

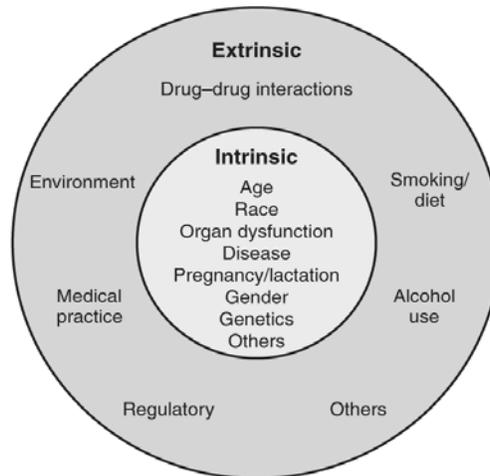
Obstetric-Fetal Pharmacology Research Units (OPRU)  
Network Steering Committee Meeting  
March 29, 2011, Bethesda, MD

# Applications of Pharmacogenomics in Drug Development & Regulatory Review - Recent relabeling of Drug Products -

Shiew-Mei Huang, Ph.D.  
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OTS, CDER, FDA  
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## Factors Affecting Drug Exposure/Response



<Huang S-M, Temple R, Clin Pharmacol Ther 84: 287-294, 2008>

<FDA Clinical Pharmacology guidance documents:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>

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### Comparative exposure and dose recommendation in subgroups with various patient factors

Group	Ethnic factor	Fold change in exposure (AUC)	Initial dose (mg)	Daily dose (mg)
1	Control	1-fold	10-20	5-40
2	Hepatic impairment	1.1-fold (mild) 1.2-fold (moderate)	10-20 10-20	5-40 5-40
3	Renal impairment	1-fold (mild) 1-fold (moderate) 3-fold (severe)	10-20 10-20 5	5-40 5-40 ≤10
4	Race	2-fold (Asians)	5	5-20
5	Cyclosporine	7-fold		5
6	Gemfibrozil	1.9-fold		10
7	Lopinavir/ritonavir	5-fold		10

(Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); Labeling from <http://www.accessdata.fda.gov/scripts/cder/drugsatfda>); November 2007 labeling

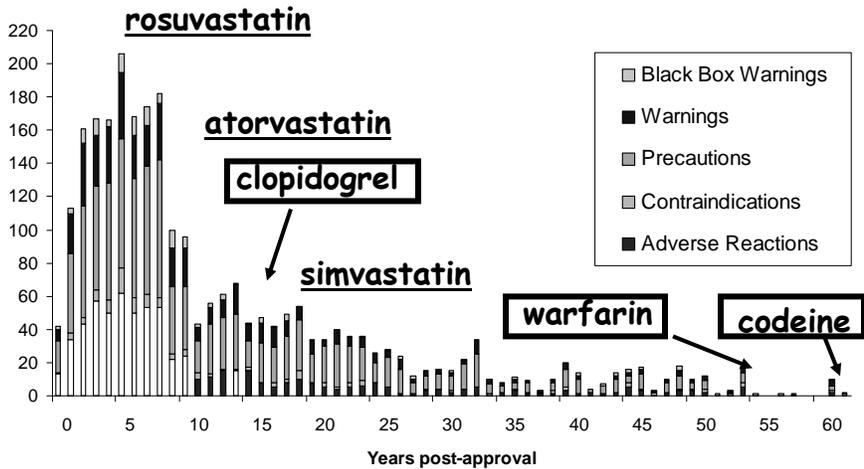
→ Current practice: Adjust the dose to achieve similar systemic exposure → Only the first step

<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>

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### Safety-Related Labeling Changes

(changes made Oct 2002-Aug 2005, n=2645 label changes for 1601 NDA/BLA entries)



Modified from: T Mullin, CDER, Office of Planning and Analysis, OTS presentation, May 2009

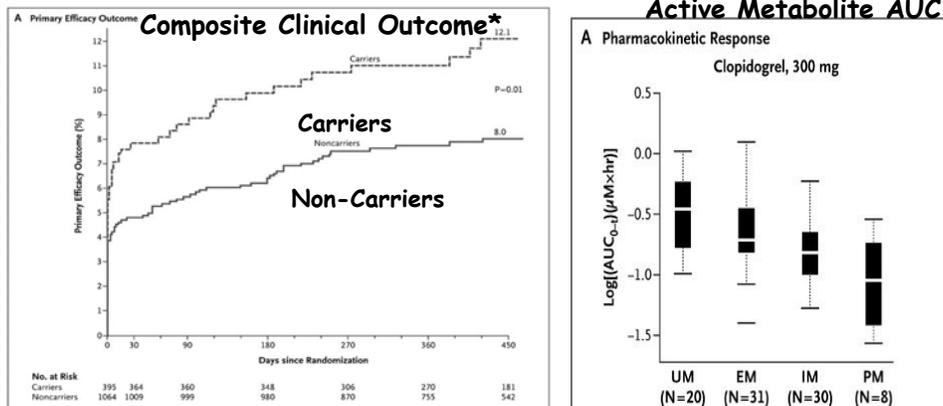
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# Labeling Example (1)

Updating labeling  
 Genetic Data ↔  
 Drug Interaction warning

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## CYP2C19 and Clopidogrel



Carriers: with at least one variant allele (EM+IM)  
 Non-carriers: with two wild-type alleles (UM+PM)  
 \*Outcome: a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for angina  
 Reference: *N Engl J Med* 2009; 361:1033-41  
 Another study also examined MDR1

## March 2010 Relabeling

### WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- Effectiveness of Plavix depends on activation ... by ... CYP2C19
- Poor metabolizers ..... exhibit higher cardiovascular event rates following ... acute coronary syndrome (ACS) or ... percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify .. CYP2C19 genotype ...
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

### WARNINGS AND PRECAUTIONS

- Avoid concomitant use with drugs that inhibit CYP2C19 (e.g., omeprazole)

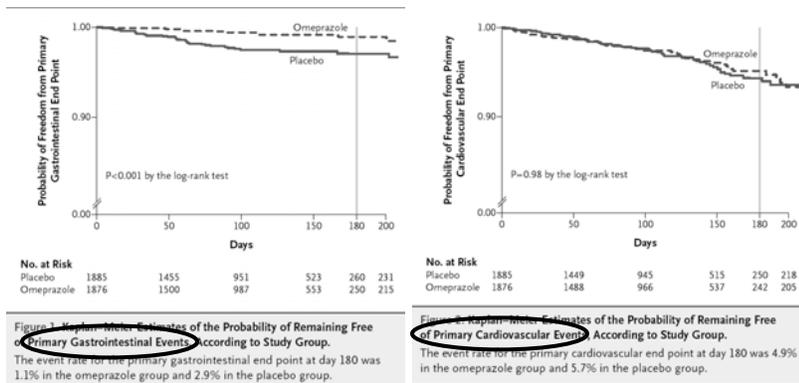
Drugs at the FDA (Plavix, "HIGHLIGHTS")

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020839s042lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf)

<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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## October 2010 Publication



→ Among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper gastrointestinal bleeding. There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but our results do not rule out a clinically meaningful difference in cardiovascular events due to use of a PPI.

D.L. Bhatt et al, COGENT trial | October 6, 2010 | (DOI: 10.1056/NEJMoa1007964)

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## Clopidogrel and Pharmacogenetic Test in Clinical Practice (one example)

- Vanderbilt University Medical Center joins Scripps Clinic, starting to routinely test for variations in CYP2C19 gene before antiplatelet therapy
- Test for \*1 (wild), 2, 3 (loss-of-function), 17 (gain-of-function)
- Individual clinicians to decide treatment options
  - If homozygous for loss-of-function
    - prasugrel
  - If contraindications for prasugrel
    - increase the dose from 75 to 150 mg or ticagrelor when it is available

<http://www.theheart.org/article/1139495.do> (October 21, 2010)

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## Clopidogrel Use in Pediatrics

- "Current Studies suggest that a dose of 0.2 to 1 mg/kg/day may be an appropriate starting point"
  - Buck ML, University of Virginia pharmacotherapy newsletter: Pediatric Pharmacotherapy, May 2010, <http://www.healthsystem.virginia.edu/alive/pediatrics/PharmNews/201005.pdf>
- Median Starting dose is 1.3 mg/kg/day (0.2-8.9 mg/kg/day) -- Children's Hospital in Boston
  - Maltz LA, et al, *Pediatr Cardiol* 2009; 30:99-105
- No pharmacogenetic information in pediatrics
- "The clopidogrel dose (0.2 mg/kg) used in the pivotal CLARINET study was potentially inadequate to demonstrate efficacy"-- FDA review
  - Krudys K et al, *Clinical Pharmacology Review*, July 2010, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM242999.pdf>

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# Clinical Utility

**Editorial**

*Clinical Pharmacology & Therapeutics* (2010) **88** 6, 729-733. doi:10.1038/dpt.2010.229

## What Is Clinical Utility and Why Should We Care?

L J Lesko<sup>1</sup>, I Zineh<sup>1</sup> and S-M Huang<sup>1</sup>

<sup>1</sup>Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

Correspondence: L Lesko, (lawrence.lesko@fda.hhs.gov); I Zineh, (Issam.Zineh@fda.hhs.gov); S-M Huang, (ShiewMei.Huang@fda.hhs.gov)

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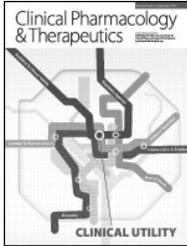
**State of the Art**

*Clinical Pharmacology & Therapeutics* (2010) **88** 6, 765-773. doi:10.1038/dpt.2010.230

## Assessing the Clinical Utility of Diagnostics Used in Drug Therapy

J Woodcock<sup>1</sup>

<sup>1</sup>Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA



**December 2010**

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**State of the Art**

*Clinical Pharmacology & Therapeutics* (2010) **88** 6, 774-778. doi:10.1038/dpt.2010.233

## Enrichment of Clinical Study Populations

R Temple<sup>1</sup>

<sup>1</sup>Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

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# Clinical Utility (2)

## Cisplatin & ototoxicity

**Table 1 Expected results for 1,000 patients tested using a test with a sensitivity of 24% and a specificity of 98%**

	Unselected patient population	Test-positive patients	Test-negative patients	PPV	NPV	+LR	-LR	OR
<b>Prevalence 50%</b>								
Responder	500	120	380					
Nonresponder	500	10	490					
Test values		0		92%	56%	12	0.78	15
<b>Prevalence 5%</b>								
Responder	50	12	38					
Nonresponder	950	19	931					
Test values				39%	96%	12	0.78	15

Responder: person testing positive for disease or genetic trait condition (e.g., ototoxicity). Sensitivity = 100 times the number of true-positive results divided by the true-positive plus false-negative results. Specificity = 100 times the number of true-negative results divided by the number of true-negative plus false-positive results. PPV = 100 times the number of true positives divided by the number of true positives plus false positives. NPV = 100 times the number of true negatives divided by the true negatives plus false negatives. +LR = sensitivity (true positive) divided by (100% minus specificity) (false positive). -LR = (100% minus sensitivity) (false negative) divided by specificity (true negative). OR = PPV x NPV / ((100 - PPV) x (100 - NPV)).

+LR, positive likelihood ratio; -LR, negative likelihood ratio; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

**Prevalence and Clinical Utility**

PK Honig<sup>1</sup>

I was perplexed that none of the articles in December's issue on clinical utility mentioned in any detail the importance of disease/trait prevalence as part of the discussion on the clinical utility of diagnostic tests and enrichment strategies for clinical trials.<sup>1-3</sup> Most

**Response to "Prevalence and Clinical Utility"**

LJ Lesko<sup>1</sup> and S-M Huang<sup>1</sup>

**To the Editor:** We thank Dr Honig for raising the issue of prevalence of a disease or genetic trait condition in a given patient population and its importance in evaluating the clinical utility of a screening or diagnostic test.<sup>1</sup> We recognize that sensitivity and specificity are intrinsic characteristics of a screening or diagnostic test and are unaffected by prevalence. By contrast, estimates of a



**April 2011**

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## Clinical Utility (2)

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**& Huang S-M, *Clin Pharmacol Ther* 89(4): 489-490 (April 2011)**

#### Prevalence and Clinical Utility

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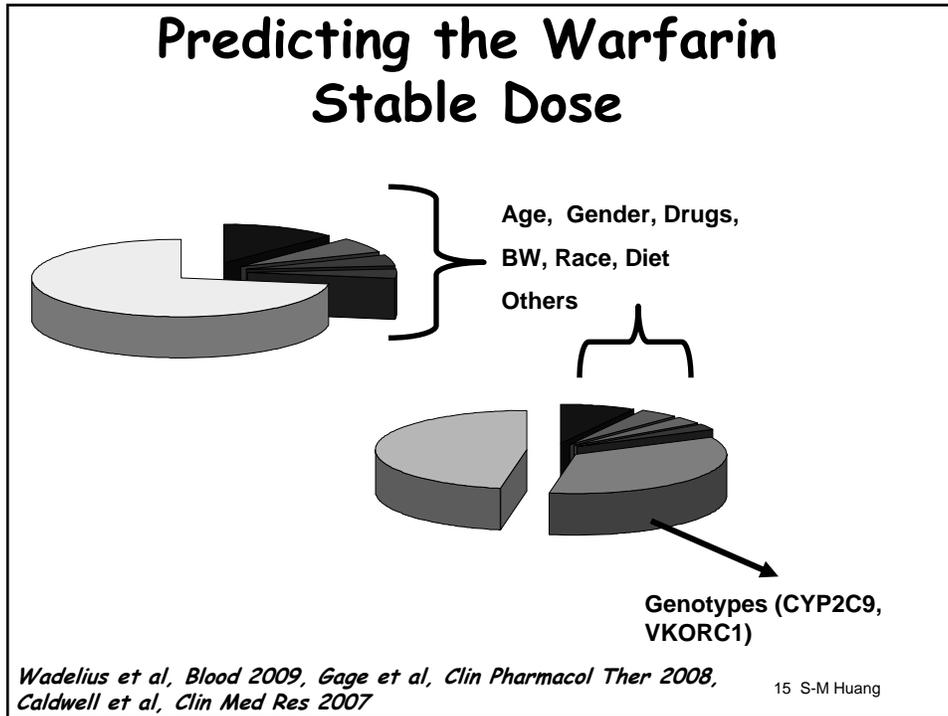
**April 2011**  
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## Labeling Example (2)

### Warfarin

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### *Frequency of VKORC1*

-1639 G>A	AA	AG	GG
<b>Caucasians (N=297)</b>	19%	56%	25%
<b>Spanish (N=105)</b>	32%	40%	28%
<b>Chinese (N=104)</b>	80%	18%	2%
<b>African Americans (N=159)</b>	0%	21%	79%

Asians may need a lower dose

<Sconce et al. Blood 2005, Yuan et al. Human Mol Genetics 2005, Schelleman et al. Clin Pharmacol Ther 2007, Montes et al Br J Haemat 2006>

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# Public Debates

**AACC**  
 JULY 28, 2008  
 SPECIAL SECTION  
 WWW.AACC.ORG

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See ARTICLES page 206

**POINT/COUNTERPOINT**

**The Critical Path of Warfarin Dosing: Finding an Optimal Dosing Strategy Using Pharmacogenetics**

LJ Lesko<sup>1</sup>

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**Warfarin and Pharmacogenomic Testing: The Case for Restraint**

DA Garcia<sup>1</sup>

*LJ Lesko, Clin Pharmacol & Ther, September 2008*  
*DA Garcia, Clin Pharmacol & Ther, September 2008*

**Is Warfarin Pharmacogenomic Testing Ready for Prime Time?**  
*Today's Debate to Focus on Implementation Issues*  
*By Charles Laveone*

**Opponents Want More Data**  
*Warfarin Debate, page 1*

*AACC warfarin Debate: Hallworth, Huang, Eby, Linder, Jaffer, July 28, 2008*  
[http://www.aacc.org/publications/cln/2008/July/dailies/Pages/mon\\_daily1.aspx](http://www.aacc.org/publications/cln/2008/July/dailies/Pages/mon_daily1.aspx)

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## January 2010 Relabeling

VKORC1			CYP2C9			
	*1*1	*1*2	*1*3	*2*2	*2*3	*3*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	.5-2 mg	.5-2 mg
AA	3-4 mg	3-4 mg	.5-2 mg	.5-2 mg	.5-2 mg	.5-2 mg

*Drugs at the FDA (COUMADIN, "Initial Dosage")*  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/009218s1081bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s1081bl.pdf)  
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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## Warfarin Use in Pediatrics

- **Warfarin Pharmacogenomics in Pediatric Patients – Pilot Project**  
**Critical Path Initiative**  
**Collaborators**  
 Greg Kearns – Kansas City  
 Ron Hines – Milwaukee  
 Cheryl Takao – Los Angeles
- **PG in Pediatric Heart Transplantation (Un. of Pittsburgh)**

Burckart G, presentation at PPAG (Pediatric Pharmacy Advocacy Group), Memphis, TN, March 19, 2011

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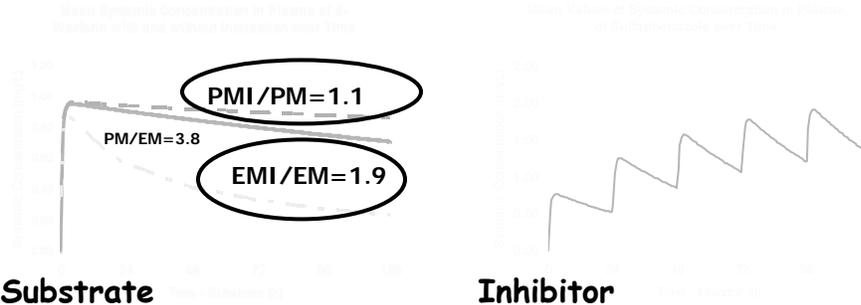
## Genotype- Specific Inhibition Effect

Pop 1: CYP2C9 EM; Pop 2: CYP2C9 PM,  
 M/F=1.0; Age 20-40 yr  
*S-warfarin: SD 10 mg on day 1*  
*Sulfaphenazole: QD 2000 mg 5 days*

7-OH Warfarin	EM (*1/*1)	PM (*3/*3)
CL <sub>int</sub> (uL/min/pmol CYP)	0.034	0.005

Using SimCYP® V8.20

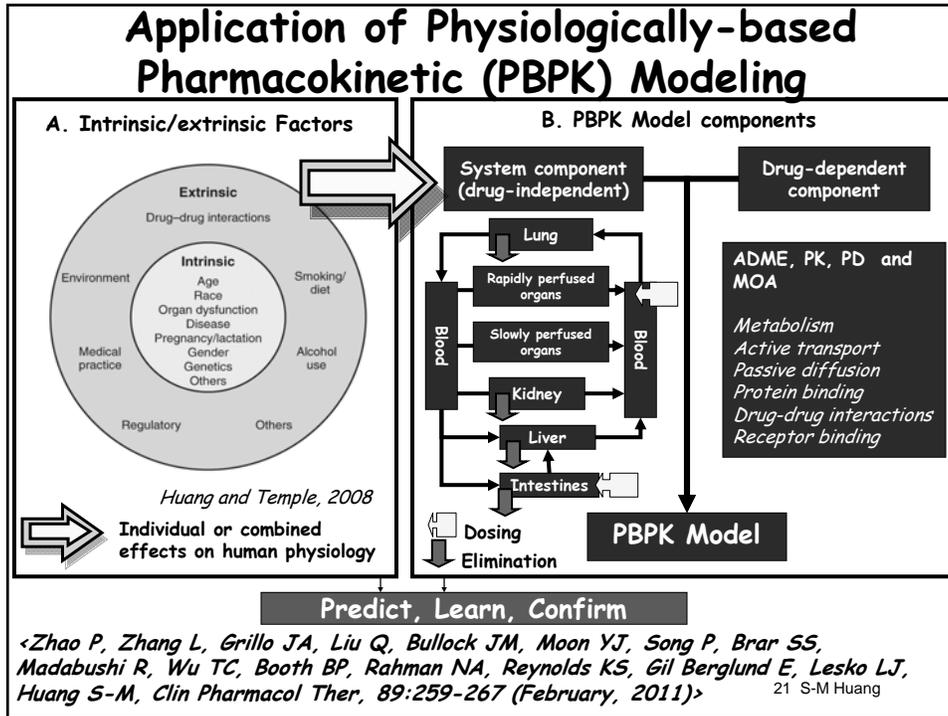
— EM Control      - - - EM + Inh.      — EM Control  
 — PM Control      - - - PM + Inh.      — PM Control



<Zhao P, Zhang L, Lesko, L, Huang S-M, LOL presentation, Merrimac, WI, September 2009>

→ **Which population needs dose adjustment?**  
 (e.g., atroxetine lableing)

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# Labeling Example (3)

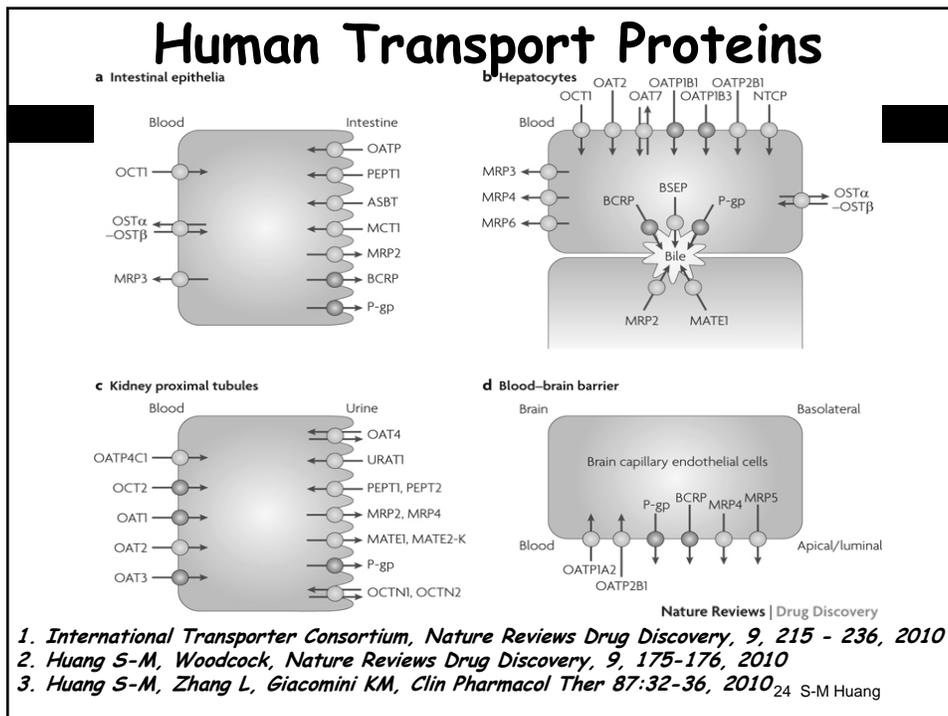
## Statins & Transporters

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## Drugs Withdrawn from the US Market due to Safety Concerns

Withdrawn	Approved	Drug name	Use	Risk
			<b>CYP/transporter inhibitor</b>	
1998	1997	Mibefradil	High blood pressure/Chronic stable angina	Torsades de Pointes; Drug-drug interactions
1998	1997	Bromfenac	NSAID	Acute liver failure
1998	1985	Terfenadine	Antihistamine	Torsades de Pointes; Drug-drug interactions
1999	1988	Astemizole	Antihistamine	Torsades de Pointes; Drug-drug interactions
1999	1997	Grepafloxacin	Antibiotics	Torsades de Pointes
2000(2002)*	2000	Alosetron*	Irritable bowel syndrome in women	Ischemic colitis; complications of constipation
2000	1993	Cisapride	Heartburn	Torsades de Pointes; Drug-drug interactions
2000	1997	Troglitazone	Diabetes	Acute liver failure
2001	1997	Cerivastatin	Cholesterol lowering	Rhabdomyolysis; Drug-drug interactions
2001	1999	Rapacuronium	Anesthesia	Bronchospasm
2003	1993	Levomethadyl	Opiate dependence	Fatal arrhythmia
			<b>CYP/transporter substrate</b>	
2004	1999	Rofecoxib	Pain relief	
2005	2001	Valdecoxib	Pain relief	
2005(2006)*	2004	Natalizumab*	Multiple sclerosis	Brain infection
2005	2004	99m Tc**	Diagnostic aid	Cardiopulmonary arrest
2005	1975	Pemoline	ADHD	Liver failure

*Huang, S-M, et al, "Principles of Gender-Specific Medicine", Ed., Legato M, Academic Press, 2004, pp 848-859 ; Huang, S-M, et al, Toxicology Mechanisms and Methods, 16: 89-99, 2006*



Applications of pharmacogenomics in drug development and regulatory review- recent relabeling of drug products OPRU meeting, March 28, 2011, Bethesda, MD

## Significant Drug Interactions

**Table 1 Selected transporter-mediated clinical significant drug-drug interactions**

Gene	Aliases	Tissue	Function	Interacting drug	Substrate (affected drug)	Changes in substrate plasma AUC (AUC ratios)
<b>ABC transporters of clinical importance in the absorption, disposition, and excretion of drugs</b>						
ABCG1	P-gp, MDR1	Intestinal enterocyte, kidney proximal tubule, hepatocyte (canalicular), brain endothelia	Efflux	Dronedaron Quinidine Ranolazine Tipranavir/ritonavir Tipranavir/Ritonavir	Digoxin Digoxin Digoxin Loperamide Saquinavir/ritonavir	2.6-fold 1.7-fold 1.6-fold 0.5-fold 0.2-fold
ABCG2	BCRP	Intestinal enterocyte, hepatocyte (canalicular), kidney proximal tubule, brain endothelia, placenta, stem cells, mammary gland (lactating)	Efflux	GF120918	Topotecan	2.4-fold
<b>SLC transporters of clinical importance in the disposition and excretion of drugs</b>						
SLCO1B1	OATP1B1, OATP-C, OATP2, LST-1	Hepatocyte (sinusoidal)	Uptake	Lopinavir/ritonavir Cyclosporine Rifampin (single dose) Cyclosporine	Bosentan Pravastatin Glyburide Rosuvastatin	5-48 fold <sup>a</sup> 9.9-fold 2.3-fold 7.1-fold <sup>b</sup>
SLCO1B3	OATP1B3, OATP-8			Cyclosporine	Pitavastatin	4.6-fold
SLC22A2	OCT2	Kidney proximal tubule	Uptake	Lopinavir/ritonavir Cimetidine Cimetidine Cimetidine	Rosuvastatin Dofetilide Pindolol Metformin	2.1-fold 1.5-fold 1.5-fold 1.4-fold
SLC22A6	OAT1	Kidney proximal tubule, placenta	Uptake	Probenecid Probenecid Probenecid	Cephadrine Cidofovir Acyclovir	3.6-fold 1.5-fold 1.4-fold
SLC22A8	OAT3	Kidney proximal tubule, choroid plexus, brain endothelia	Uptake	Probenecid	Furosemide	2.9-fold

The transporters listed are the likely transporters, however, because the studies are *in vivo*, it is not possible to assign definitively specific transporters to these interactions. ABC, adenosine triphosphate-binding cassette; AUC, area under the curve; BCRP, breast cancer resistance protein; LST, liver-specific transporter; MDR, multidrug resistance; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; P-gp, p-glycoprotein; SLC, solute carrier.

<sup>a</sup>Minimum pre-dose plasma level ( $C_{Trough}$ ) data from day 4 (48-fold), day 10 (fivefold) after coadministration. <sup>b</sup>Interaction could be partly mediated by BCRP.

Modified from ref. 2 and other sources.

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**Zhang L, Huang S-M, Lesko LJ, Clin Pharmacol Ther 89(4): 481-484 (April 2011) 25 S-M Huang**

**Development of a Drug Transporter Database: UCSF-FDA TransPortal**

Kari M. Morrissey<sup>1</sup>, Chris Wen<sup>1</sup>, Susan J. Johns<sup>2</sup>, Shiew-Mei Huang<sup>3</sup>, Lei Zhang<sup>3</sup>, Kathleen M. Giacomini<sup>1</sup>

<sup>1</sup> Department of Bioengineering and Therapeutic Sciences and <sup>2</sup> Pharmaceutical Chemistry, University of California, San Francisco, CA  
<sup>3</sup> Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

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**ABSTRACT**

Drug transporters are key determinants of absorption, distribution and elimination therapeutic and adverse drug effects. Though a large body of data are available on developers, regulatory agencies and academic scientists about transporters important transporters from the ATP-Binding Cassette (ABC) and Solute Carrier (SLC) transporter expression levels, subcellular localization, inhibitors, substrates and clinical drug-drug Path to build a public drug transporter database to serve as a central resource for drug transporters.

**DATABASE SCREENSHOTS**

Drug Transporters in Selected Organs & Direction of Trans

**Syncytiotrophoblast**

Localization Information  
qPCR Expression Data

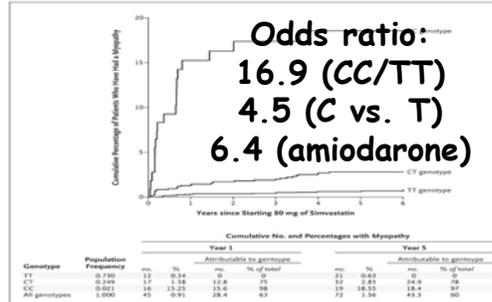
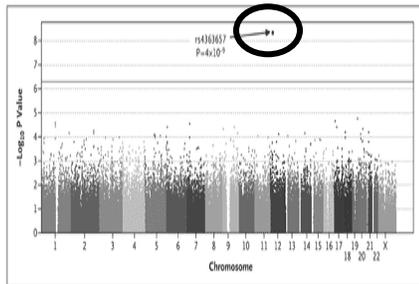
**Localization Information**

<http://bts.ucsf.edu/fdatransporter/>

**Morrissey KM, et al, Clin Pharmacol Ther 89(1): 540, PII-06 (February 2011) 26 S-M Huang**

# Pharmacogenetics (simvastatin) - Myopathy -

## Genomewide Association



1. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, according to SLCO1B1 rs4149056 Genotype (c.521T>C)
2. Association replicated in another 40 mg group

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The SEARCH Collaborative Group. *N Engl J Med* 2008; 359: 789-799 (UK)

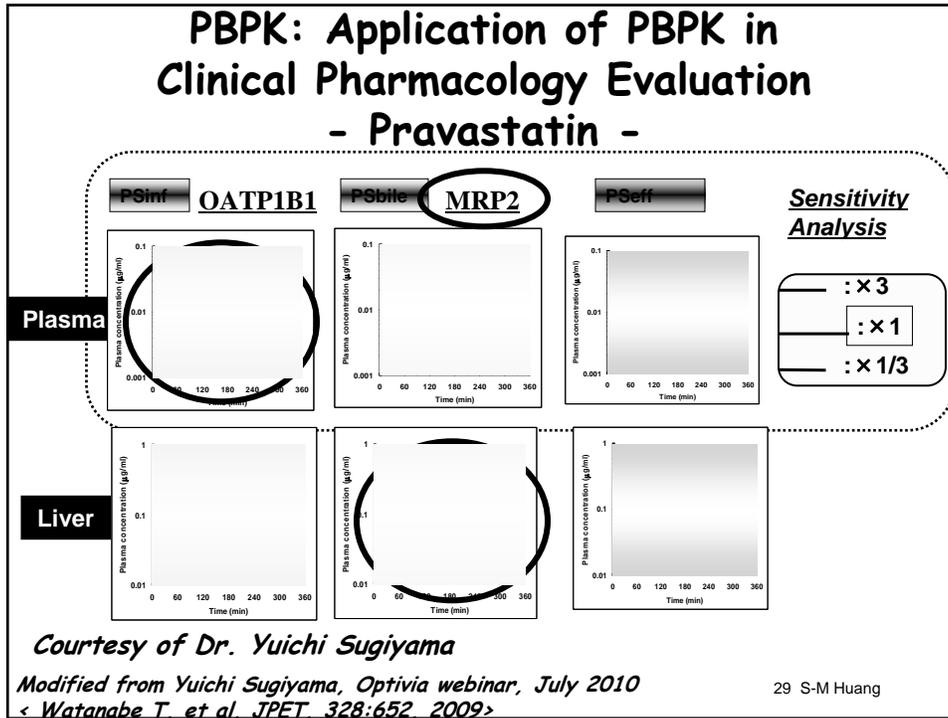
## OATP1B1 Inhibition

"Eltrombopag is an inhibitor of OATP1B1 transporter. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 (e.g., rosuvastatin) and consider reduction of the dose of these drugs."

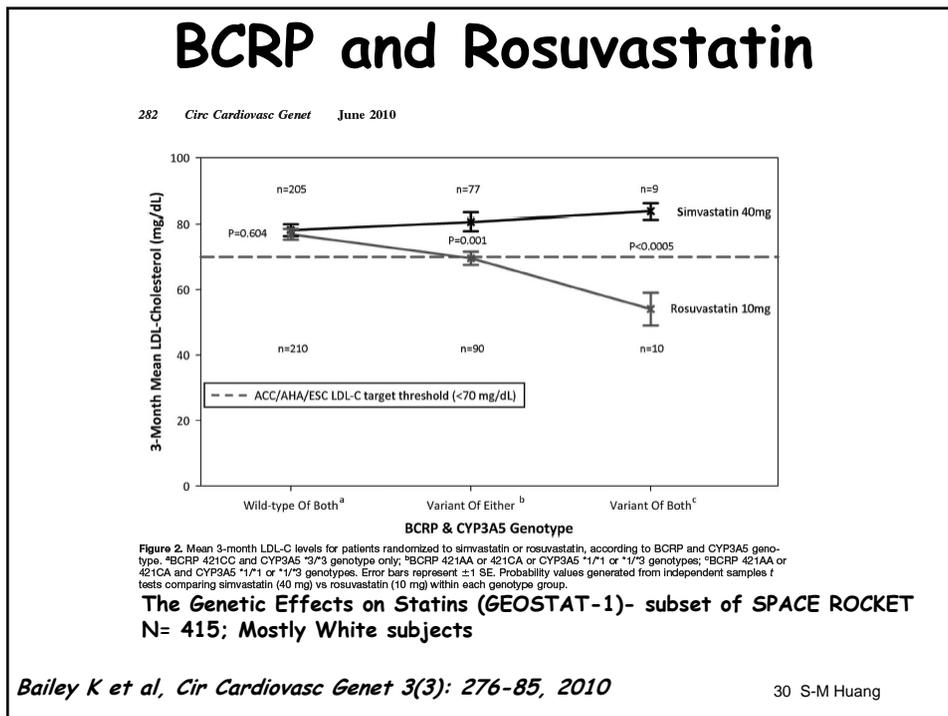
The following were listed as OATP1B1 substrates:  
"benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin"

*Drugs at the FDA (Promacta, November 2008, "Highlights" and "Drug Interactions")*  
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.La>  
*bel\_ApprovalHistory*  
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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# Labeling Example (4)

## Codeine & Metabolism

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**  
These highlights do not include all the information needed to use Codeine sulfate tablets safely and effectively. See full prescribing information for Codeine sulfate tablets.

**Codeine sulfate tablets for oral use**      CII  
Initial U.S. Approval: 1950

**INDICATION AND USAGE**  
Codeine sulfate is an opioid analgesic indicated for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. (1)

**DOSAGE AND ADMINISTRATION**  
Usual adult dosage: 15 to 60 mg up to every 4 hours as needed. (2)  
Doses above 60 mg may fail to give commensurate pain relief, and may be associated with an increased incidence of undesirable side effects. (2)

**DOSAGE FORMS AND STRENGTHS**  
Codeine sulfate tablets: 15 mg, 30 mg, and 60 mg. (3)

**CONTRAINDICATIONS**

- Hypersensitivity to codeine sulfate or any component of the product. (4)
- Respiratory depression in the absence of resuscitative equipment (4)
- Acute or severe bronchial asthma or hypercarbia (4)
- Paralytic ileus (4)

**WARNINGS AND PRECAUTIONS**

- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.1)
- Controlled substance: Codeine sulfate is a Schedule II controlled substance with an abuse liability similar to other opioids. (5.2)
- CNS effects: Additive CNS depressive effects, including respiratory depression, hypotension, profound sedation, coma, or death when used in conjunction with alcohol, other opioids, or illicit drugs. (5.3)
- Elevation of intracranial pressure: May be markedly exaggerated in the presence of head injury, other intracranial lesions. (5.4)
- Hypotensive effect: Increased risk with compromised ability to maintain blood pressure. (5.5)
- Antidepressants: May cause excessive sedation, acute hypotension and excessive anticholinergic effects. Use with caution in reduced dosages to persons receiving MAO inhibitors or tricyclic antidepressants. (7.4)
- Metabolic enzymes: Concomitant use of cytochrome P-450 2D6 and 3A4 **strong inducers or inhibitors may result in an altered response to codeine.** Monitor analgesic activity and adverse drug reactions. (7.5)

**USE IN SPECIFIC POPULATIONS**

- Pregnant patients (8.1), Labor and delivery (8.2), Nursing mothers (8.3), Geriatric patients (8.5), Renal impairment (8.6), Hepatic impairment (8.7): Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects. The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby.

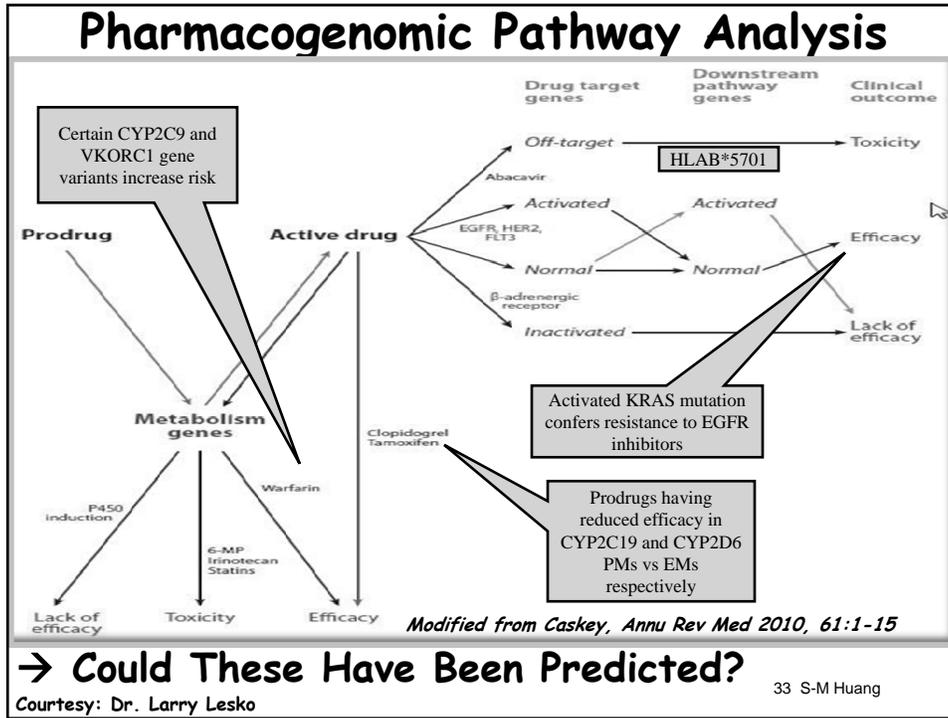
See 17 for PATIENT COUNSELING INFORMATION

Revised: 7/2009

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/022402s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022402s000lbl.pdf)

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## FDA Guidance for Industry

### Guidance for Industry

#### Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-501), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lawrence Lesko at 301-796-1565 or Shiew-Mei Huang at 301-796-1541, or (CDER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800, or Changning Hauschild at 301-827-3047, or (CDRH) Frances Kalish at 301-796-5408.

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<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>

**Send in your comments**

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)

February 2011  
Clinical Pharmacology

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Applications of pharmacogenomics in drug development and regulatory review- recent relabeling of drug products OPRU meeting, March 28, 2011, Bethesda, MD

## Summary

- Individual variations in drug response may be attributed to various intrinsic and extrinsic factors; genetics is one of the factors and needs to be considered along with other factors
- It is important to assess safety, effectiveness and dose-exposure response in various subgroups during drug development and apply the results of exposure-response to better define optimum individual dosing regimens

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## Summary (2)

- As the pharmacogenetics/ pharmacogenomics information becomes available, its association with the safe and effective use of drugs has been incorporated in the drug label and some tests have been incorporated into clinical practice
- Challenges need to be continued to be addressed in the translation of genetic information to product labeling and clinical practice

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## Summary (3)

- There is an urgent need for pediatric information
- Collaboration is key to future successes
- Application of modeling/simulation (e.g., PBPK) is critical to optimal study design and to addressing issues related to multiple inhibitors/multiple patient factors
- Various guidance documents in development will discuss premarketing evaluation of pharmacogenetics in early phase clinical studies, drug interactions, others

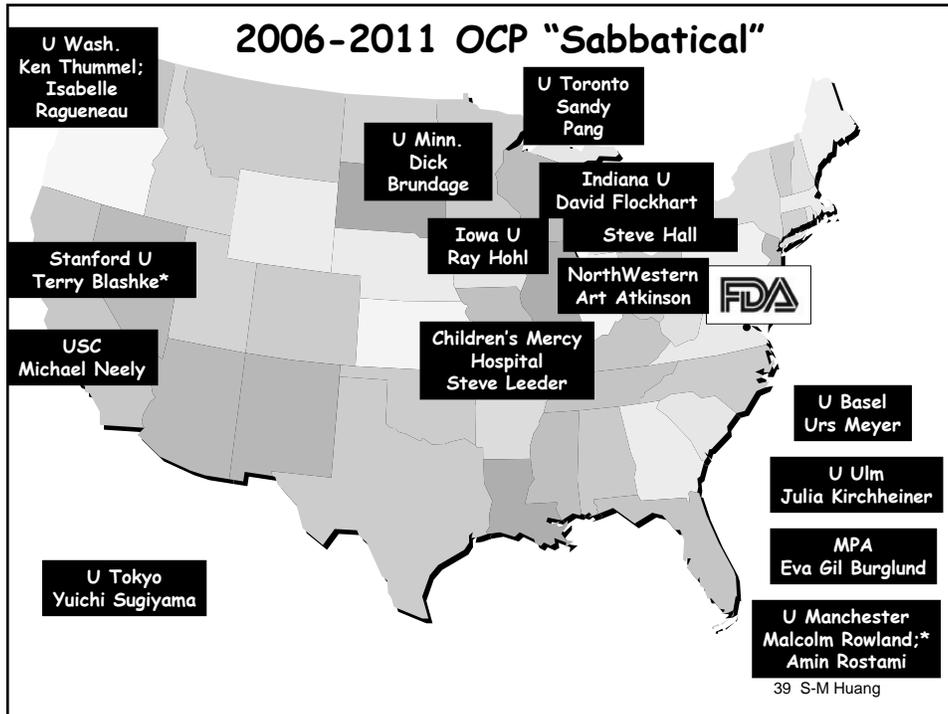
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## Acknowledgement

- Office of Clinical Pharmacology (OCP)/OTS



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## References

FDA Drug Development and Drug Interactions Website;  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>

Genomics at the FDA:  
<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm>

Drugs@FDA;  
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

Clinical Pharmacology Guidance for industry:  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>

Pediatric Study Review:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.htm>

