

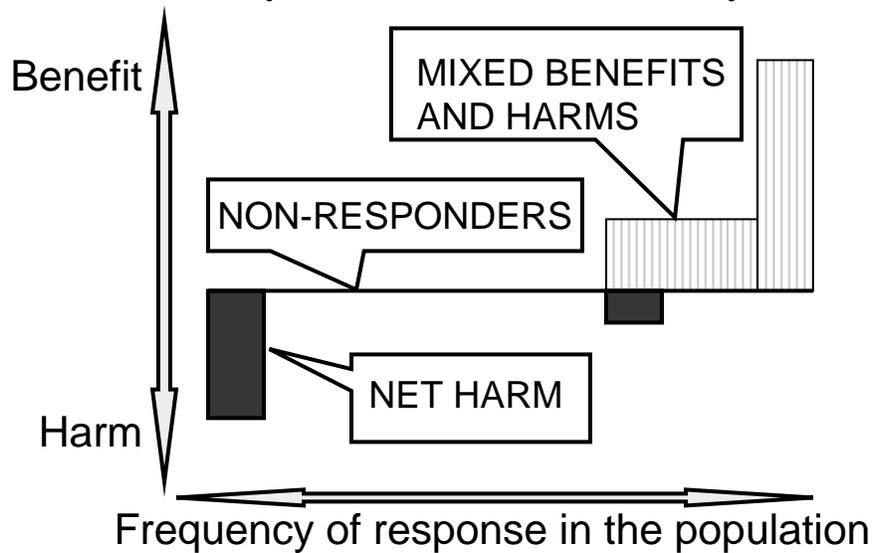
VCU AAPS Student Chapter
March 8, 2011, Richmond, VA

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

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OTS, CDER, FDA
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1

Variability of Patient Response

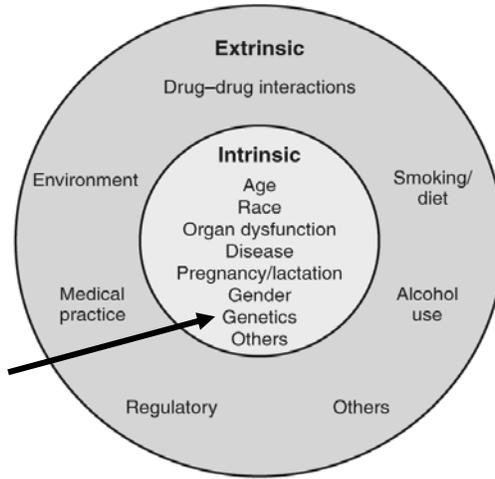


Barbara Evans, *Notre Dame Law Review* 85(2):419-524, 2010
http://www.nd.edu/~ndlrev/archive_public/85ndlr2/Evans.pdf

2

Factors Affecting Drug Exposure/Response

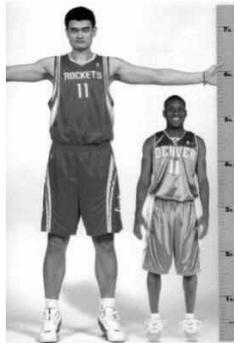
**Genetics
is one of
the
factors!**



<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>



**Dose Adjustment in Patients
with Various Factors
- based on exposure changes -**

4

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

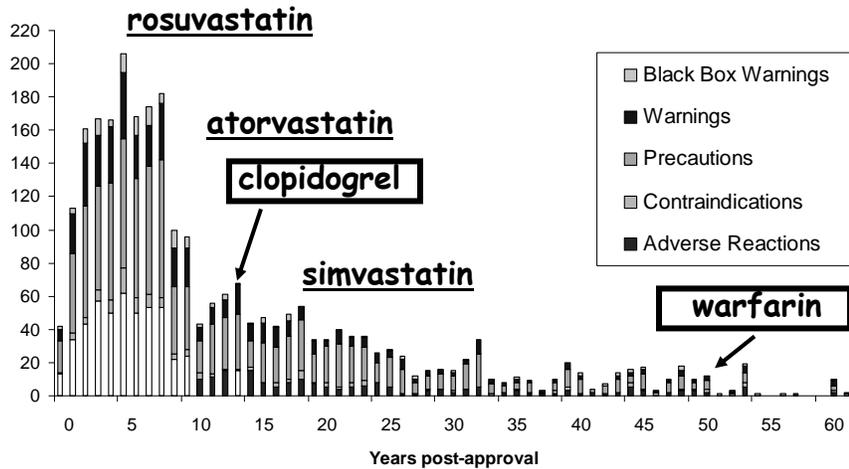
→ Current practice: Adjust the dose to achieve similar systemic exposure → Only the first step

<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

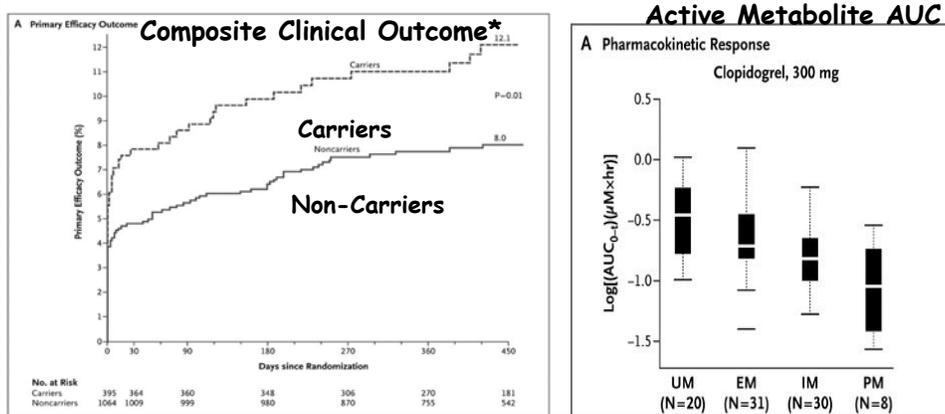
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Labeling Example (1)

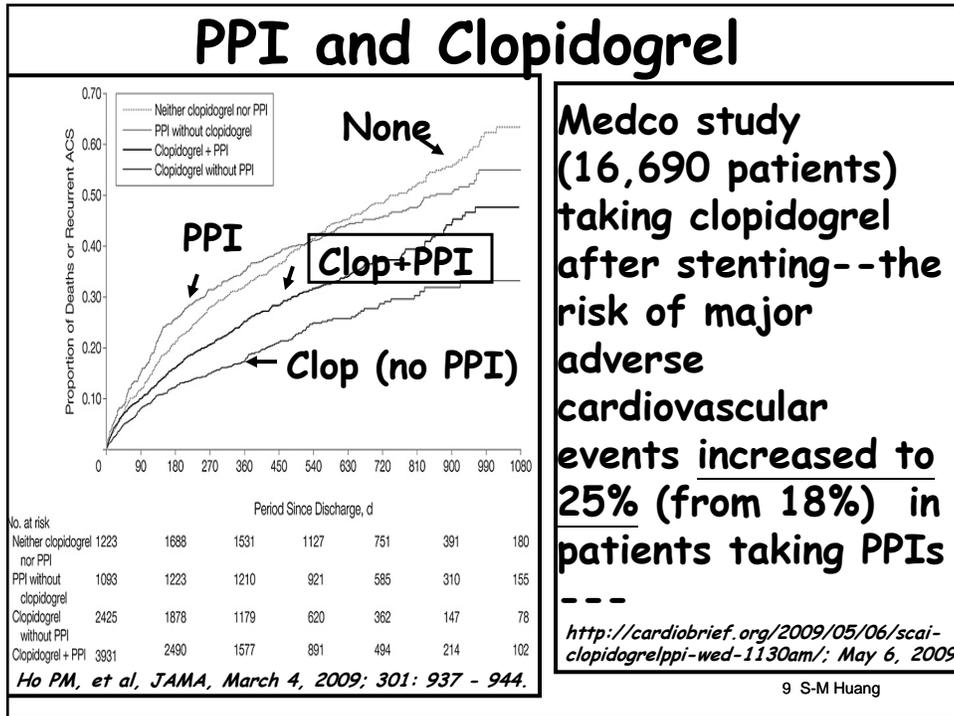
Updating labeling
 Genetic Data \leftrightarrow
 Drug Interaction warning

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CYP2C19 and Clopidogrel



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



FDA Actions

January 2009: Early communication
 Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel.....

January 26, 2009
http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

May 2009: Labeling changes
 CYP2C19 poor metabolizer status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolizers has yet to be determined

Drugs at the FDA (Plavix, "DOSAGE and ADMINISTRATION-Pharmacogenetics", & "PRECAUTIONS- Drug Interactions)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020839s040lbl.pdf
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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FDA U.S. Food and Drug Administration A-Z Index Search GO

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

Safety Share Email this page Print this page Change Font Size

Home > Safety > MedWatch The FDA Safety Information and Adverse Event Reporting Program > Safety Information

MedWatch The FDA Safety Information and Adverse Event Reporting Program

Safety Information

Safety Alerts for Human Medical Products

- 2009 Safety Alerts for Human Medical Products
- 2008 Safety Alerts for Human Medical Products
- 2007 Safety Alerts for Human Medical Products
- 2006 Safety Alerts for Human Medical Products
- 2005 Safety Alerts for Human Medical Products
- 2004 Safety Alerts for Human Medical Products
- 2003 Safety Alerts for Human Medical Products
- 2002 Safety Alerts for Human Medical Products
- 2001 Safety Alerts for Human Medical Products

Clopidogrel (marketed as Plavix) and Omeprazole (marketed as Prilosec) - Drug Interaction

Audience: Cardiovascular healthcare professionals, pharmacists

[Posted 11/17/2009] FDA notified healthcare professionals of new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole. Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

Other drugs that are expected to have a similar effect and should be avoided in combination with clopidogrel include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

Recommendations for healthcare professionals are provided in the "Information for Healthcare Professionals" sheet.

[11/17/2009 - Information for Healthcare Professionals - FDA]
 [11/17/2009 - Public Health Advisory - FDA]
 [11/17/2009 - Follow-Up to January 2009 Early Communication - FDA]

Previous Medwatch Alert:
 [01/26/2009] Clopidogrel bisulfate (marketed as Plavix) Early Communication

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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/2010/020839s042bl.pdf
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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August 2010 Relabeling

2.3 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response [see *Clinical Pharmacology (12.5)*], an appropriate dose regimen for this patient population has not been established.

2.4 Use with Proton Pump Inhibitors (PPI)

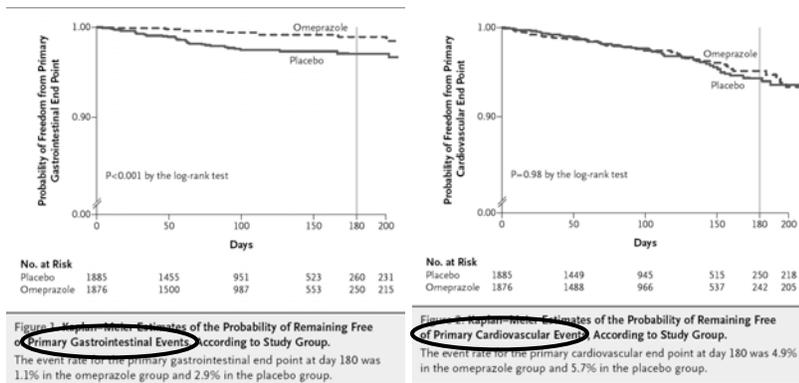
Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of Plavix. Avoid using omeprazole concomitantly or 12 hours apart with Plavix. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.1)* and *Clinical Pharmacology (12.5)*].

Drugs at the FDA

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s048lbl.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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Clinical Utility

Editorial

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

What Is Clinical Utility and Why Should We Care?

L J Lesko¹, I Zineh¹ and S-M Huang¹

¹Office 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)

State of the Art

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

Assessing the Clinical Utility of Diagnostics Used in Drug Therapy

J Woodcock¹

¹Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

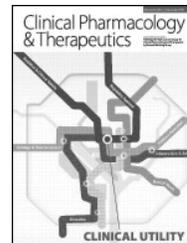
State of the Art

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

Enrichment of Clinical Study Populations

R Temple¹

¹Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA



December 2010

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Labeling Example (2)

Warfarin

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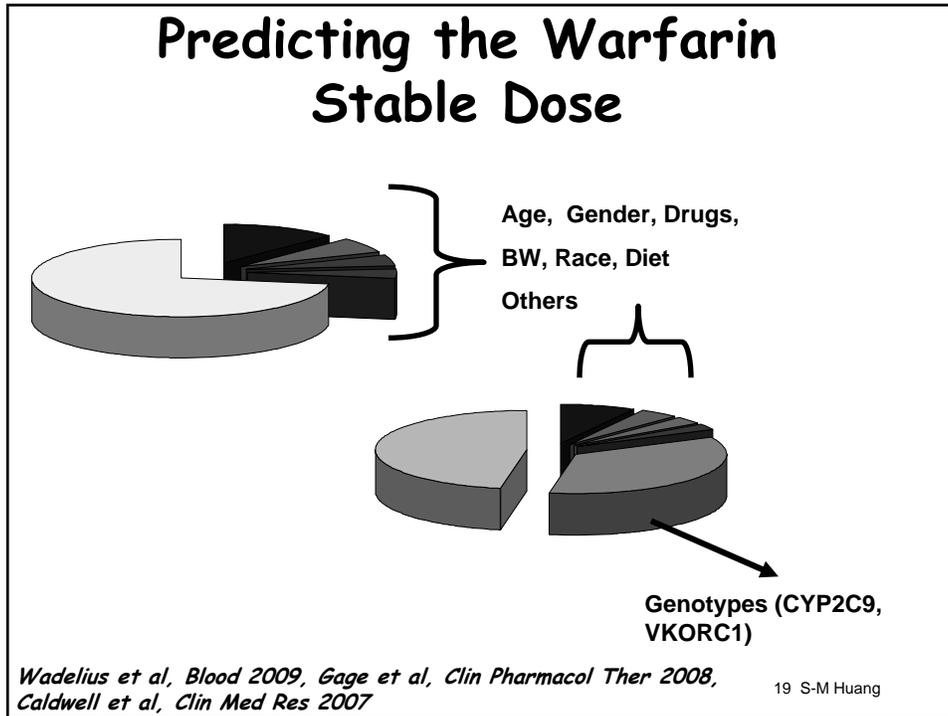
Clinical Importance of Risk: Warfarin Eludes Patients Who Need It the Most

- **Underutilization of warfarin and high rate of noncompliance due to physician and patient fear of bleeding**
 - Prescribed to only 2/3 of appropriate candidates
- **Other reasons for not starting warfarin treatment in A Fib patients (n = 300)**
 - 28% prefer treatments without INR monitoring
 - 20% fear of bleeding
 - 18% would have difficulty to get INR monitored

Choudhry et al, Br Med J, 2006, Patient Record Review on File at Astra-Zeneca, White et al, Am J Med 1999, Wolf, Arch Int Med 1987, Birman-Deych et al, Stroke 2006

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<Courtesy of Myong-Jin Kim, CDER presentation, September 2009>



Frequency of VKORC1

-1639 G>A	AA	AG	GG
Caucasians (N=297)	19%	56%	25%
Spanish (N=105)	32%	40%	28%
Chinese (N=104)	80%	18%	2%
African Americans (N=159)	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> 20 S-M Huang

Public Debates

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

See ARTICLES page 206

POINT/COUNTERPOINT

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

LJ Lesko¹

Warfarin and Pharmacogenomic Testing: The Case for Restraint

DA Garcia¹

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 Laveaux

Opponents Want More Data
Warfarin Debate, page 1

AACC warfarin Debate: Hallworth, Huang, Eby, Linder, Jaffer, July 28, 2008
http://www.aacc.org/publications/clin/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/2010/009218s108lbl.pdf
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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Warfarin Drug Interactions -Jan 2010 Labeling

Specific Drugs Reported		
acetaminophen	fenofibrate	oxymetholone
alcohol†	fenoprofen	pantoprazole
allopurinol	fluconazole	paroxetine
aminosalicylic acid	fluorouracil	penicillin G, intravenous
amiodarone HCl	fluoxetine	pentoxifylline
argatroban	flutamide	phenylbutazone
aspirin	fluvastatin	phenytoin†
atenolol	fluvoxamine	piperacillin
atorvastatin†	gefitinib	piroxicam
azithromycin	gemfibrozil	pravastatin†
bivalirudin	glucagon	prednisone†
capecitabine	halothane	propafenone
cefamandole	heparin	propoxyphene
cefazolin	ibuprofen	propranolol
cefoperazone	ifosfamide	propylthiouracil†
cefotetan	indomethacin	quinidine
cefoxitin	influenza virus vaccine	quinine
ceftriaxone	itraconazole	rabeprazole
celecoxib	ketoprofen	ranitidine†
cerivastatin	ketorolac	rofecoxib
chenodiol	lansoprazole	sertraline
chloramphenicol	lepirudin	simvastatin
chloral hydrate†	levamisole	stanozolol
chlorpropamide	levofloxacin	streptokinase
cholestyramine†	levothyroxine	sulfamethizole
cimetidine	liothyronine	sulfamethoxazole
ciprofloxacin	lovastatin	sulfapyrazole
cisapride	mefenamic acid	sulfisoxazole
clarithromycin	methimazole†	sulindac
clofibrate	methylidopa	tamoxifen
COUMADIN overdose	methylphenidate	tetracycline
cyclophosphamide†	methylsalicylate ointment (topical)	thyroid
danazol	metronidazole	ticarcillin
dextran	miconazole (intravaginal, oral, systemic)	ticlopidine
dextrothyroxine	morizine hydrochloride†	tissue plasminogen activator (t-PA)
diazoxide	nalidixic acid	tolbutamide
diclofenac	naproxen	tramadol
dicumarol	neomycin	trimethoprim/sulfamethoxazole
diflunisal	norfloxacin	urokinase
disulfiram	ofloxacin	valdecoxib
doxycycline	olsalazine	valproate
erythromycin	omeprazole	vitamin E
esomeprazole	oxandrolone	zafirlucast
ethacrynic acid	oxaprozin	zileuton
ezetimibe		

† indicates medications affecting blood coagulation which may modify hemostasis

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s1081bl.pdf

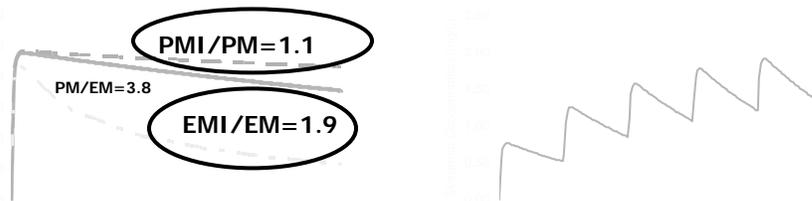
Genotype- Specific Inhibition Effect

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 _{int} (uL/min/pmol CYP)	0.034	0.005

Using SimCYP® V8.20

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



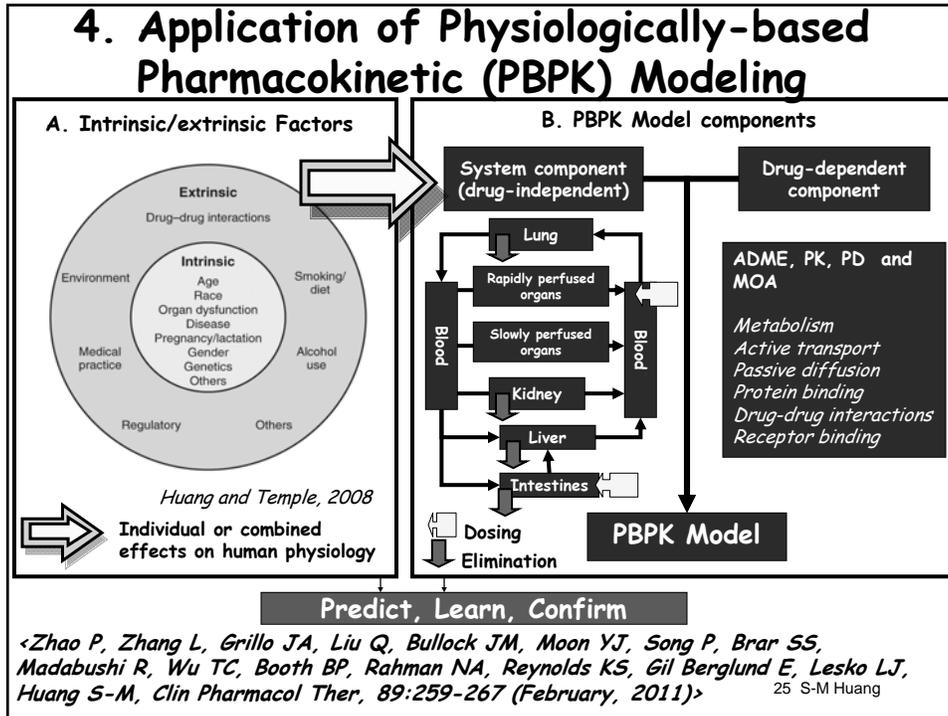
Substrate

Inhibitor

<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
			CYP/transporter inhibitor	
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
2004	1999	Rofecoxib	Pain relief	
2005	2001	Valdecocixib	Pain relief	
			CYP/transporter substrate	
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

Pharmacogenetics (simvastatin) - Myopathy -

Genomewide Association

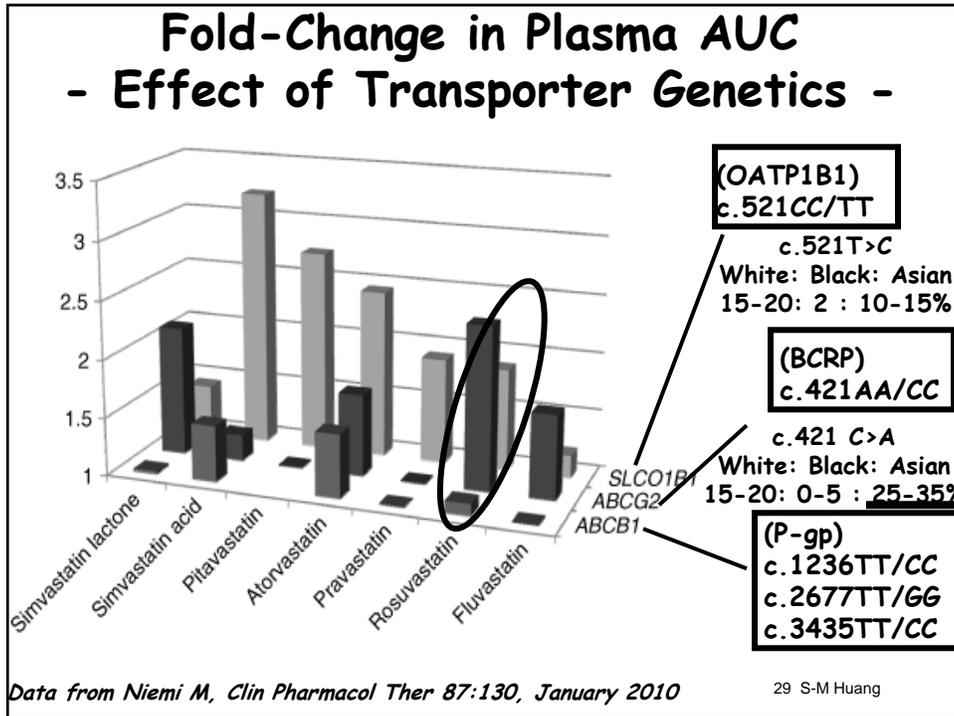
Odds ratio:
16.9 (CC/TT)
4.5 (C vs. T)
6.4 (amiodarone)

Genotype	Population Frequency	Year 1		Year 5	
		Attributable to genotype	% of total	Attributable to genotype	% of total
TT	0.740	12	0.34	0	0.03
CT	0.249	12	1.28	10	1.23
CC	0.011	14	13.25	13.4	39
All genotypes	1.000	48	0.91	14.4	13.3

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)



Dosing Based on Transporter Genetics? - Are We Ready? -

SLCO1B1 c.521T>C genotype

	TT	TC	CC	Normal dose range*
Simvastatin	80 mg	40 mg	20 mg	5-80 mg/day
Pitavastatin	4 mg	2 mg	1 mg	1-4 mg/day
Atorvastatin	80 mg	40 mg	20 mg	10-80 mg/day
Pravastatin	80 mg	40 mg	40 mg	10-80 mg/day
Rosuvastatin	40 mg	20 mg	20 mg	5-40 mg/day
Fluvastatin	80 mg	80 mg	80 mg	20-80 mg/day

Data from Niemi M, Clin Pharmacol Ther 87:130, January 2010 30 S-M Huang

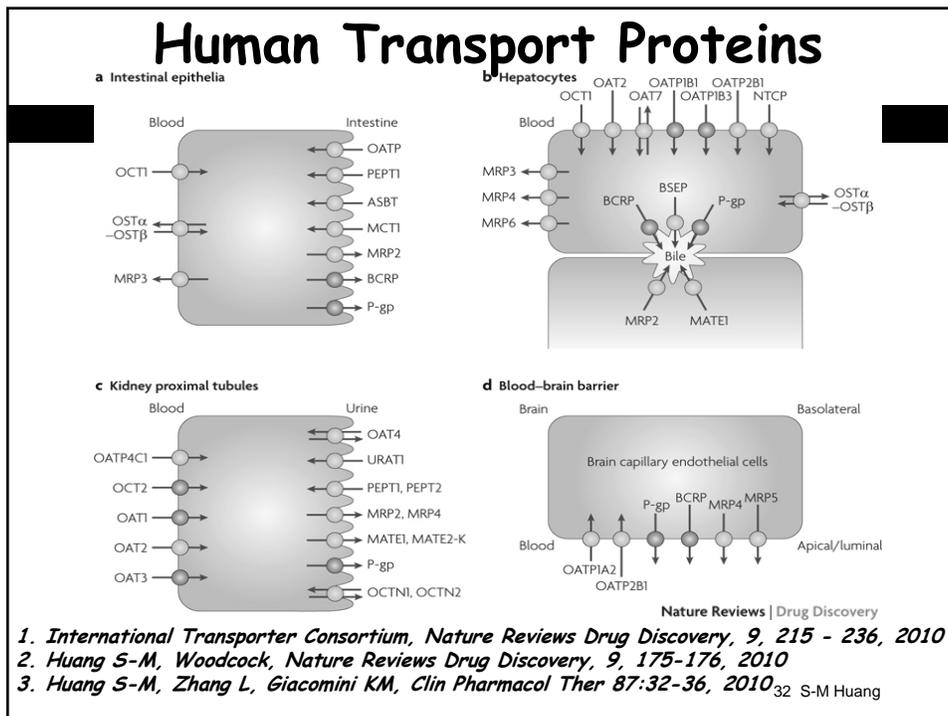
OATP1B1 Inhibition

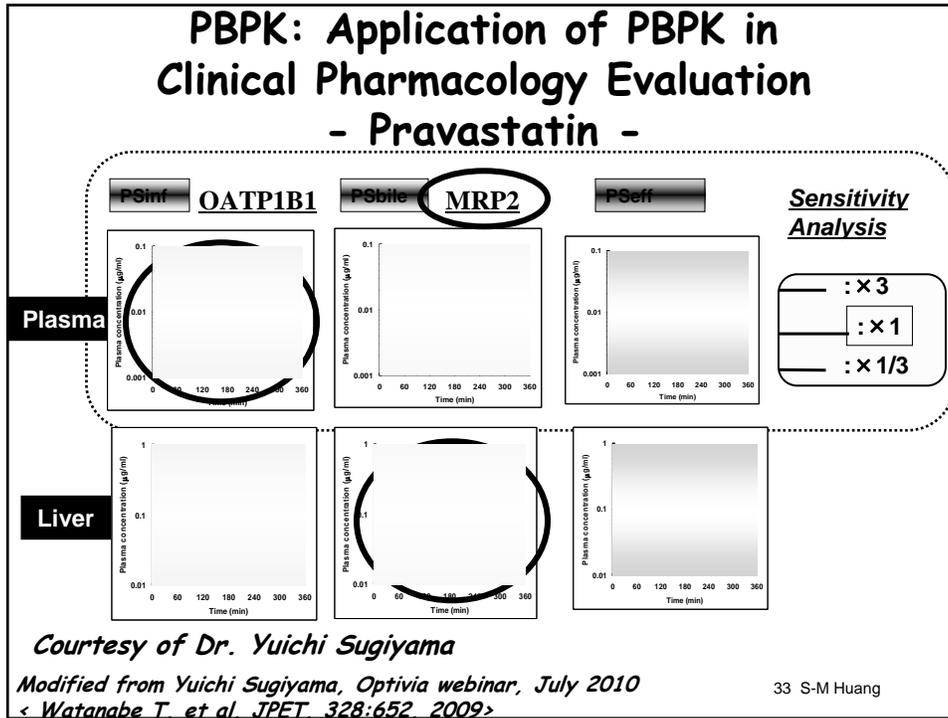
"Eltrombopag is an inhibitor of OATP1B1 transporter. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 (e.g., rosuvastatin) and consider reduction of the dose of these drugs."

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

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Labeling Example (4)

Abacavir & HLA genotyping

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Abacavir Hypersensitivity & HLA Genotyping

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*
	no. of patients/total no. (%)		
Clinically diagnosed			
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)
Immunologically confirmed			
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)

Boxed Warning

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir.

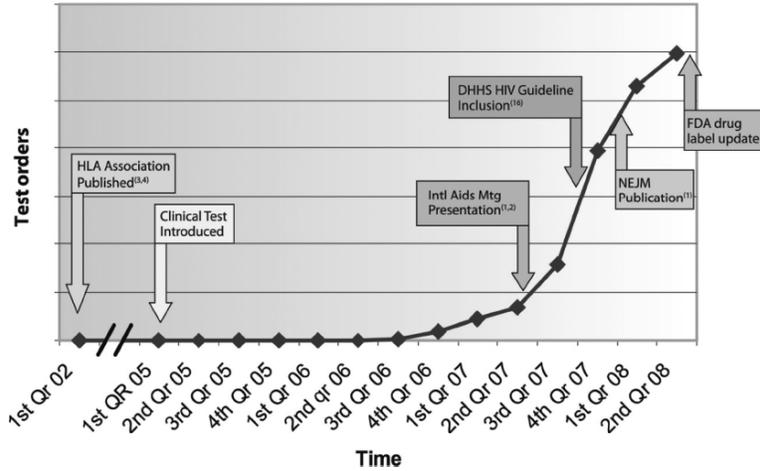
Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction.

Drugs at the FDA (Ziagen, July 2008, "Highlights" and "Boxed Warning")
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020977s019,020978s0221bl.pdf
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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Abacavir Hypersensitivity

HLA-B*5701 test orders by Qr 2002-2008



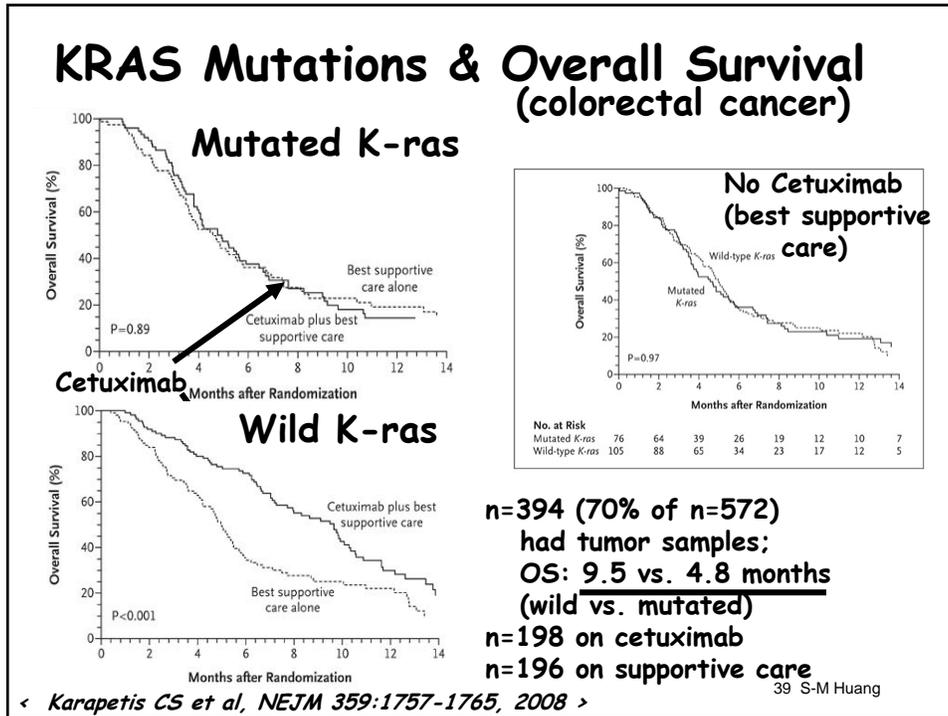
< Lai-Goldman, Faruki, *Genet Med* 2008; 10 (12): 874-878 >

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Labeling Example (5)

Cetuximab
&
KRAS

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INDICATIONS and USAGE

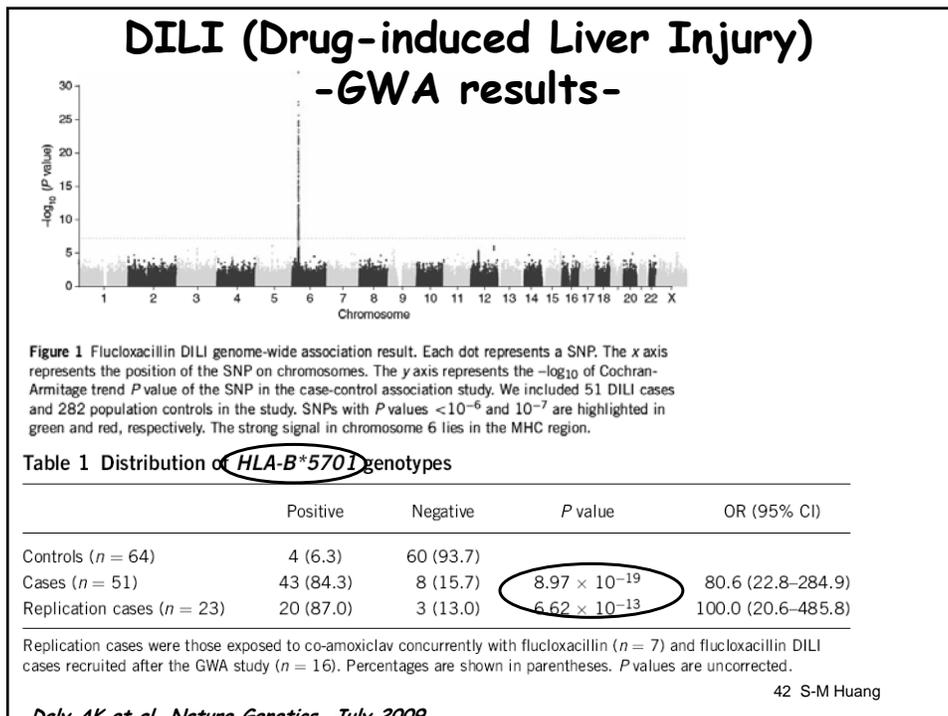
Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations.

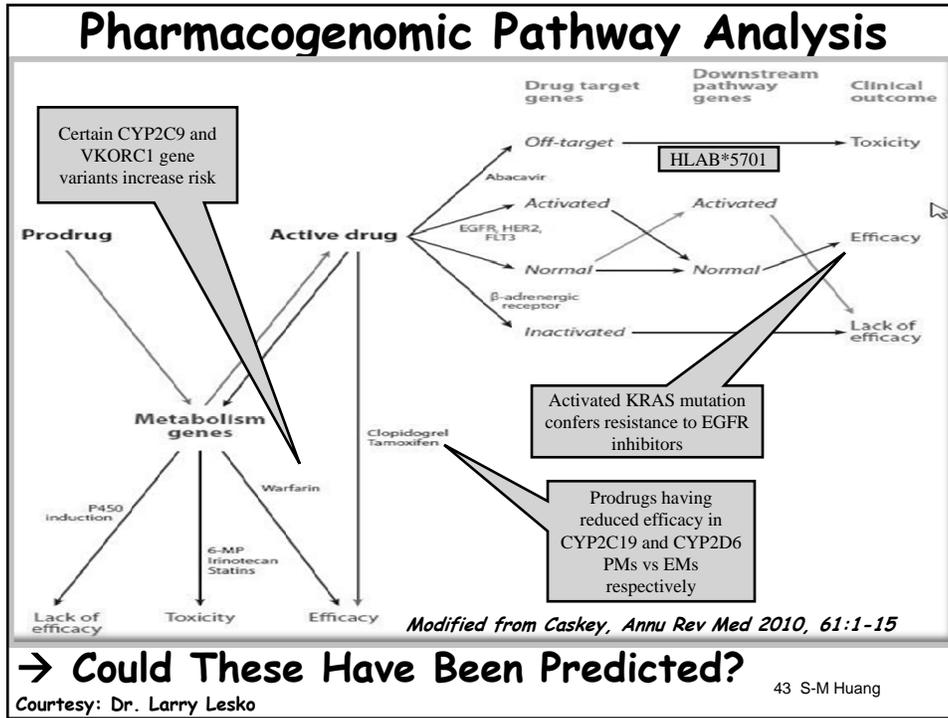
Drugs at the FDA (Erbitux, July 2009)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125084s167lbl.pdf

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

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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 Changming Hauschildt at 301-827-3047, or (CDRH) Frances Kalush at 301-796-5408.

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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)

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Clinical Pharmacology

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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)

- 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

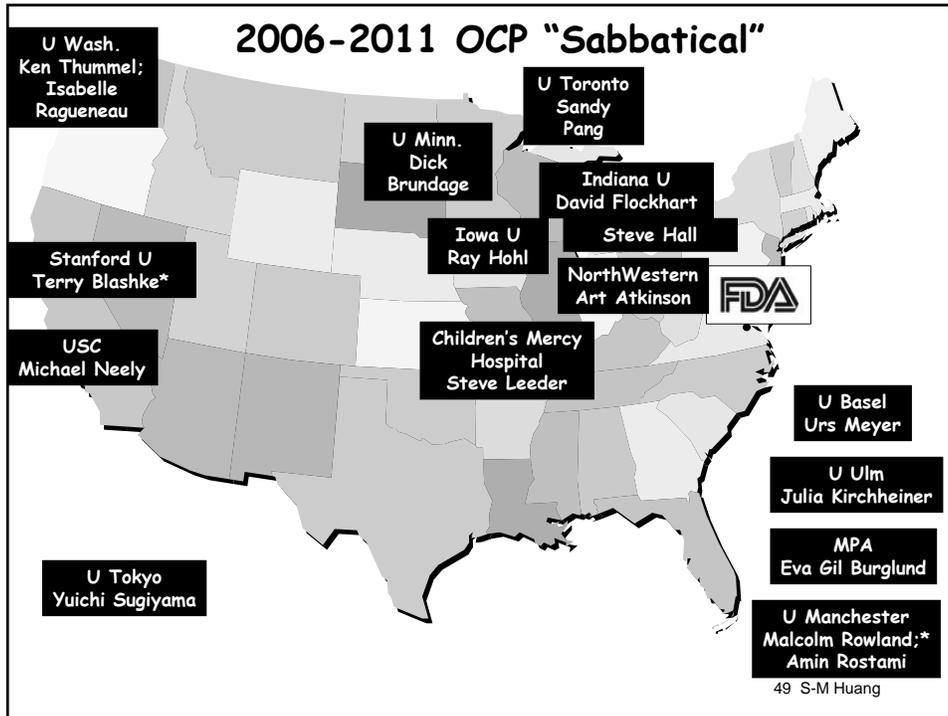
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