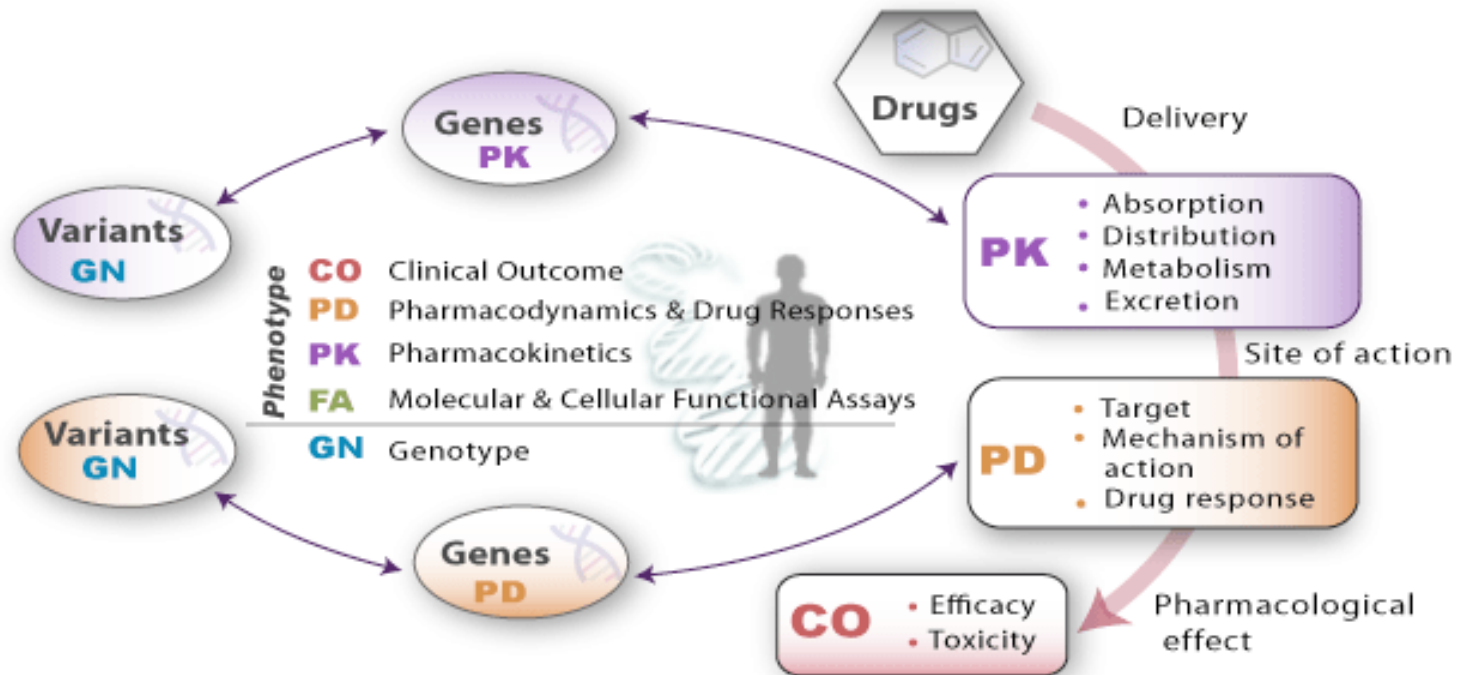


# Pharmacogenomics

<http://www.pharmgkb.org/>



Michelle Whirl-Carrillo, PhD

Department of Genetics

# Pharmacogenetics Defined

<http://www.pharmgkb.org/>

**“The role of genetics in drug responses.”**

**F. Vogel, 1959**



# January 15, 2001



PharmGKB -- <http://www.pharmgkb.org/>



# Genotype $\leftrightarrow$ Phenotype Associations

Relate genetic information (genotypes)

1. ATCGCCGGATACCTAGAGAC...
2. ATCGCCGGAGACCTAGAGAC...

to observable traits (phenotypes), e.g.

1. Responds well to cholesterol medication
2. Develops hepatotoxicity



# Pharmacogenetics: A Case Study

Individuals respond differently to the anti-leukemia drug 6-mercaptopurine.



Most people metabolize the drug quickly. Doses need to be high enough to treat leukemia and prevent relapses.



Others metabolize the drug slowly and need lower doses to avoid toxic side effects of the drug.

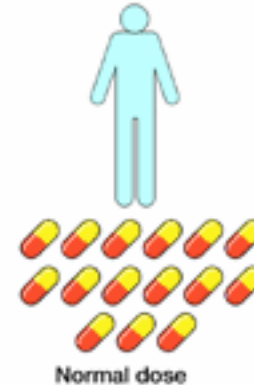


A small portion of people metabolize the drug so poorly that its effects can be fatal.

The diversity in responses is due to variations in the gene for an enzyme called TPMT, or thiopurine methyltransferase.



After a simple blood test, individuals can be given doses of medication that are tailored to their genetic profile.



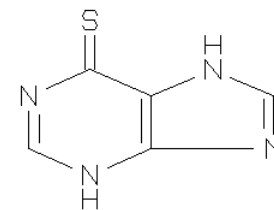
Normal dose



Dose for an extra slow metabolizer (TPMT deficient)

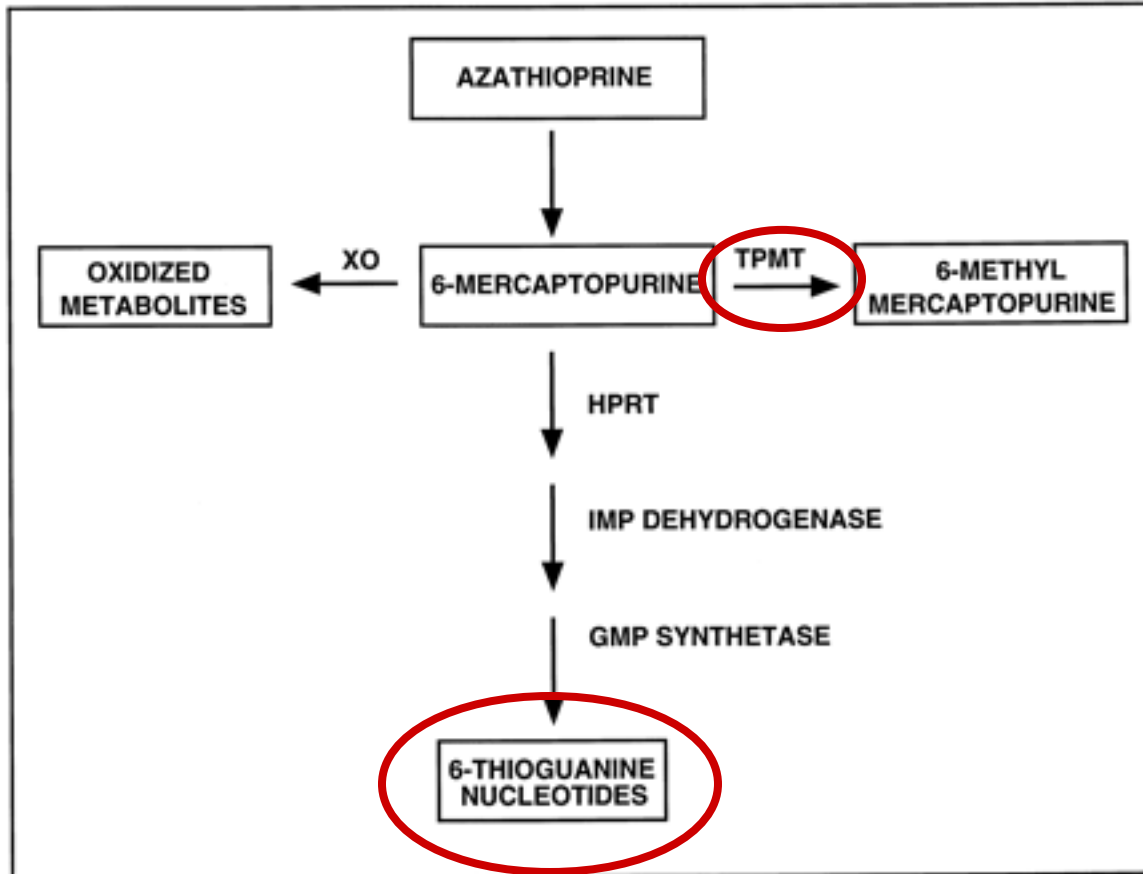
# Purine Analogs

- 6-mercaptopurine, 6-thioguanine, azathioprine
- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, after transplant
- Interferes with nucleic acid synthesis
- Therapeutic index limited by myelosuppression



# Metabolism of 6-MP

Weinshilboum (Mayo Clinic) 2001



# TPMT Effect on Thioguanines

- TPMT levels drastically affect thioguanine levels
- More TPMT = less thioguanines = less efficacy against disease
- Less TPMT = more thioguanines = increased risk of severe marrow toxicity
- Considerable variability in TPMT levels in population





# 6-MP and TPMT Story Summary

- Observation of clinical variability
  - toxicity
- Observation of cellular variability
  - TPMT activity, TGN concentrations
- Observation of genetic variability
  - base-pair variations (SNPs) in TPMT gene



# Pharmacogenetic Process

1. Identify variation in drug response
2. Associate it with genetic variation
3. Evaluate clinical significance
4. Develop screening tests
5. Individualize drug therapy



# Clinical Promise of PGx

- Focus treatment by identifying patients with genetic backgrounds likely to respond
- Reduce adverse events by predicting who is at risk
- A way to save drugs in the pipeline that are very effective only in subpopulations
- Better understanding of drug interactions



NEWS

# Preventing Toxicity With a Gene Test

To test or not to test? That is the question clinicians are asking about screening for genes that affect how the body metabolizes drugs

For more than 30 years, doctors have been using a powerful cell-killing compound to cure leukemia in children. This wonder drug—6-mercaptopurine (6MP), synthesized by the late Gertrude Elion and George Hitchings—has saved thousands of lives. But it has a dark side. Researchers discovered more than 20 years ago that it is extremely toxic in patients with an inherited metabolic flaw. The drug can accumulate rapidly, wiping out essential bone marrow and leading to infections.

About 8 years ago, teams led by William Evans of St. Jude Children's Research Hospital in Memphis, Ten-

community remains skeptical. Like other promised benefits of genomic medicine, this one has run into complaints about its cost (\$100 to \$300 per test), technical issues about how to recalibrate drug doses, and doubts about physicians' ability to under-



U.S. Food and Drug Administration (FDA) seems unlikely to recommend one.

The resistance has surprised champions of genomic medicine. A leader in pharmacogenetic studies, Russ Altman of Stanford University, acknowledges that genotyping for drug risks has been a hard sell. In all, says FDA pharmacogenetic expert Larry Lesko, about 20 drug labels now mention reactions that may be influenced by genetic differences, but none recommends a gene test or related dose guidelines. Adds Altman: "Everyone thought *TPMT* would be the big one to do first. I must admit there is not a single case of a genetic variation where the standard of care is to test first. ... We have not yet broken through."

Still, the *TPMT* case suggests that genomic medicine is gaining momentum, albeit slowly. Geno-

# Pharmacogenetics is **NOT** Routinely Used

- Science still early
  - Limited data in public domain
- Many genetic variations not clinically significant
- Fragmentation of drug markets is worrisome to drug companies
- Costs for genotyping and who pays
- Ethical issues in testing individual genotype
- Unclear how to deliver information to the practitioner



# PharmGKB

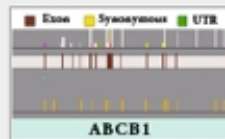
<http://www.pharmgkb.org/>

**Our Mission:** To collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response. We curate primary genotype and phenotype data, annotate gene variants and gene-drug-disease relationships via literature review, and summarize important PGx genes and drug pathways.

## Find Data By Type

You can find what you're looking for by browsing or searching the four major data types we store. If you need a pointer, check out our [tutorial](#). You can also do a general search in the search box at the top of the page.

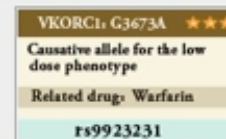
### Genes



- Important PGx genes
- Pharmacokinetic genes
- Pharmacodynamic genes
- Genotyped genes

find genes   [examples](#)  
hint: enter a gene, rsid, drug, disease

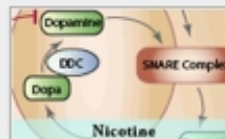
### Variants



- Annotated SNPs by gene
- Annotated SNPs by drug
- Annotated SNPs by disease
- Download all annotated SNPs

find variants   [examples](#)  
hint: enter a gene, rsid, drug, disease

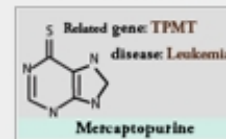
### Pathways



- Pathways by therapeutic categories
- Pharmacokinetic pathways
- Pharmacodynamic pathways
- All pathways

find pathways   [examples](#)  
hint: enter a gene, drug, disease

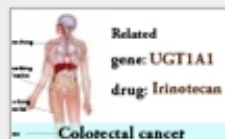
### Drugs & Small Molecules



- Drugs by therapeutic categories
- Drugs with genetic information
- Drugs with data

find drugs   [examples](#)  
hint: enter a gene, rsid, drug, disease

### Diseases



- Diseases with genetic information
- Diseases with curated information
- All diseases

find diseases   [examples](#)  
hint: enter a gene, rsid, drug, disease

### Opportunities to Contribute:

[Seeking Input on PGx Drug Relabeling Opportunities](#)

### Curators' Favorite Papers

- Pharmacogenetics of lithium response in bipolar disorder [GN](#)
- Variants of ADAMTS1 modify the effectiveness of statins in reducing the risk of myocardial infarction [PD GN](#)
- Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI [CO GN](#)

Updated 11/8/10.  
See the [archives](#) for more.

### PGx in the News

- FDA's Lesko Provides Update on Personalized Medicine Efforts; Three Guidances Slated for Release
- Pfizer Discusses Early Work on Cholesterol-Lowering Drug Targeting PCSK9
- Note to Subscribers
- Clinical Data Planning to Exit Genetic Testing Business to Fully Focus on Drug Development

See more news.  
 [Subscribe to RSS feed.](#)

# Pharmacogenetics vs. Pharmacogenomics

- **Pharmacogenetics**: study of individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response (SIMPLE relationship)
- **Pharmacogenomics**: study of genomic influence on drug response, often using high-throughput data (sequencing, SNP chip, expression, proteomics) (COMPLEX interactions)



# PGx Flow & Mission

PharmGKB curates information that establishes knowledge about the relationships among drugs, diseases and genes, including their variations and gene products. Our mission is to catalyze pharmacogenomics research.

## Click for more information

genotyped  
genes



608

variants  
of interest



617

drugs



545

pathways



56

diseases



542

important  
PGx genes



39

SNP  
arrays



2

downloads  
& services



## Search PharmGKB: ?

Go

e.g. a gene ("ABCB1"), drug ("irinotecan") or disease ("neoplasm")



# Drug-SNP Associations

## codeine

- Overview
- Properties
- Genetics
- Pathways
- Curated Relationships
- Non-curated Publications
- Downloads/Cross-references

### In-Depth Annotations (☆☆☆)

1. **rs59421388 at chr22:40853554** in [CYP2D6](#)

This variant is part of the reduced functioning haplotype CYP2D6\*29, which is found at an estimated allele frequency of 20% in African Tanzanians.

Variant Name:

CYP2D6: 3183G>A; 3271G>A

Related Drugs:

[citalopram](#), [codeine](#), [desipramine](#), [fluoxetine](#), [fluvoxamine](#), [gefitinib](#), [haloperidol](#), [imipramine](#), [morphine](#), [tramadol](#)

Related Diseases:

[Cystic Fibrosis](#), [Depression](#), [Hypertension](#), [Neoplasms](#), [Pain](#), [Parkinson Disease](#), [Schizophrenia](#)

Evidence:

<http://www.pharmgkb.org/search/annotatedGene/cyp2d6/variant.jsp>

2. **rs61736512 at chr22:40855078** in [CYP2D6](#)

This variant is part of the reduced functioning haplotype CYP2D6\*29, which is found at an estimated allele frequency of 20% in African Tanzanians.

Variant Name:

CYP2D6: 1659G>A; 1747G>A

Related Drugs:

[citalopram](#), [codeine](#), [desipramine](#), [fluoxetine](#), [fluvoxamine](#), [gefitinib](#), [haloperidol](#), [imipramine](#), [morphine](#), [tramadol](#)

Related Diseases:

[Cystic Fibrosis](#), [Depression](#), [Hypertension](#), [Neoplasms](#), [Pain](#), [Parkinson Disease](#), [Schizophrenia](#)

Evidence:

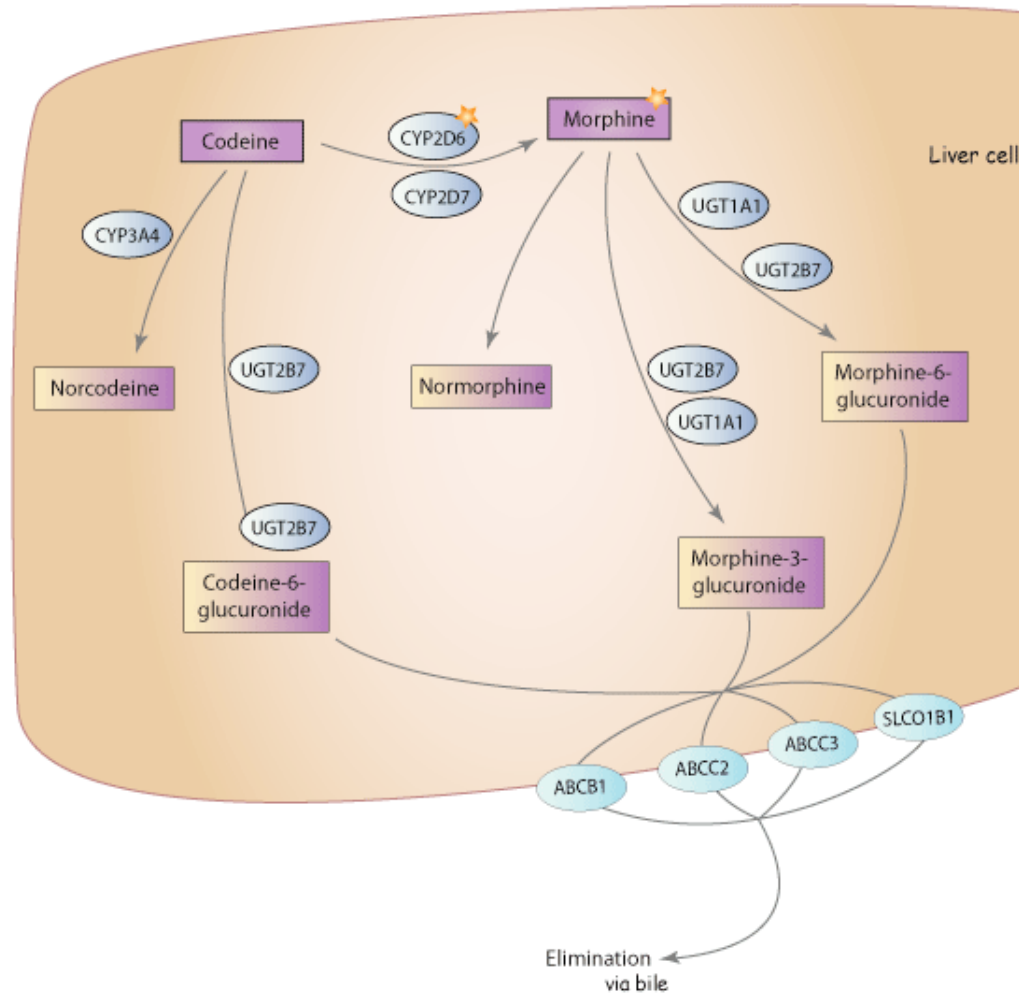
<http://www.pharmgkb.org/search/annotatedGene/cyp2d6/variant.jsp>

# Example: Codeine & CYP2D6

- Codeine is a commonly used opioid
  - must be metabolized into morphine for activity
- CYP2D6 is the metabolizing enzyme
- 7% of caucasians are missing one copy of the gene
  - codeine does not work effectively



# Candidate Genes Involved in Metabolism of Codeine and Morphine



# About CYP2D6

- Decreased or no activity in about 10% of Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes the primary metabolism of
  - propafenone
  - Codeine
  - $\beta$ -blockers
  - tricyclic antidepressants
- Inhibited by
  - **fluoxetine**
  - **haloperidol**
  - **paroxetine**
  - **quinidine**



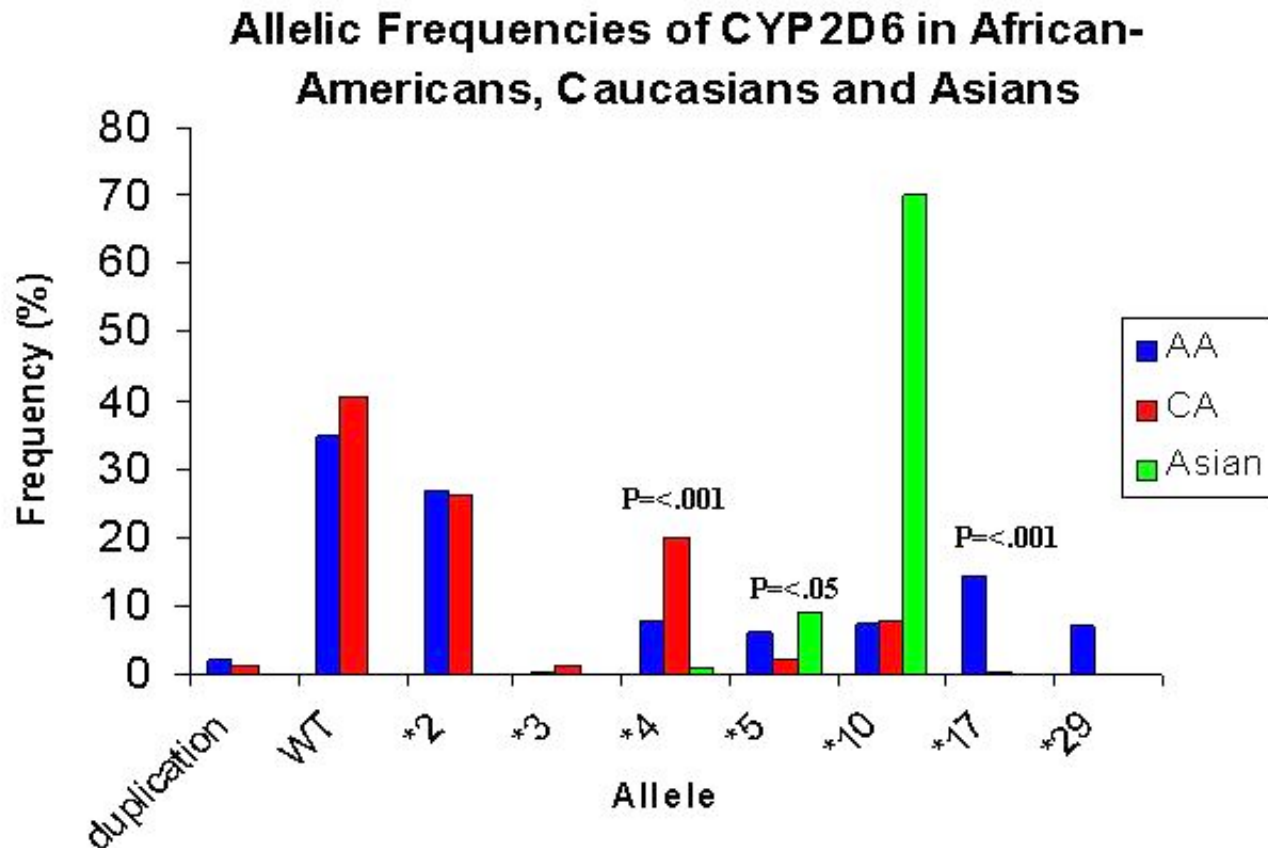
# CYP2D6 Alleles Are Complicated

- 125 alleles as of October 2008
- 10 alleles where haplotype has not been determined
- 38 alleles have no activity
- 10 alleles have decreased activity
- Can be >1 copy (up to 13) of gene on one chromosome, resulting in increased activity

<http://www.cypalleles.ki.se/cyp2d6.htm>



# Allelic Frequencies of CYP2D6



Wan Y et al. Pharmacogenetics 2001, 11:489-499.  
Gaedigk A et al. Clin Pharmacol Ther. 2002  
Jul; 72(1): 76-89.

# Copy number polymorphisms = CNPs

- Increasing evidence for variation in the number of copies of a gene in humans
- Won't necessarily be picked up with normal genotyping technology
- Associated with cancers, genetic diseases, and now with drug response variation
- Methods for quantifying transcript level, to detect CNPs are coming down in costs



# Pseudo-PGx Example Bidil

- Combination pill containing two medications for heart failure (hydralazine & isosorbide dinitrate)
- Clinical trials did not show overall benefit
- Subgroup of African-descent patients showed benefit
- BiDil approved for use in African-descent patients
- NOT genotyping patients for this





# PGx Example Irinotecan

- Powerful anti-neoplastic used in colon/rectal cancers
- Use is limited by severe, life-threatening neutropenia and diarrhea side effects
- Side effects related to patient genotype of UGT1A1 (helps metabolize irinotecan)
- Test now marketed for evaluating UGT1A1 genotype prior to initiation of treatment





## FDA News

### FOR IMMEDIATE RELEASE

P05-53  
August 22, 2005

### Media Inquiries:

Julie Zawisza, 301-827-6242

### Consumer Inquiries:

888-INFO-FDA

### FDA Clears Genetic Test That Advances Personalized Medicine Test Helps Determine Safety of Drug Therapy

Today, FDA cleared for marketing a new blood test that will help doctors make personalized drug treatment decisions for some patients. The Invader UGT1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. Doctors can use this information to help determine the right drug dosage for individual patients, and minimize harmful drug reactions.

"This test represents the power of DNA-based testing to provide individualized medical care," said Daniel Schultz, MD, Director of FDA's Center for Devices and Radiological Health. "These technologies can significantly improve patient management and reduce the risk of ineffective or even harmful drug therapy by telling doctors how to individualize drug dosing."

The Invader assay joins a growing list of genetic tests used by physicians to personalize treatment decisions, including the Roche AmpliChip, used to individualize dosage of antidepressants, antipsychotics, beta-blockers, and some chemotherapy drugs, and TRUGENE HIV-1 Genotyping Kit, used to detect variations in the genome of the human immunodeficiency virus that make the virus resistant to some anti-retroviral drugs.

The Invader assay detects variations in a gene called UGT1A1 that produces the enzyme UDP-glucuronosyltransferase. This enzyme is active in the metabolism of certain drugs, such as irinotecan, a drug used in colorectal cancer treatment. Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. For a patient with a particular UGT1A1 gene variation, a dose of irinotecan that is safe for another person might be too high for this patient, raising the risk of certain side effects. The Invader assay was studied in 66 patients who were receiving irinotecan therapy. The study showed that persons with one type of genetic variation have a five times greater risk of experiencing irinotecan toxicity.

"With the growing interest in individualizing drug therapy, FDA's approval of this assay provides physicians and patients with important information on the proper dosage of drugs metabolized and cleared from the body by the UGT1A1 pathway," said Lawrence Lesko, PhD, Director of FDA's Office of Clinical Pharmacology and Biopharmaceutics in the Center for Drug Evaluation and Research. "Information on the UGT1A1 genotype can be an integral part of drug labels and will guide health professionals on how to dose medications such as irinotecan."

# Gene-Drug FDA Examples

- **HLA-B\*1501** and 1502 alleles
  - hypersensitivity responses which can lead to a rash and skin reactions that may become serious and life-threatening
  - **abacavir** (Ziagen), **carbamazepine** (Carbatrol, Tegretol)
- **CYP2D6\*3, \*4, \*5, \*6, \*10, \*17** and **\*29** alleles
  - confer "poor metabolism"
  - **tamoxifen** (Novaldex); CYP forms appear to predict poorer prognosis for long term survival
  - **fluoxetine** (Prozac) and **atomoxetine** (Strattera)
- **VKORC1 A/A** and **A/B** haplotypes and **CYP2C9\*2** and **\*3** alleles
  - interactions at the target site and the removal from the body
  - **warfarin** (Coumadin)
    - Patients with combinations of these alleles can experience elevated INR measures and increased risk of dangerous bleeding events

# Gene-Drug FDA Examples

- **UGT1A1\*28** allele
  - reduced clearance of the active form SN-38 of the anticancer drug **irinotecan** (Camptosar) which can lead to neutropenia and a life-threatening diarrhea
- **TPMT\*2, \*3A, and \*3C** alleles
  - in homozygous patients leads to decreased clearance
  - **6-mercaptopurine** (Purinethol) or the pro-drug **azothiaprine** (Imuran) used to treat acute lymphoblastic leukemia and autoimmune diseases leading to rapid bone marrow suppression that is severe and can become fatal
- **SLC01B1** (rs4363657) and **OATP1B** (rs4149056)
  - found in liver can determine the blood levels of a wide range of drugs
  - **simvastatin** (Zocor) and **pravastatin** (Pravachol) are associated with development of myopathies
- **ADRB2 Arg16** allele of the beta-2 adrenergic receptor
  - linked in homozygous patients to a sub-class of asthma and lack of long-term responsiveness to treatment with **albuterol** (Ventolin)

# PGx Info in FDA-Approved Drug Labels

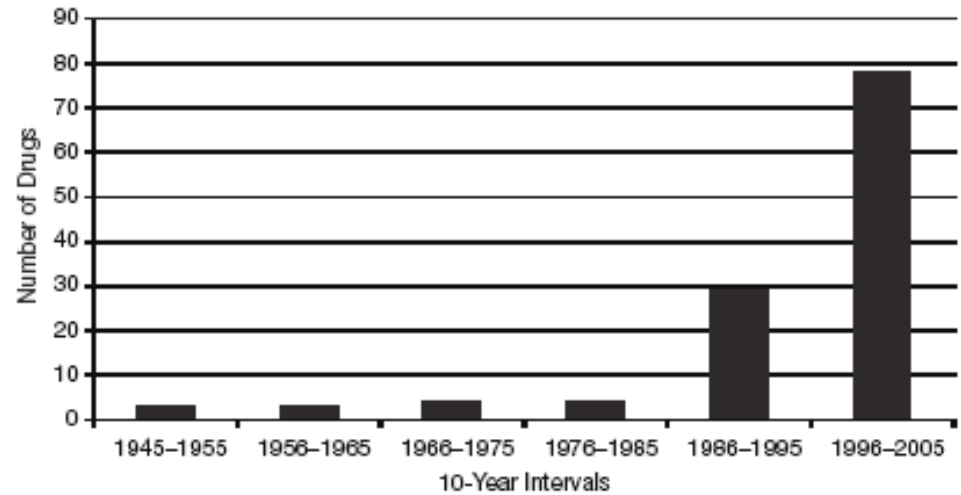
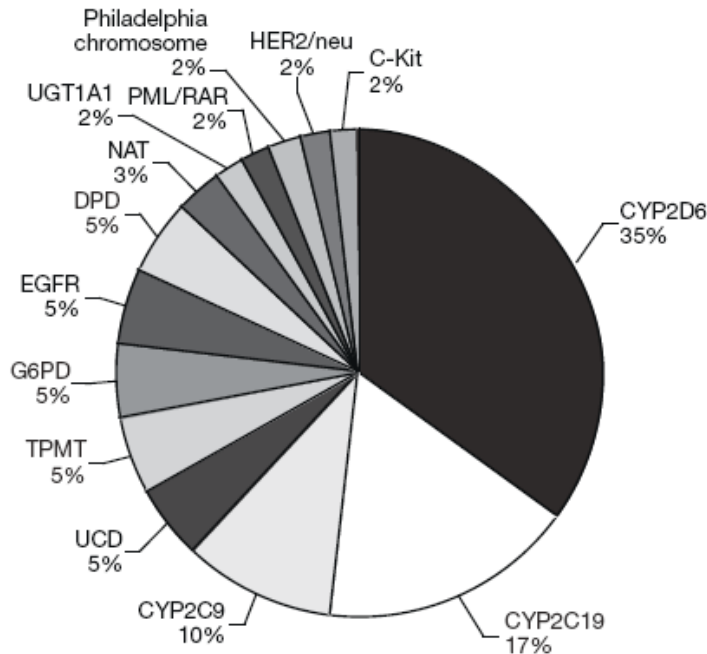
Frueh et al, *Pharmacotherapy* 2008 28:992-998.

- Reviewed labels of FDA approved drugs
  - to identify those that contained PGx biomarker information
  - to collect prevalence information on the use of those drugs for which PGx information was included in drug labelling
- 1200 drug labels reviewed for 1945-2005
  - 121 drug labels contain PGx info
    - 69 labels refer to human genomic biomarkers
      - 62% (43) pertained to cytochrome p450s with CYP2D6 most common
    - 52 labels referred to microbial genomic biomarkers
- 24.3% of prescriptions in 2006 (8.8 million out of 36.1 million) processed by a large pharmacy benefits manager received one or more drugs with human genomic biomarker information in the drug label.



# PGx Info in FDA-Approved Drug Labels

Frueh et al, *Pharmacotherapy* 2008 28:992-998.



Pharmacogenomic biomarkers identified in drug labels with human genomic information (1945-2005), and percentage of drug labels associated with each.

Number of drugs that were approved With pharmacogenomic information in their drug labels during each 10-year period from 1945-2005

# Conclusions from Drug Data 1945–2005

“Nearly one fourth of all outpatients received one or more drugs that have pharmacogenomic information in the label for that drug.

The incorporation and appropriate use of pharmacogenomic information in drug labels should be tested for its ability to improve drug use and safety in the United States.”

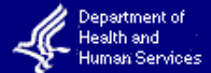
Frueh et al, *Pharmacotherapy* 2008 28:992–998



# Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels



U.S. Food and Drug Administration



CENTER FOR DRUG EVALUATION AND RESEARCH

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## Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade. In order to provide a reference for genomic biomarkers in labels of FDA-approved drug products, we created the table shown below. Genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. In the context of drug labels, these genomic biomarkers can be classified on the basis of their specific use, for example:

- Clinical response and differentiation,
- Risk identification,
- Dose selection guidance,
- Susceptibility, resistance and differential disease diagnosis,
- Polymorphic drug targets.

The table portrays a view on valid genomic biomarkers in the context of FDA-approved drug labels. It provides a comprehensive list of these markers and links to pharmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provide pharmacogenomic information with no immediate recommendation for a specific action (i.e. genetic testing); however a few labels recommend or require genetic testing thereby specifying the use of these markers for reaching a therapeutic decision.

[http://www.fda.gov/cder/genomics/genomic\\_biomarkers\\_table.htm](http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm)

PharmGKB -- <http://www.pharmgkb.org/>





# List of FDA Required or Recommended Biomarker Tests in Drug Labels

Biomarker	Test <sup>13</sup>	Drug Example	User Prevalence (%) (n=36.1 million)
CYP2C9	Recommended	Warfarin	2.0896
EGFR	Required	Cetuximab	0.0001
G6PD deficiency	Recommended	Dapsone	0.0257
G6PD deficiency	Recommended	Rasburicase	0.0000
HER2/neu overexpression	Required	Trastuzumab	0.0003
TPMT variants	Recommended	Azathioprine	0.1168
TPMT variants	Recommended	Mercaptopurine	0.0541
TPMT variants	Recommended	Thioguanine	0.0012
UGT1A1 variants	Recommended	Irinotecan	0.0002
Urea cycle enzyme deficiency	Recommended	Valproic acid	0.48
Total			2.768

CYP = cytochrome P450; EGFR = human epidermal growth factor receptor; G6PD = glucose-6-phosphate dehydrogenase; HER2/neu = human epidermal growth factor receptor 2; TPMT = thiopurine S-methyltransferase.

# Most Common Major Drug ADRs

- QT prolongation (heart problems)
- Liver failure
- Severe dermatological rash
  
- Many other minor ADRs
  - Minor rash
  - Abdominal discomfort
  - Dry mouth
  - Drowsiness or activation
  - Headache



# Arrhythmia

- QT prolongation and arrhythmia risk is the single commonest cause of drug withdrawal or relabeling in the last decade

## Glaxo Pulls Raxar, Cites Side Effects

By STEPHEN D. MOORE

Staff Reporter of THE WALL STREET JOURNAL

Glaxo Wellcome PLC withdrew an antibiotic called Raxar from more than 30 countries where it is sold, warning that the risk of rare side effects outweighs potential benefits.

Glaxo acquired rights to Raxar, known generically as grepafloxacin, three years ago from Otsuka Pharmaceutical Co. of Japan. But Raxar has been a commercial flop, with anemic sales of £10 million (\$16.5 million) last year.

Heart-rhythm abnormalities had been observed in some patients during clinical trials and cited in the drug's prescribing instructions to physicians. Glaxo said it has monitored those heart-rhythm side effects more closely in additional clinical studies that, together with recent reports of patient deaths potentially linked with Raxar, prompted the decision to withdraw the drug.

"A recent review of data highlighted the fact that seven patients died [of heart-related events] while taking Raxar," a spokeswoman said. "We haven't yet established a causal relationship—but we can't rule it out either." Separately, three other patients taking Raxar have developed a rare condition called torsade de pointes that also involves irregular heartbeat.

An estimated 2.65 million prescriptions for Raxar have been filled since the drug was launched in August 1997.

Raxar is the second so-called quinolone antibiotic linked with side effects in recent months. Earlier this year, U.S. medical regulators advised physicians to limit use of Trovan, a quinolone from Pfizer Inc., after the drug was linked to severe liver side effects.

Meanwhile, drug makers Bayer AG and SmithKline Beecham PLC are counting on promising new quinolone antibiotics to provide big sales boosts, but one analyst said that the clinical data assembled for those drugs is much more impressive than Raxar's.

In New York Stock Exchange composite trading yesterday, Glaxo American depositary shares rose 25 cents to \$59.8125.

Wall Street Journal Oct. 28, 1999

# PGx Example Warfarin

- Warfarin used for anticoagulation widely in medicine
- Narrow therapeutic index, final dose difficult to predict -> trial and error
- Three genes known to affect warfarin dose: CYP2C9, VKORC1 and CYP4F2
- Recent results suggest warfarin dose will be predicted more accurately using genotypes + demographic/clinical variables



# Warfarin Dosing

- Know variation in CYP2C9
  - but only accounted for < 15% of variation
- Vitamin K epoxide reductase (VKORC1)
  - Found in rat-poison-resistant rats
  - Non-coding SNP explains 35% of variation
  - VKORC1: -1639 G>A allele
- Clinical trials now underway to predict warfarin dose required based on genotype



# The NEW ENGLAND JOURNAL of MEDICINE

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VOL. 360 NO. 8

## Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium\*

### ABSTRACT

#### BACKGROUND

Genetic variability among patients plays an important role in determining the dose of warfarin that should be used when oral anticoagulation is initiated, but practical methods of using genetic information have not been evaluated in a diverse and large population. We developed and used an algorithm for estimating the appropriate warfarin dose that is based on both clinical and genetic data from a broad population base.

#### METHODS

Clinical and genetic data from 4043 patients were used to create a dose algorithm that was based on clinical variables only and an algorithm in which genetic information was added to the clinical variables. In a validation cohort of 1009 subjects, we evaluated the potential clinical value of each algorithm by calculating the percent

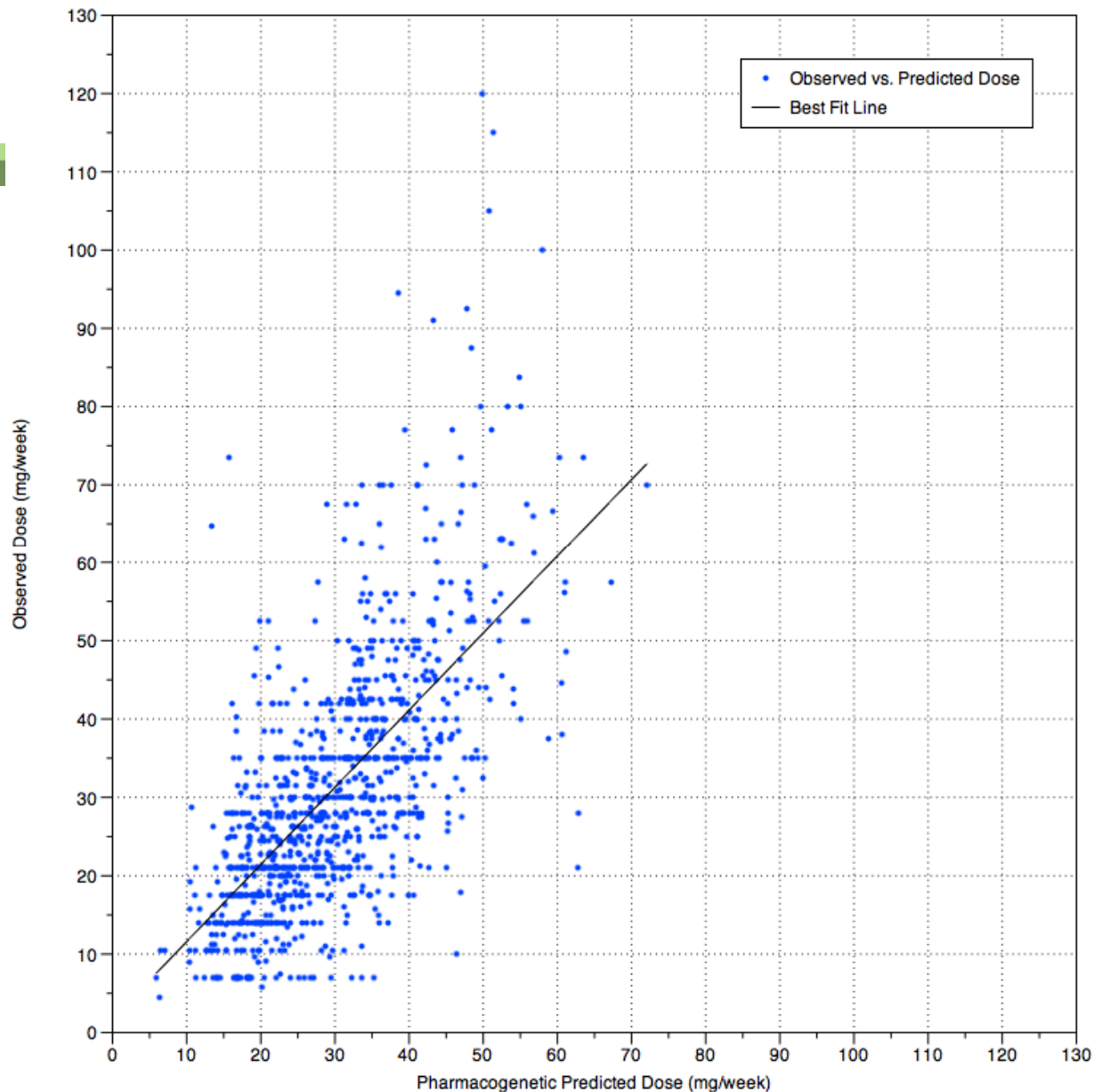
Address reprint requests to the International Warfarin Pharmacogenetics Consortium at 300 Pasteur Dr., Ln. 301, Mailstop 5120, Stanford, CA 94305, or at [iwpc@pharmgkb.org](mailto:iwpc@pharmgkb.org).

\*The members of the International Warfarin Pharmacogenetics Consortium are listed in the Appendix. The members of the writing committee take responsibility for the content of this article.

N Engl J Med 2009;360:753-64.

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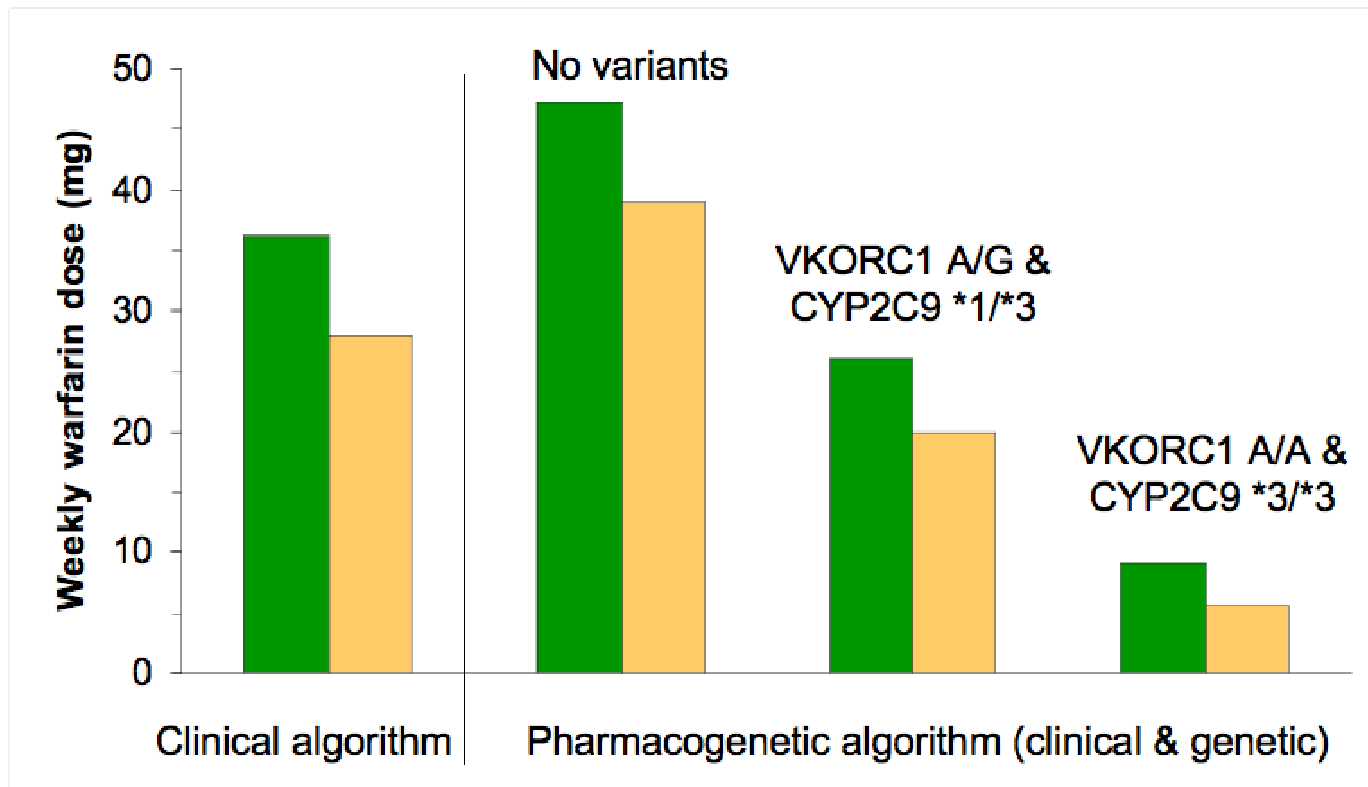
# Observed vs. Predicted Dose with PGx



# Sample Patient

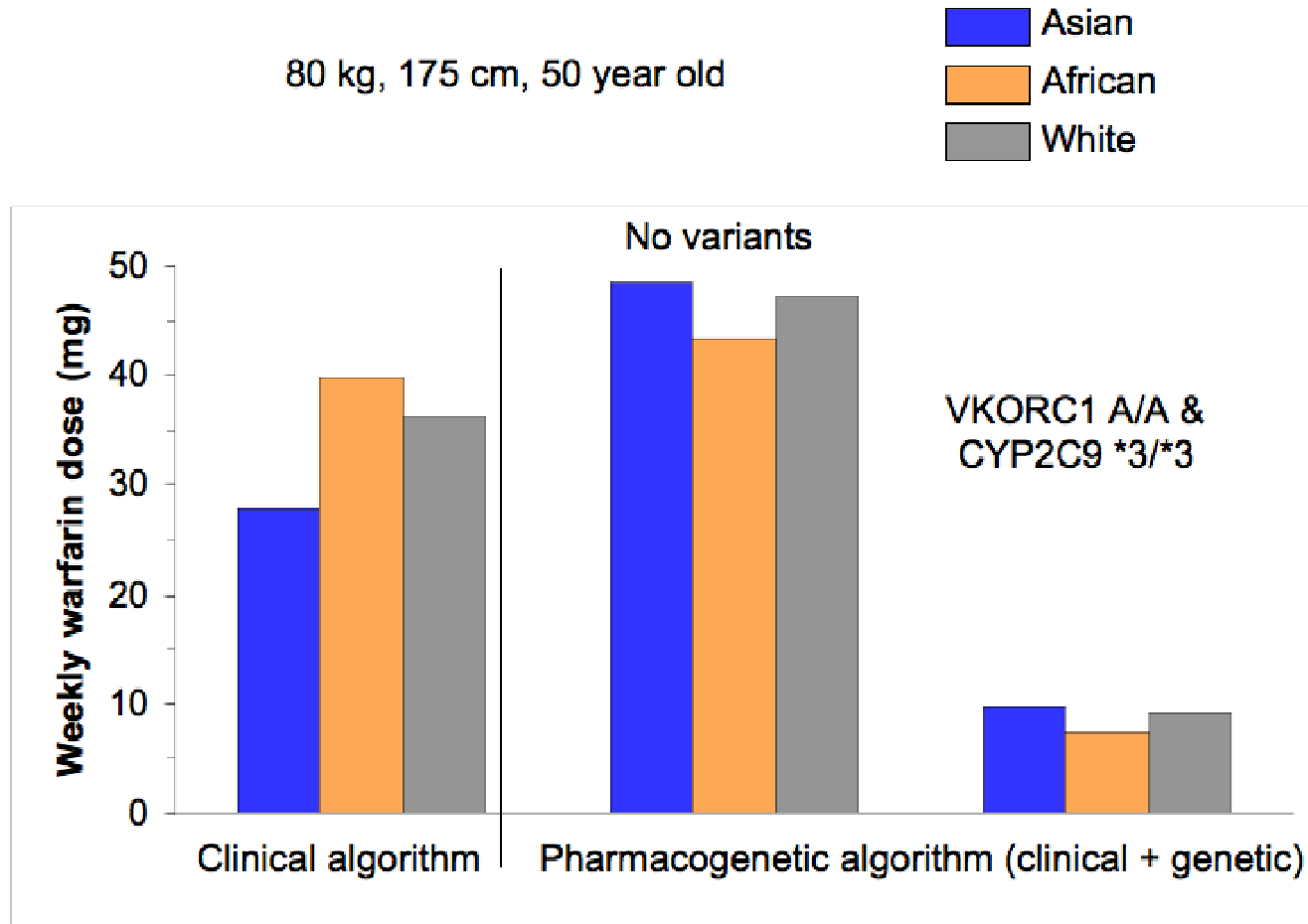
80 kg, 175 cm, 50 year old  
non-Asian, non-African

■ no amiodarone  
■ amiodarone





# Genotype Bigger Influence Than Race



Is the algorithm using  
genetics+clinical variables  
better than clinical alone, or  
fixed dose of 5 mg/day?



# PGx algorithm better than clinical or fixed, with mean error 8.5 mg/week ( $R^2 \sim 43\%$ )

Comparison of prediction performance on derivation and validation cohorts relative to final stable warfarin dose of the pharmacogenetic algorithm, clinical-only algorithm, and fixed 35 mg/week starting dose.

	Derivation MAE <sup>a</sup> in mg/week (Std Error), $R^2$	Validation MAE in mg/week <sup>***</sup> (Std Error), $R^2$
<u>Pharmacogenetic algorithm</u> <sup>*, **</sup>	8.3 (1.7) $R^2 = 47\%$	8.5 (1.7) $R^2 = 43\%$
Clinical-only algorithm <sup>**</sup>	10.0 (2.0) $R^2 = 27\%$	9.9 (1.9) $R^2 = 26\%$
Fixed 35 mg/week	13.3 (2.4) $R^2 = 0\%$	13.0 (2.3) $R^2 = 0\%$

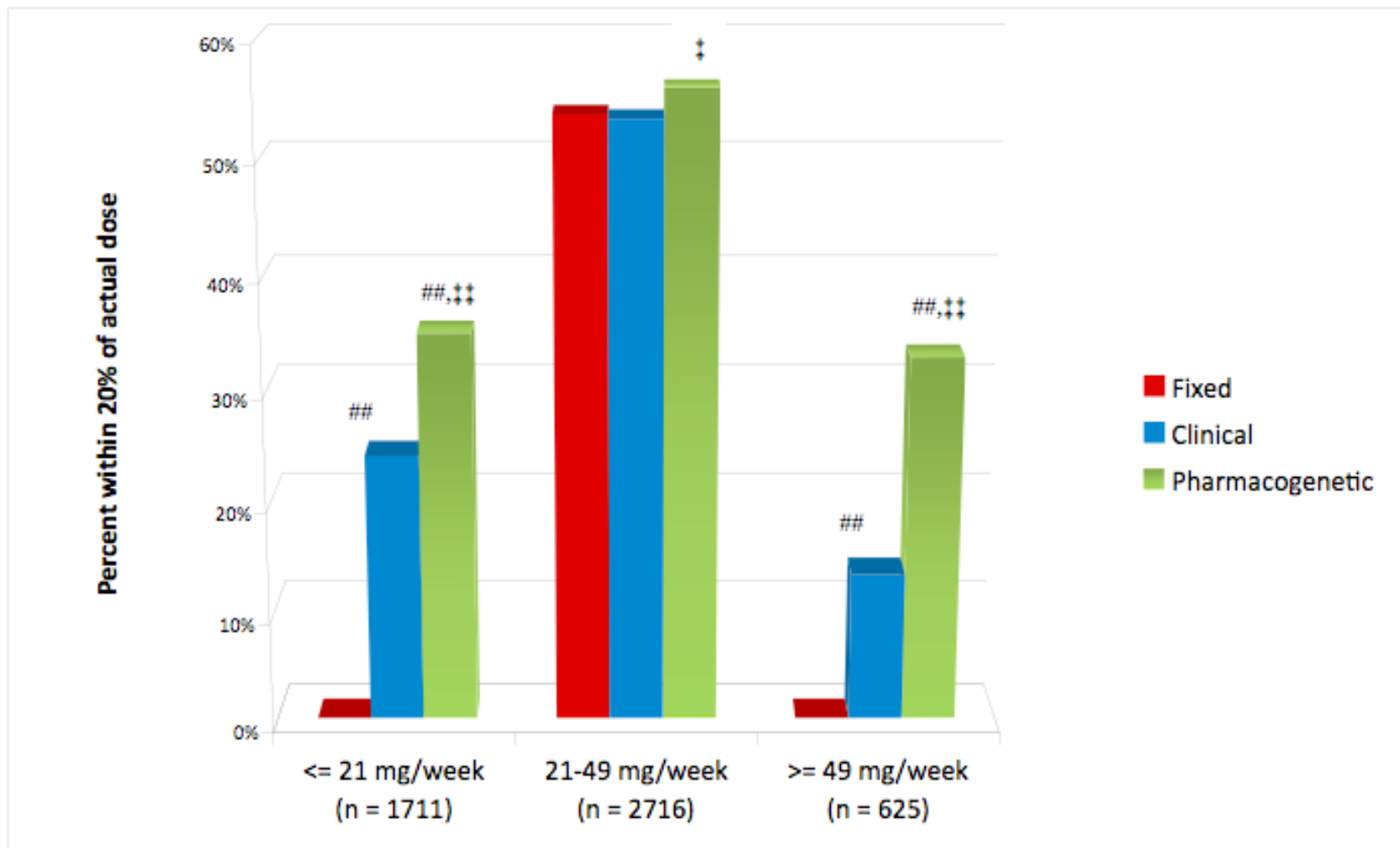
Are these differences  
clinically significant?



# PGx predicts more doses within 20% of actual, less over/underestimates

Training plus validation cohorts (n = 5052)			
Dosing approach	Ideal dosing*	Underestimate*	Overestimate*
I. Actual dose $\leq$ 21 mg/week (n=1711)			
<u>Pharmacogenetic</u>	35.0% <sup>##,††</sup> <sub>~</sub>	5.4% <sup>##,††</sup> <sub>~</sub>	59.7% <sup>##,††</sup> <sub>~</sub>
Clinical	24.0% <sup>##</sup>	1.2% <sup>##</sup>	74.8% <sup>##</sup>
Fixed 5 mg/day	0%	0%	100%
II. Actual dose > 21 mg/week to < 49 mg/week (n=2716)			
<u>Pharmacogenetic</u>	55.9% †	25.9% <sup>##,††</sup> <sub>~</sub>	18.2% <sup>##,††</sup> <sub>~</sub>
Clinical	53.3%	31.0% <sup>##</sup>	15.6% <sup>##</sup>
Fixed 5 mg/day	53.7%	8.9%	37.4%
III. Actual dose $\geq$ 49 mg/week (n=625)			
<u>Pharmacogenetic</u>	32.8% <sup>##,††</sup> <sub>~</sub>	66.7% <sup>##,††</sup> <sub>~</sub>	0.5%
Clinical	13.3% <sup>##</sup>	86.2% <sup>##</sup>	0.5%
Fixed 5 mg/day	0%	100%	0%

# Predicting dose within 20% of actual for entire cohort (N=5,052)



# High Profile Results

- Associated Press
- Wall Street Journal
- Bloomberg News
- Reuters
- Health Day
- US News & World Report.
- MedPage Today
- Florida Alligator
- CBCnews.ca
- medGadget
- Genome Web
- News-Medical.net (Australia)
- Scripps Howard News Service
- AMA Morning Rounds
- Red Orbit
- OrthoSupersite
- NIGMS release
  - PharmaLive
  - Science Daily
  - Pharmacy Choice



## EDITORIALS



# Pharmacogenetics — Tailoring Treatment for the Outliers

Janet Woodcock, M.D., and Lawrence J. Lesko, Ph.D., F.C.P.

If it were not for the great variability among individuals, medicine might as well be a science and not an art.

— Sir William Osler (1892)

Over the past half century, biomedical science has developed randomized, controlled clinical-trial methods that can distinguish treatment effects from the noise of human variability. Positive results from tests of a treatment in a randomized, controlled trial provide great confidence that an intervention improves a prespecified outcome in a population defined by explicit entry criteria.

patients who required therapeutic anticoagulation.<sup>1</sup> For each patient, the investigators identified the stable warfarin maintenance dose that resulted in the desired therapeutic international normalized ratio (INR). The range of doses that were needed to achieve the target pharmacodynamic effect in this large, geographically diverse cohort is shown in Figure 1. The investigators found that doses predicted by a pharmacogenetic algorithm — one that included both clinical and genetic factors — were better correlated with the empirically determined maintenance doses than were those predicted by a clinical algorithm; both algorithms outperformed a standard dose of 5 mg



In the case of other treatments, outliers are uncommon. For example, the drug 6-mercaptopurine is metabolized by the enzyme thiopurine methyltransferase. About 1 of every 300 people in the

studies. These differences in evidence seem appropriate to the circumstances of the risks.

A better understanding of individual differences in the response, either positive or negative, to

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#### EDITORIALS

medicines should be an overarching goal for pharmacotherapy over the next decade. Pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not “average.” In some cases, randomized, controlled trials will be needed to determine whether pharmacogenetic testing is worthwhile; in others, less rigorous approaches will suffice. Given the expected volume of genetic information and the relative paucity of randomized, controlled trials involving marketed drugs, we need clear thinking about what is required for the adoption of pharmacogenetic testing.

From the Center for Drug Evaluation and Research, Food and Drug Administration, White Oak, MD.

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2. Relling MV, Hancock ML, Rivera GK, et al. Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. *J Natl Cancer Inst* 1999;91:2001-8.
3. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354-62.
4. Mallal S, Phillips E, Carosi G, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;358:568-79.
5. Food and Drug Administration. Information on carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics). (Accessed January 30, 2009, at <http://www.fda.gov/cder/drug/>)

# Thank You

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