3A4, 2D6, 1A1	Glucuronidation
Tamoxifen	2C9, 2D6	

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

Tamoxifen and CYP2D6 SNPs

- Tamoxifen's bio-conversion to endoxifen is handled primarily 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

Tamoxifen

◎ Upside:

- used to decrease the risk of breast cancer recurrence by undergoing a bio-transformation to endoxifen, which then binds to estrogen receptors (ER α) on cells and decreases cancer proliferation.

◎ Downside:

- Frequency of hot flashes increases
- Physicians often prescribe SSRIs to reduce this side effect

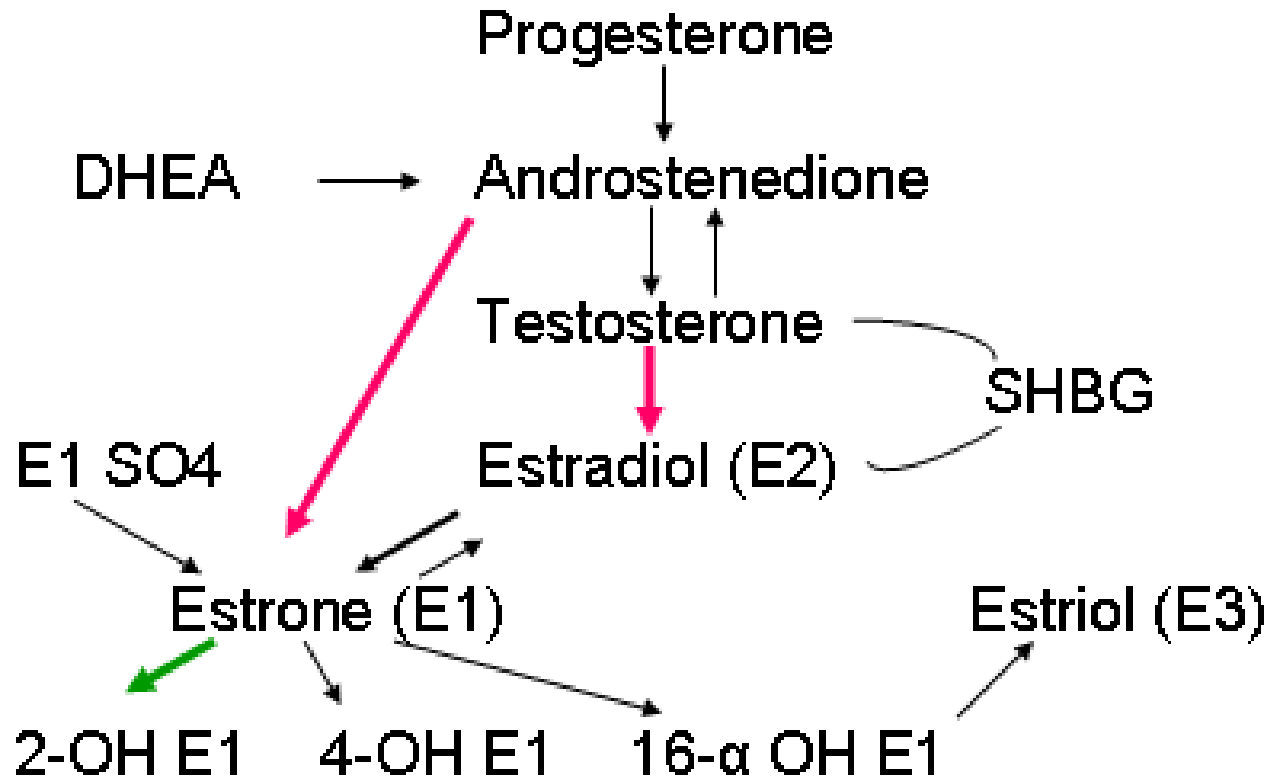
Tamoxifen, SSRIs and CYP2D6

- Women (normal CYP2D6 genotype) taking tamoxifen but taking either Paxil or Zoloft had lower concentration of endoxifen in the blood.
- Paxil and Zoloft inhibit CYP2D6 enzyme whereas Effexor does not.
- **Clinical implications: Genomic testing essential if healthcare professional is concerned about efficacious dose of Tamoxifen with or without SSRIs.**
 - Jin, Y., et al., 2005. J. Natl. Cancer Institute. 97 (1); 30-39

Aromatase Inhibitors and Detox Pathways

<u>Drug</u>	<u>Phase I</u>	<u>Phase II</u>
Arimidex		N-dealkylation Hydroxylation Glucuronidation
Aromasin	3A4	
Femara	3A4	

Biosynthesis of Estrogen



Aromatase Inhibitors , Pharmacogenomics and ADR

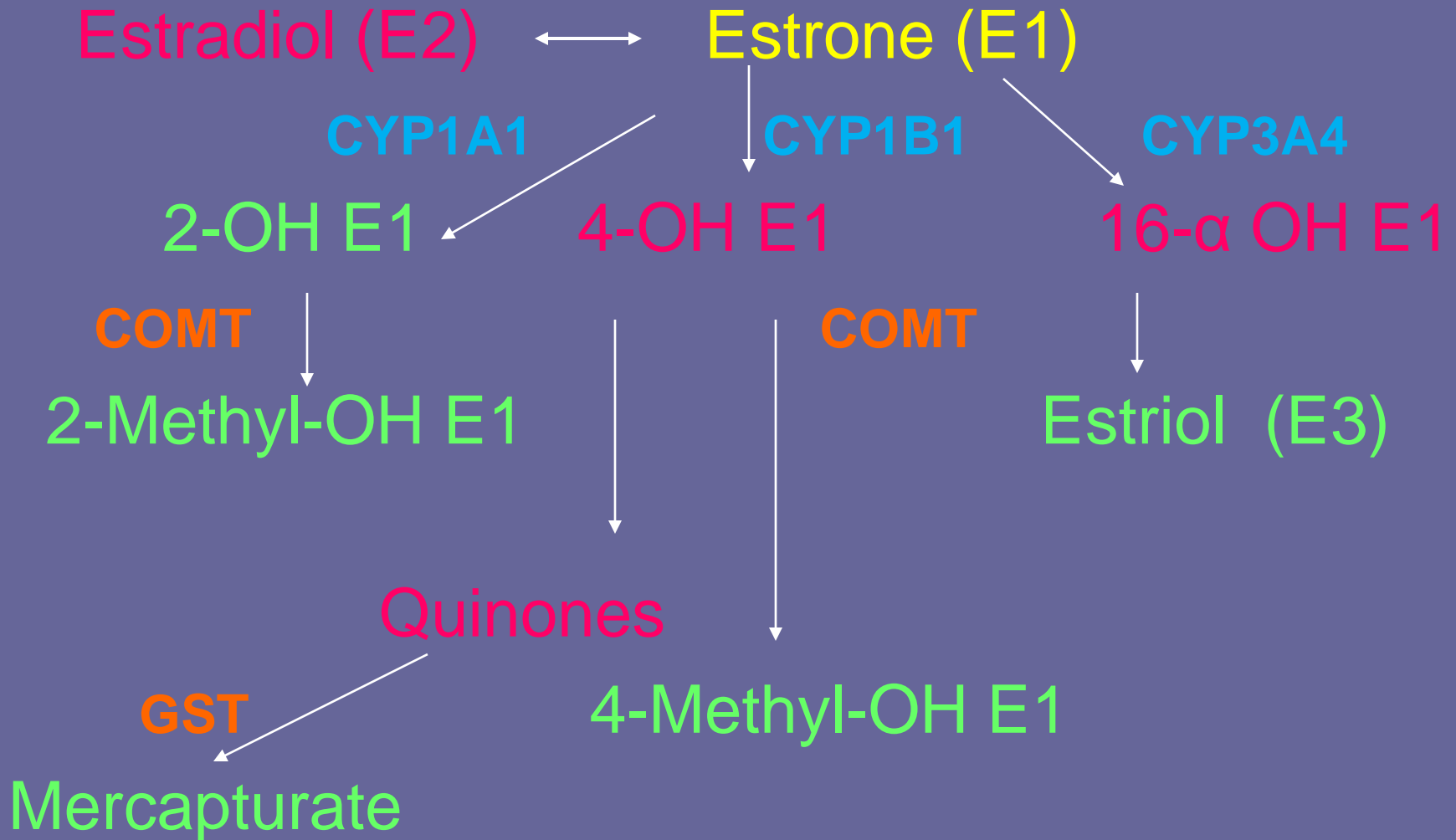
- ⦿ Does the patient have genomic SNPs associated with CYP 450 enzymes?
- ⦿ If not, are there other prescribed drugs or botanical which may induce the CYP450 enzyme responsible for the bio-transformation of Aromatase inhibitor drug?
 - Glucocorticoids Dilantin St. Johns Wort
- ⦿ If not, are there other prescribed drugs or botanical which may inhibit the CYP 450 enzymes responsible for the bio-transformation of an Aromatase inhibitor drug?
 - Ciprofloxacin Erythromycin Grapefruit
 - Cimetidine Diflucan

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.)

Estrogen Metabolism

(Phase I and II Detoxification Enzymes)



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

Grapefruit intake was significantly associated with increased risk of breast cancer (RR= 1.30) for postmenopausal 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.

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