Pharmacogenomics Will Not Be A Critical Part of Drug Dosing

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Human Genome Project Timeline

- 1985: Feasibility of sequencing human genome discussed
- 1986: 5.3 million committed to a feasibility program
- 1987: DOE designates multidisciplinary human genome centers. NIH NIGMS begins funding of genome projects.
- 1990: 15 year plan to map human genome begins
- 2000: Map completed
- 2001: Map published
- 2008: Genetic Information Nondiscrimination Act (GINA) Becomes Law, May 2008

Bottom Line: 20 years, billions and billions

Pharmacogenomics: The Questions

- Clinical relevance
- Social and ethical aspects
- Economic impact

Valid Biomarkers

- A valid biomarker is described as a "biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results." The classification of biomarkers is context specific.

- Reference is made to the requirement of testing for the biomarker:
  1 = test required;
  2 = test recommended; 2* test for at-risk populations
  3 = information only

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

Valid Biomarkers

Marker	Test	Drug with Label Change	Associated Drugs
C-kit expression	3	Imatinib	
CCR-5 chemokine receptor	1	Maraviroc	
CYP2C19	2	Voriconazole	Omeprazole Pantopazole Esmeprazole Diazepam Nelfinavir Rabeprazole
CYP2C9	2	Celacoxib	
CYP2C9	2	Warfarin	

www.fda.gov/cder/genomics/genomic_biomarkers_table.htm.

Valid Biomarkers

Marker	Test	Drug with Label Change	Associated Drugs
CYP2D6	3	Atomexatine	Venlafaxine, rispiridone, tamoxifen, timolol
CYP2D6	3	Fluoxetine	Many
5q-deletion	3	Lenalidomide	
DPD	3	Capecitabine	
EGFR	3	Erlotinib, cetuximab (head and neck cancer)	Gefitinib
EGFR	1	Cetuximab (Colon cancer)	Panitumomab, Gefitinib

Valid Biomarkers

Marker	Test	Drug with Label Change	Associated Drugs
Familial hypercholesterolemia	2	Atorvastatin	
G6PD	2	Rasburicase	Dapsone
G6PD	3	Primaquine	Chloroquine
Her-2-neu	1	Trastuzumab	Lapatinib
HLA-B*1502 allele presence	2	Carbamezapine	
NAT	3	Isoniazid, pyrazinamide, rifampin	Isosorbide Hydralazine

Valid Biomarkers

Marker	Test	Drug with Label Change	Associated Drugs
Philadelphia chromosome	3	Busulfan	
Philadelphia chromosome	1	Imatinib, Dasatinib	
PML/RAR (alpha) fusion gene presence	3	Tretinoin	Arsenic trioxide
Protein C deficiency	2	Warfarin	
TPMT	2	Azathioprine	6-mercaptopurine Thioguanine
UGT	2	Irinotecan	

Valid Biomarkers

Marker	Test	Drug with Label Change	Associated Drugs
UGT	3	Nilotinib	
Urea cycle disorder	2	Valproic acid	
VKORC1	2	Warfarin	

Clinical Relevance

- Pharmacogenomics is still in early developmental stage, prospective trials have not been performed or completed
- Environmental, behavior, disease charactersitics, other drugs and dietary factors all effect drug effect.
- Complex traits and complex response. Unlikely that a single gene will explain all variability

Social and Ethical Concerns

- Direct to consumer marketing
  - http://www.genotypediet.com/
- Genetic discrimination
- Coverage by insurance companies

Tucker L. Pharmacogenomics: Primer for Policy Makers, NHPF 2008;

Cost

- Genetic tests are expensive- $250-$3500
- Cost of the test needs to be balanced with the cost of avoiding unnecessary treatment and the cost of toxicity
- Unclear whether PG testing is cost effective

Doloresco F, etal AJHP 2008, submitted

Current State Of The Art In Using Pharmacogenomics To Determine Appropriate Doses And Drugs

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Clinical Pharmacogenetics: Already in Routine Practice

- Selective therapy
  - Her-2-neu testing for trastuzumab
  - Philadelphia chromosome for imatinib
- Minimize toxicity
  - TPMT testing for 6-mercaptopurine (6-MP)
  - UGT testing for irinotecan

Clinical Pharmacogenetics: Close to Routine and Will Be Covered Today

- Selective therapy
  - Cetuximab, panitumomab, gefitinib and erlotinib and the EGFR/Kras pathway
- Minimize toxicity
  - Tamoxifen and CYP2D6

Case: Controlling Costs

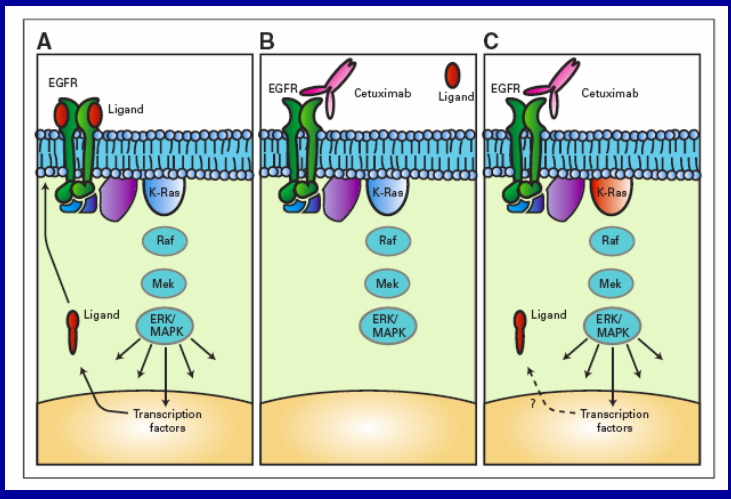
- YT is a 64-year-old man with metastatic colon cancer set to begin therapy with cetuximab. His tumor is mutated for Kras. What do you suggest?
  - Start cetuximab as planned
  - Switch to panitumumab
  - Best supportive care or phase 1 trial

The *KRAS* Oncogene

- The *KRAS* gene encodes the human cellular homolog of the transforming gene Kirsten rat sarcoma-2 virus
- KRAS is a self-inactivating signal transducer
  - It cycles from GDP bound ("off" state) to GTP bound ("on" state) in response to receptor activation
  - This response is transient due to the intrinsic GTPase activity
- *KRAS* oncogenes harbor activating mutations yielding proteins with reduced GTPase activity
- These activating *KRAS* mutations are among the most common oncogenic alterations in cancer

Malumbres, Barbacid. *Nat Rev Cancer.* 2003;3:459-65.

Mutated KRAS Activates the RAS-RAF-MEK-ERK-MAP Kinase Cell Signaling Pathway Independently Despite the Inhibition of EGFR (HER) by Cetuximab



Khambata-Ford S, et al. *J Clin Oncol.* 2007;25:3230-37. Available at www.jco.ascopubs.org. Accessed 2/18/2008.

Cetuximab and Kras Mutations

- Retrospective evaluation of individuals with metastatic colorectal cancer (n = 59) receiving cetuximab in combination with irinotecan or oxaliplatin
- Response rate in those without Kras mutation 32% (5% CR, 28% PR)
- Response rate in those with a Kras mutation 0

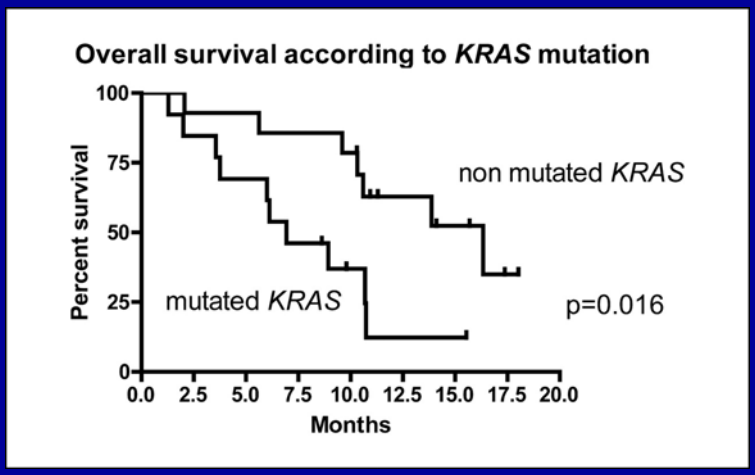
Di Foire F, et al. *Br J Cancer.* 2007;96:1166-69.

Cetuximab and Kras Mutations

- Retrospective evaluation of individuals with metastatic colorectal cancer (n = 30) receiving cetuximab in combination with irinotecan, oxaliplatin, or as a single agent
- 11 patients with a response (no Kras mutations)
- 19 patients without response (13 with a Kras mutation)

Lievre A, et al. *Cancer Res*. 2006:66:3992-95.

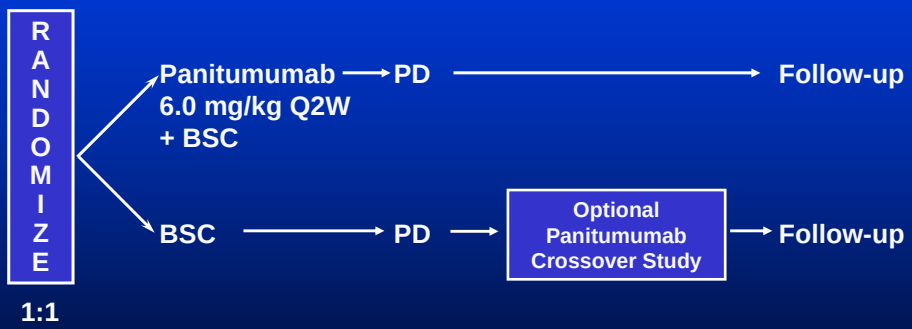
Cetuximab and Kras Mutations



Lievre A. et al. *Cancer Res*. 2006:66:3992-95.

KRAS Analysis of a Phase 3, Randomized, Controlled Trial Comparing Panitumumab vs Best Supportive Care (BSC) in Colorectal Cancer

Hypothesis: The treatment effect of panitumumab monotherapy is larger in patients with wild-type KRAS compared to patients with mutant KRAS



Randomization stratification

- **ECOG score: 0-1 vs. 2**
- **Geographic region: Western EU vs. Central & Eastern EU vs. Rest of World**

Van Cutsem, Peeters et al. *JCO.* 2007;25:1658-1664.

R.G. Amado

Results: Prevalence of Mutant *KRAS*

	Panitumumab + BSC	BSC alone	Total
Patients randomized, n	231	232	463
KRAS not tested, n (%)	11 (5)	7 (3)	18 (4)
KRAS tests failed, n (%)	12 (5)	6 (3)	18 (4)
Patients included in *KRAS* analysis, n (%)	208 (90)	219 (94)	427 (92)
Wild-type *KRAS*, n (%)	124 (60)	119 (54)	243 (57)
Mutant *KRAS*, n (%)	84 (40)	100 (46)	184 (43)

BSC, best supportive care

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Objective Tumor Response
(Central Radiology)

	KRAS					
	All Evaluable n (%)		Mutant n (%)		Wild-type n (%)	
Response	Pmab (N = 208)	BSC (N = 219)	Pmab (N = 84)	BSC (N = 100)	Pmab (N = 124)	BSC (N = 119)
CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR	21 (10)	0 (0)	0 (0)	0 (0)	21 (17)	0 (0)
SD	52 (25)	22 (10)	10 (12)	8 (8)	42 (34)	14 (12)
PD	104 (50)	149 (68)	59 (70)	60 (60)	45 (36)	89 (75)
CR, PR, SD	73 (35)	22 (10)	10 (12)	8 (8)	63 (51)	14 (12)

Pmab, panitumumab; BSC, best supportive care; CR, complete response; PR partial response; SD, stable disease; PD, disease progression

R.G. Amado

Single-Arm Studies Support the Hypothesis for *KRAS* as a Biomarker for EGFr Inhibitors

Reference	Treatment (panitumumab or cetuximab)	No of patients (WT:MT)	Objective Response N (%)	
			MT	WT
A. Liévre, et al. *(AACR Proceedings, 2007)*	cmab ± CT	76 (49:27)	0 (0)	24 (49)
S. Benvenuti, et al. *(Cancer Res, 2007)*	pmab or cmab or cmab + CT	48 (32:16)	1 (6)	10 (31)
W. De Roock, et al. *(ASCO Proceedings, 2007)*	cmab or cmab + irinotecan	113 (67:46)	0 (0)	27 (40)
D. Finocchiaro, et al. *(ASCO Proceedings, 2007)*	cmab ± CT	81 (49:32)	2 (6)	13 (26)
F. Di Fiore, et al. *(Br J Cancer, 2007)*	cmab + CT	59 (43:16)	0 (0)	12 (28)
S. Khambata-Ford, et al. *(J Clin Oncol, 2007)*	cmab	80 (50:30)	0 (0)	5 (10)

WT, wild type; MT, mutant; cmab, cetuximab; CT, chemotherapy; pmab, panitumumab

R.G. Amado

Cost of Cetuximab in Metastatic Colon Cancer (Unselected Patients)

- Single Agent
  - The LYG ranged between 1.7 and 2.0 years. The median cost per patient treated was calculated to 34,256 Euro to 45,764 Euro yielding a cost per LYG in the range between 205,536 Euro and 323,040 Euro.
- Combination with irinotecan
  - "While it is difficult to suggest whether cetuximab represents value for money, indirect comparisons suggest that the incremental cost-utility of cetuximab plus irinotecan is unlikely to be better than pound 30,000 per QALY gained"
  - Incremental cost per life-year gained with cetuximab/irinotecan therapy compared with active/best supportive care was 42 975 pounds. The incremental cost per quality adjusted life-year gained was 57 608 pounds

Tappenden P, et al. *Health Technol Assess*. 2007;11:1-128; Starling N. *Br J Cancer*. 2007;96:206-12; Norum J. *J Chemother*. 2006;18:532-7.

Case: Controlling Costs

- YT is a 64-year-old man with metastatic colon cancer about to begin therapy with cetuximab. His tumor is EGFR positive and mutated for Kras. What do you suggest?
  - Start cetuximab as planned
    - Response rates range from 0-6%
  - Switch to panitumumab
    - Response rates range from 0-6%
  - Best supportive care

EGFR, Kras, and EGFR Inhibitors

- Mounting evidence suggests that EGFR expression and wild-type Kras predict better response to EGFR inhibitors
- Why do we continue to use these expensive drugs in unselected populations
  - Many patients have already exhausted all other therapeutic options
  - EGFR inhibitors less toxic than standard chemotherapy

Case: Preventing Drug Interactions

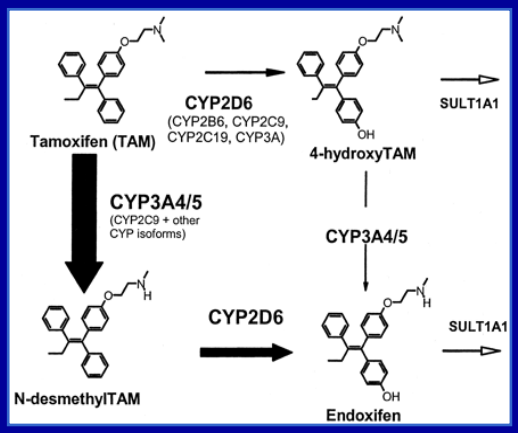
- LL is a 57-year-old postmenopausal woman with stage III breast cancer who was recently started on adjuvant tamoxifen. She comes to the clinic complaining of hot flashes and the oncology fellow gives her a prescription for fluoxetine.
  - What should you do?

Tamoxifen: Indications

Indications	Year of Approval
Metastatic breast cancer (postmenopausal)	1977
Adjuvant breast cancer (postmenopausal node +)	1986
Metastatic breast cancer (premenopausal)	1989
Adjuvant breast cancer (postmenopausal node -)	1990
Metastatic breast cancer (male)	1993
Reduction in breast cancer incidence	1998
Ductal carcinoma in situ (DCIS)	2000

http://www.fda.gov/

Tamoxifen



- 4-hydroxyTAM is more potent than tamoxifen as an estrogen antagonist
- Endoxifen has same potency and efficacy as 4-OH tamoxifen

Jin et al, J Natl Cancer Inst. 2005 Jan 5;97(1):30-9 .

CYP2D6 Polymorphism

Allele	Enzyme Activity	Caucasian	African American	Japanese
*2xn	Increased	1%-5%	0-2%	2%
*4	None	18%-23%	7%-9%	<1%
*5	None	2%-4%	6%-7%	5%-6%
*6	None	1%	<1%	N/A
*10	Reduced	4%-8%	3%-8%	39%-41%
*17	Reduced	N/A	15%-26%	N/A

Bradford LD. *Pharmacogenomics.* 2002;3:229-43.

Background

Selective serotonin reuptake inhibitors (SSRIs)

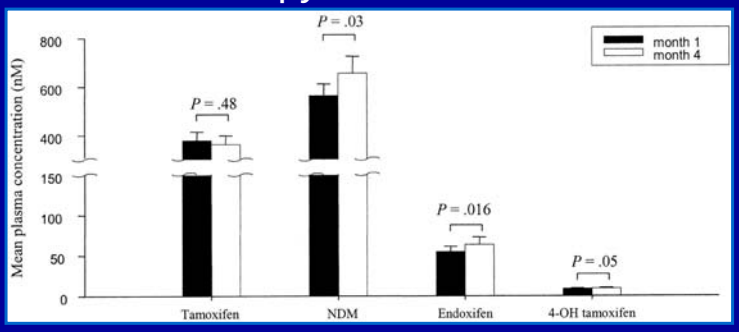
- Antidepressants that are often prescribed to treat hot flashes in women who take tamoxifen
- Paroxetine, sertraline, citalopram, fluoxetine, and venlafaxine
- Inhibition of CYP2D6 by SSRIs likely to affect metabolism of tamoxifen

Study Design and Methods

- 80 women newly diagnosed with breast cancer
- Baseline blood sample taken
- Measured plasma concentrations of tamoxifen and its metabolites (after 1 and 4 months of therapy)
- Genotype analysis (CYP2C9, CYP3A5, SULT1A1, CYP2D6)
- Examined effects of CYP2D6 inhibitors on plasma endoxifen concentrations
- Examined association of SSRIs and plasma endoxifen concentration

Results

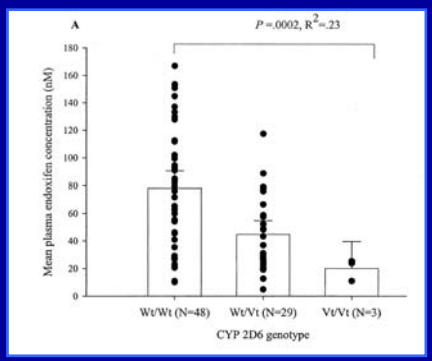
- Mean plasma concentrations of tamoxifen and its metabolites after 1 and 4 months of tamoxifen therapy



Jin et al, J Natl Cancer Inst. 2005 Jan 5;97(1):30-9 .

Results (cont.)

- CYP2D6: no significant difference in plasma concentrations of tamoxifen, NDM or 4-OH between Wt/Wt & Wt/Vt or between Wt/Wt & Vt/Vt



A significant difference in mean endoxifen plasma concentration was noted

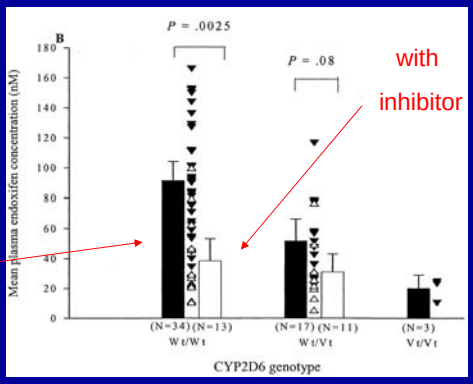
Jin et al, J Natl Cancer Inst. 2005 Jan 5;97(1):30-9 .

Results

- Lower plasma concentration of endoxifen in patients taking CYP2D6 inhibitors

without inhibitor

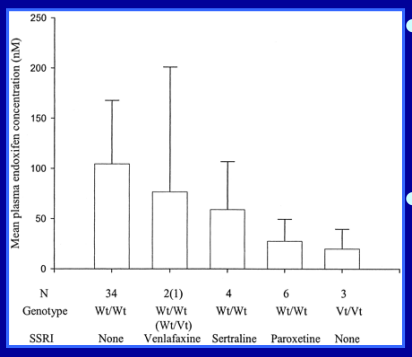
with inhibitor



Jin et al, J Natl Cancer Inst. 2005 Jan 5;97(1):30-9 .

Results

- Association between SSRIs and plasma endoxifen concentrations.



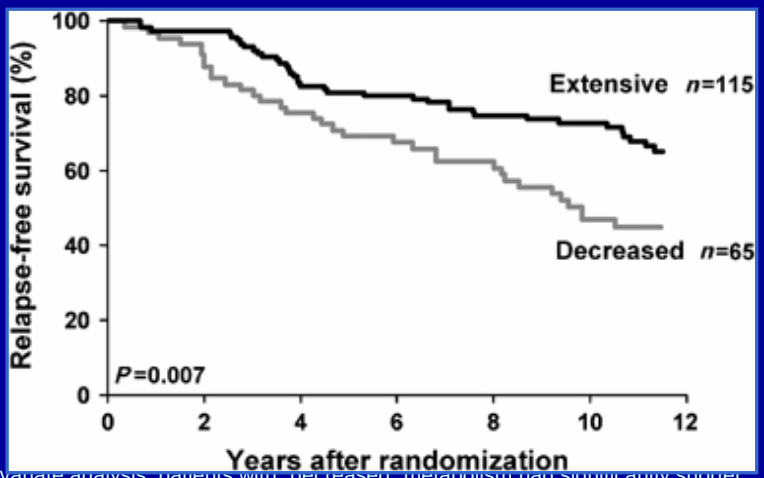
- **Venlafaxine (weak inhibitor) seemed to have *little* effect on endoxifen concentration**
- **Paroxetine (strong inhibitor) seemed to have a *large* effect on endoxifen concentration**

Jin et al, J Natl Cancer Inst. 2005 Jan 5;97(1):30-9 .

Design

- Retrospective evaluation of a prospective adjuvant tamoxifen trial (NCCTG 89-30-52) in postmenopausal women with surgically resected ER-positive breast cancer (stages I–III) to determine the role of genetic variation in *CYP2D6*
- "Extensive" metabolizers were defined as patients without a *CYP2D6*4* allele who were not prescribed a CYP2D6 inhibitor
- "Decreased" CYP2D6 metabolism was defined as patients with one or two *4 alleles, or the confirmation that a CYP2D6 inhibitor was coadministered with tamoxifen (regardless of genotype)

Kaplan–Meier Estimates of RFS Based on CYP2D6 Metabolism



In a multivariate analysis, patients with "decreased" metabolism had significantly shorter time to recurrence (*P* = .034; HR=1.91) and worse RFS (*P* = .017; HR=1.74) relative to patients with "extensive" metabolism.

Goetz MP, et al. ***Breast Cancer Res Treat.*** **2007;101:113–21.**

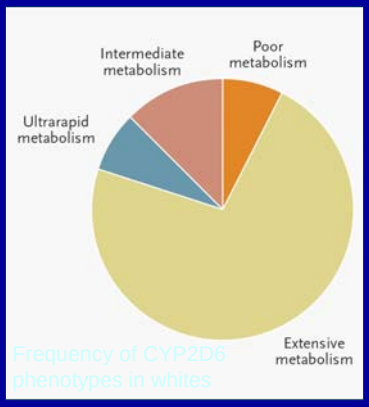
CYP2D6 Substrates

- **25% of all therapeutic drugs, 50 of the 100 best selling drugs**

Substrates of CYP2D6

Beta blockers	Cardioactive drugs	Antidepressants	Antipsychotics	Others
alprenolol	amiodarone	amitriptyline	haloperidol	amphetamine
carvedilol	encainide	clomipramine	perphenazine	codeine
S-metoprolol	flecainide	desipramine	risperidone	dexfenfluramine
propafenone	lidocaine	doxepin (E-isomers)	thioridazine	methoxyamphetamine
propranolol	mexiletine	fluoxetine	zuclopenthixol	ondansetron
timolol	perhexiline	fluvoxamine		phenacetin
		imipramine		phenformin
		maprotiline		tamoxifen
		nortriptyline		tramadol
		paroxetine		
		venlafaxine		

Using Genetic Information to Predict Drug Metabolism: The AmpliChip CYP450



Depending on your own spelling of the CYP450 genes, you may need much higher or much lower doses of a many different drugs to get the benefit.

Caraco Y. *N Engl J Med,* 2004;

Case: Preventing Drug Interactions

- LL is a 57-year-old postmenopausal woman with stage III breast cancer who was recently started on adjuvant tamoxifen. She comes to the clinic complaining of hot flashes and the oncology fellow gives her a prescription for fluoxetine.
  - What should you do?
    - Start fluoxetine as planned
    - Pick another SSRI with less CYP2D6 inhibition (sertraline)
    - Switch to an aromatase inhibitor

