

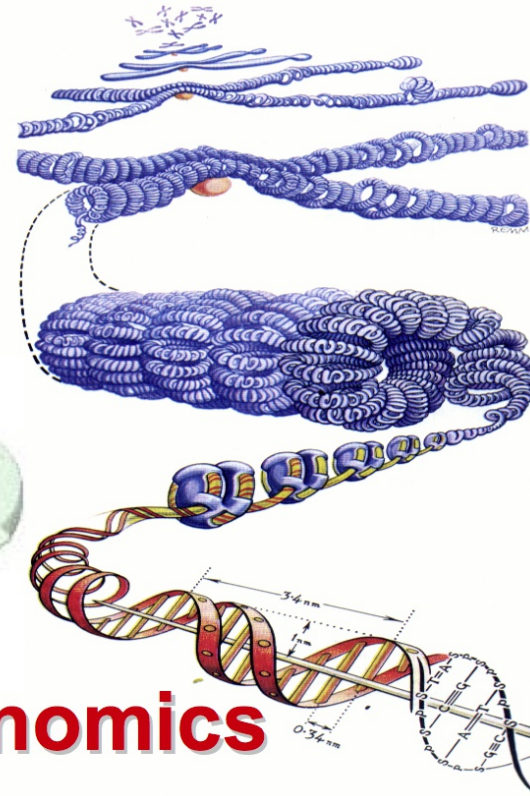
# Your Genes and Your Health

<http://bio84.stanford.edu/>

## Pharmacogenomics

<http://bio84.stanford.edu/10%20Drug%20Development.html>

### Drugs and Genes



### Pharmacogenomics

Doug Brutlag, Professor Emeritus  
Biochemistry and Medicine (by courtesy)  
Stanford University School of Medicine

# Personalized Medicine



Courtesy of Felix W. Frueh US FDA

# Personalized Medicine

---

- Medicine is personal:
  - We are all different.
  - Some of our differences translate into how we react to drugs as individuals.
  - This is why personalized medicine is important to everyone.
- Why does someone need twice the standard dose to be effective?
- Why does this drug work for you but not me?
- Why do I have side-effects and you don't?
- Why do some people get cancer and others don't?
- Why is anecdotal information irrelevant to your own health and treatment?

# Is Medicine a Science or an Art?

---

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

- Sir William Osler, Physician 1892
- Johns Hopkins School of Medicine
- Johns Hopkins Hospital
- Father of modern medicine

# The Goal of Personalized Medicine

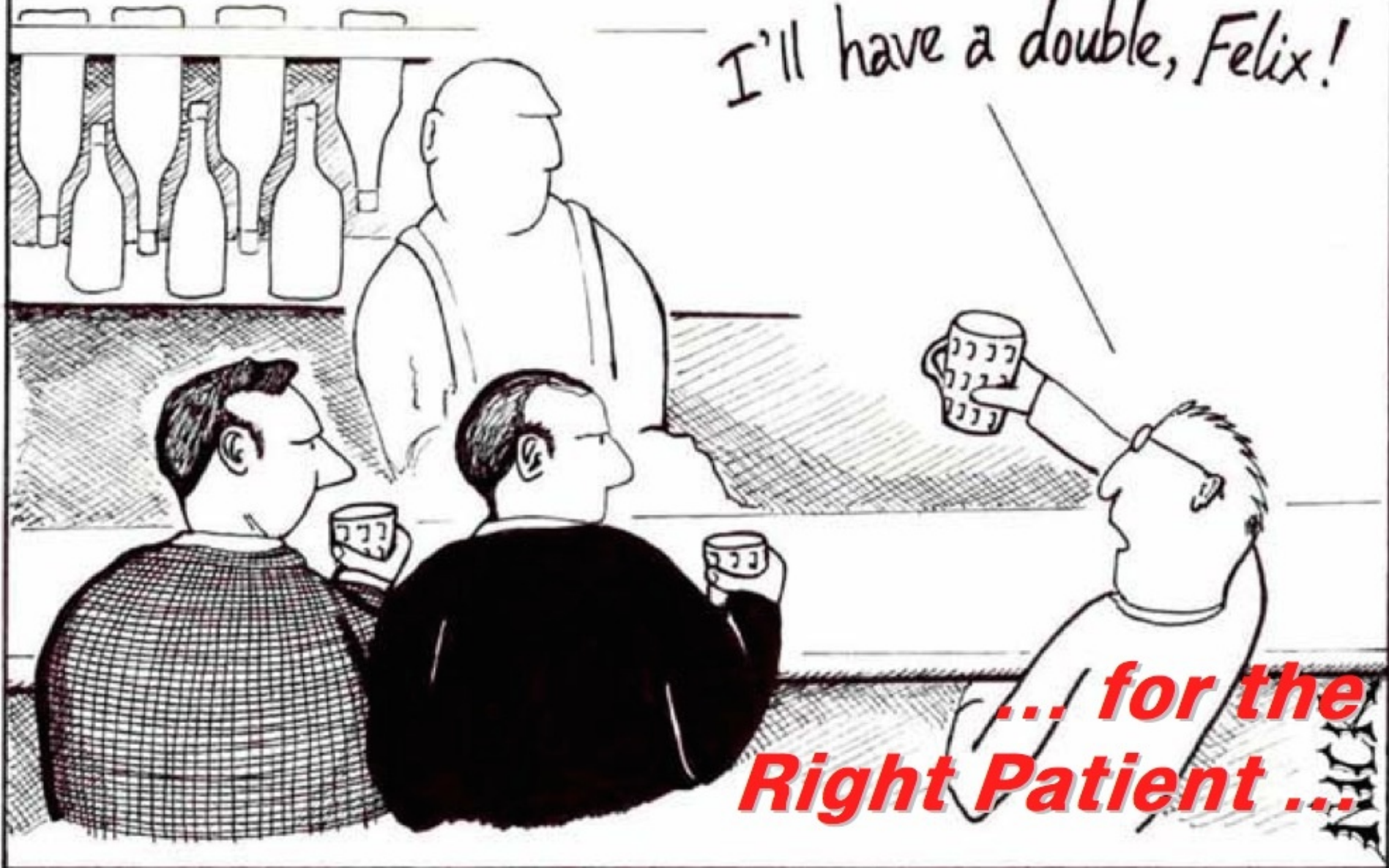
by Felix Frueh

---

- The **Right** Dose of
- The **Right** Drug for
- The **Right** Indication for
- The **Right** Patient at
- The **Right** Time.

**at the Right Dose ...**

I'll have a double, Felix!



***... for the  
Right Patient ...***

# Variability of Disease

## Example: Leukemia and Lymphoma

<b>1950</b>	"Disease of the Blood"	
<b>1960</b>	Leukemia	Lymphoma
<b>1970</b>	Chronic Leukemia Acute Leukemia Preleukemia	Indolent Lymphoma Aggressive Lymphoma
<b>2007</b>	<p>~38 Leukemia types identified:</p> <ul style="list-style-type: none"> <li>Acute myeloid leukemia (~12 types)</li> <li>Acute lymphoblastic leukemia (2 types)</li> <li>Acute promyelocytic leukemia (2 types)</li> <li>Acute monocytic leukemia (2 types)</li> <li>Acute erythroid leukemia (2 types)</li> <li>Acute megakaryoblastic leukemia</li> <li>Acute myelomonocytic leukemia (2 types)</li> <li>Chronic myeloid leukemia</li> <li>Chronic myeloproliferative disorders (5 types)</li> <li>Myelodysplastic syndromes (6 types)</li> <li>Mixed myeloproliferative/myelodysplastic syndromes (3 types)</li> </ul>	<p>~51 Lymphomas identified:</p> <ul style="list-style-type: none"> <li>Mature B-cell lymphomas (~14 types)</li> <li>Mature T-cell lymphomas (15 types)</li> <li>Plasma cell neoplasm (3 types)</li> <li>Immature (precursor) lymphomas (2 types)</li> <li>Hodgkin's lymphoma (5 types)</li> <li>Immunodeficiency associated lymphomas (~5 types)</li> <li>Other hematolymphoid neoplasms (~7 types)</li> </ul>

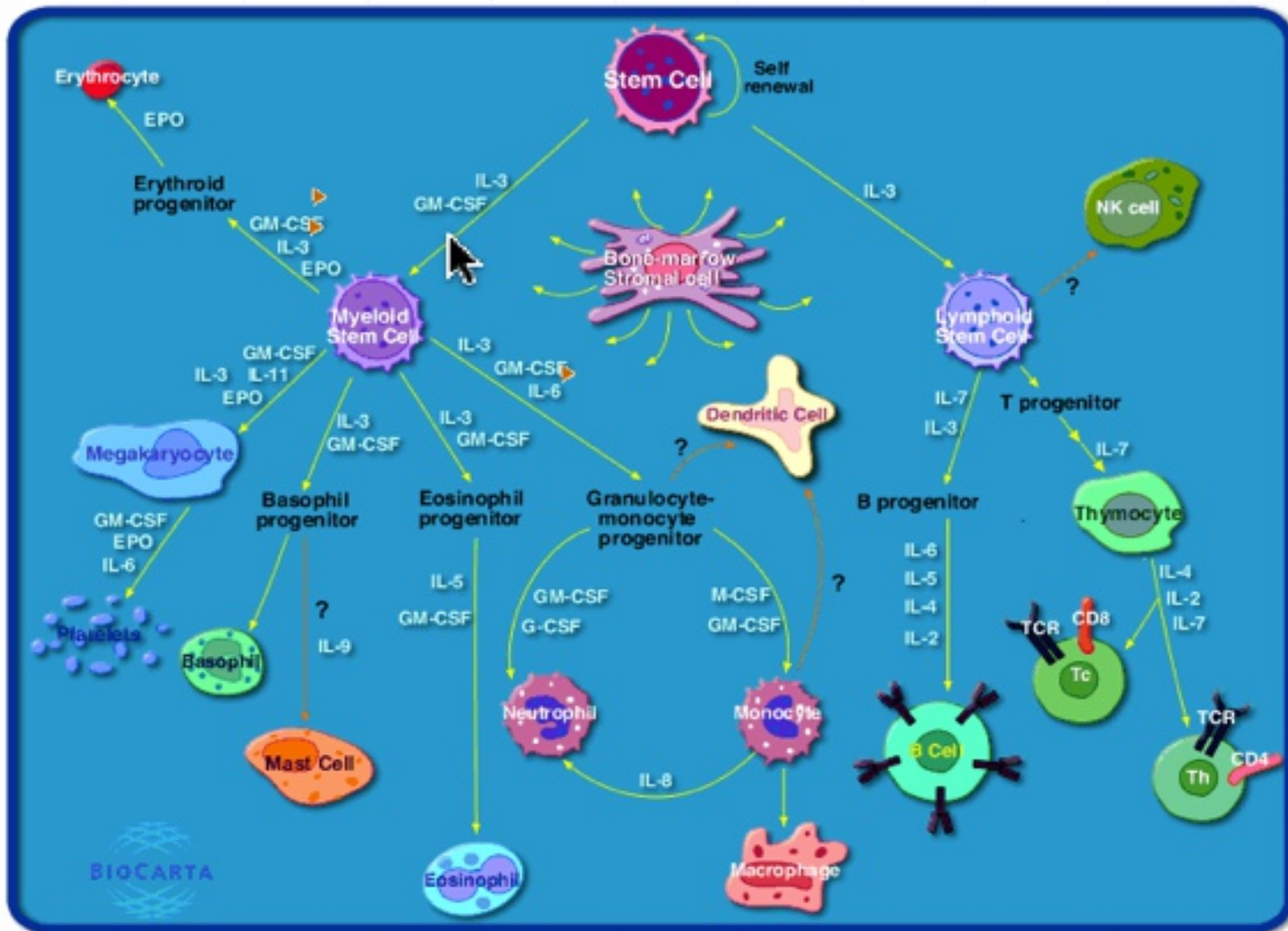
5 Year  
Survival

~ 0%

~ 70%

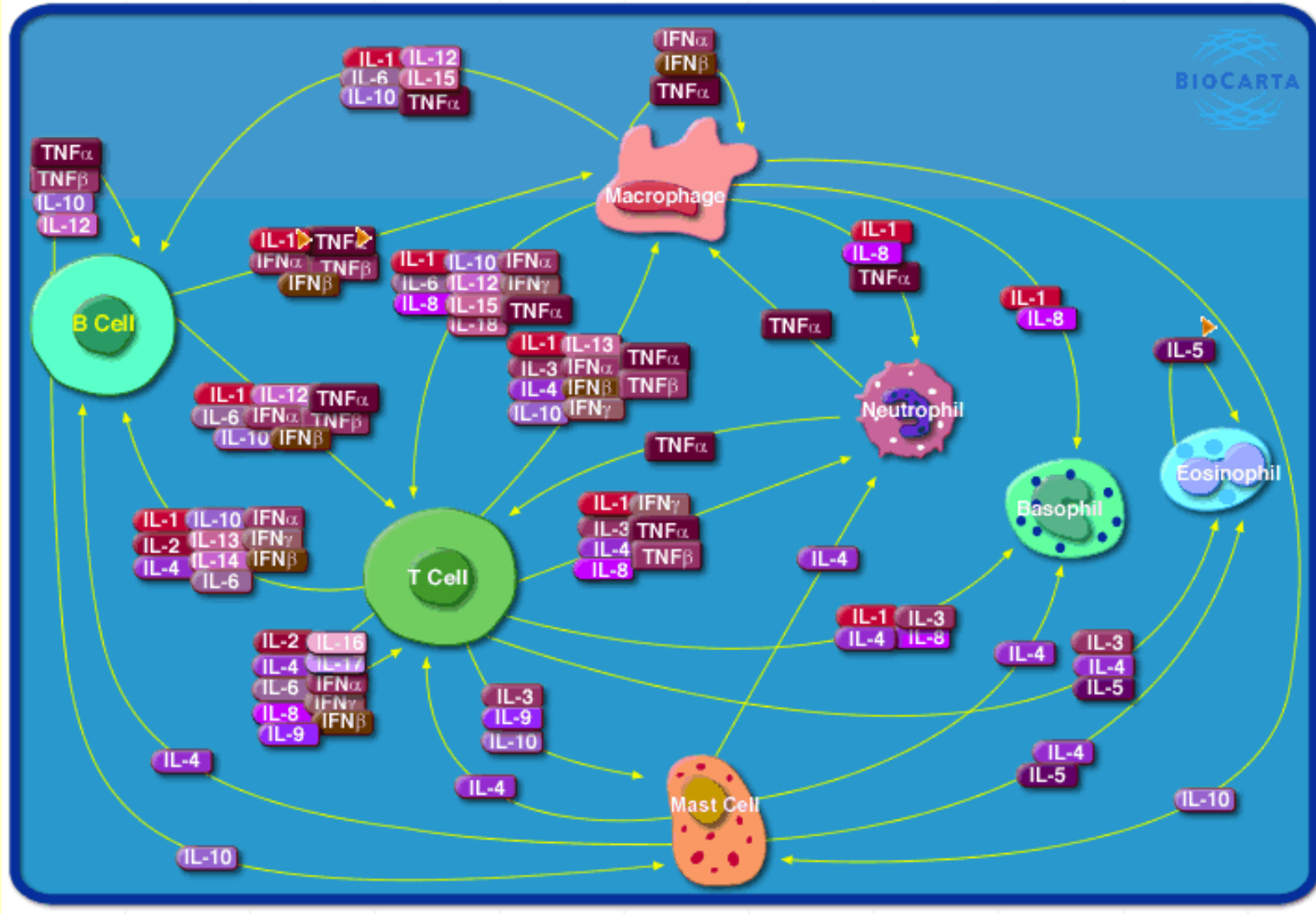
# Hematopoiesis

[http://www.biocarta.com/pathfiles/h\\_stemPathway.asp](http://www.biocarta.com/pathfiles/h_stemPathway.asp)



# Cytokine Network

[http://www.biocarta.com/pathfiles/h\\_cytokinePathway.asp](http://www.biocarta.com/pathfiles/h_cytokinePathway.asp)



# Targeted Drug Therapies

---

- Targeted therapy: wave of the Future
  - Mark D. Pegram et al. 2005 J. Clin Oncol.10, 1776-81
- Therapeutic strategies targeting ERBB2
  - Grand Rounds, Mark Pegram, Prof. of Medicine
- Antibody therapeutics in Cancer
  - Sliwkowski M, Mellman I. Science. 2013 Sep 13;341(6151):1192-8.
- Reviews of Targeted Therapies.
  - "Molecular Targeted Therapy"[Majr]
- FDA Fast Tracks Approval of Targeted Drug Therapies
  - <http://p.nytimes.com/email/re?location=InCMR7g4BCKC2wiZPk>



# FDA Fast Tracks Targeted Cancer Therapies

<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm427601.htm>



U.S. Food and Drug Administration

Search FDA



[← back to Consumer Updates](#)

## Pancreatic Cancer: Targeted Treatments Hold Promise





# FDA Consumer Updates

<http://www.fda.gov/ForConsumers/ConsumerUpdates/default.htm>



U.S. Food and Drug Administration

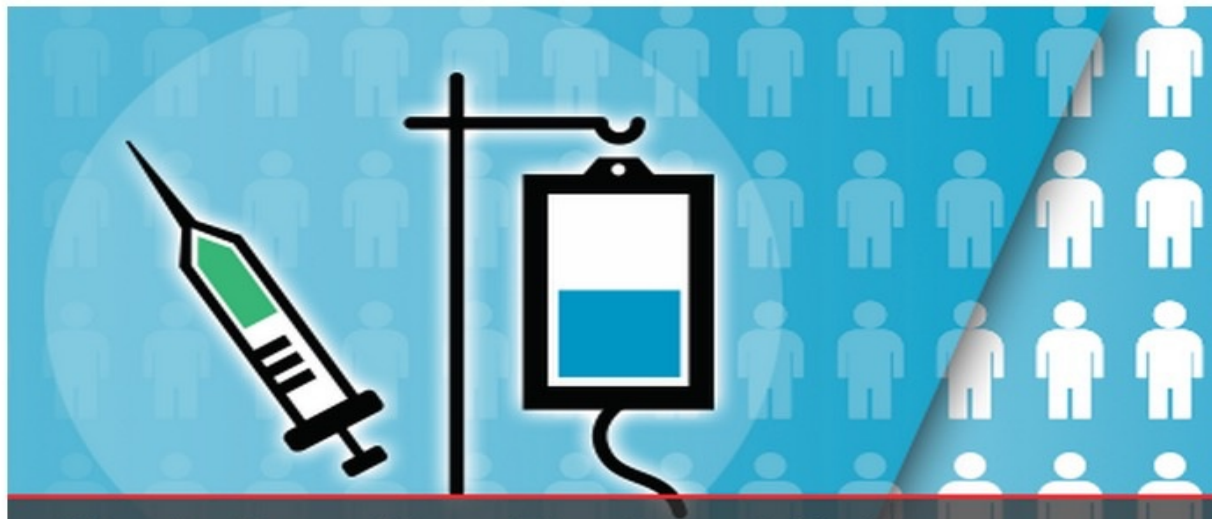
Search FDA



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## Consumer Updates

 [Get Consumer Updates by E-mail](#)  [Consumer Updates RSS Feed](#)



### Biosimilars: More Treatment Options Are on the Way

What will biosimilars mean for patients?

# Pharmacogenetics & Pharmacogenomics

---

- Pharmacogenetics: The role of genetics in drug responses.
  - F. Vogel. 1959
- Pharmacogenomics: The science that allows us to predict a response to drugs based on an individual's genetic makeup.
  - Felix Frueh, Associate Director of Genomics, FDA

# Pharmacogenetics & Pharmacogenomics

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

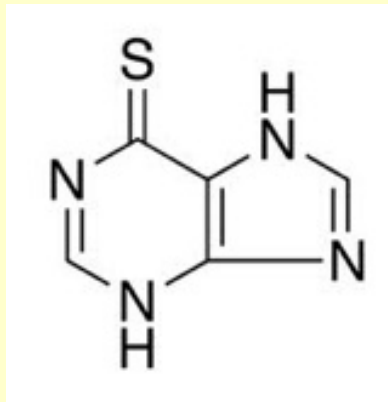
---

- **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)
  - PharmGKB Website: <http://www.pharmgkb.org/>

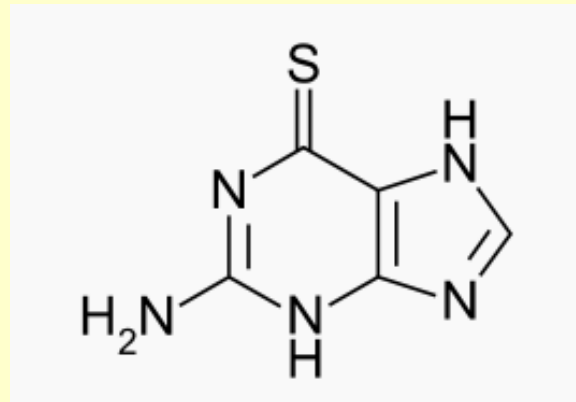
# Purine Analogs:

## A Case Study in Pharmacogenetics

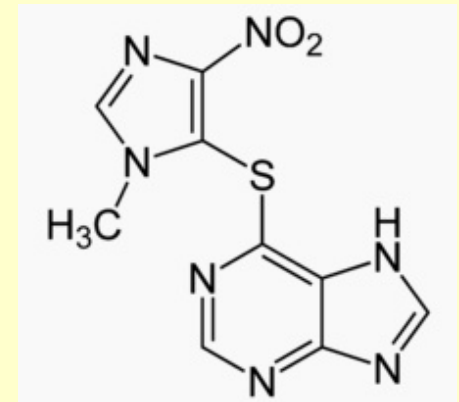
- 6-mercaptopurine, 6-thioguanine, azathioprine
- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, after transplant
- Interferes with DNA synthesis
- Therapeutic index limited by myelosuppression (treatment limited by immune suppression side effect)



6-mercaptopurine

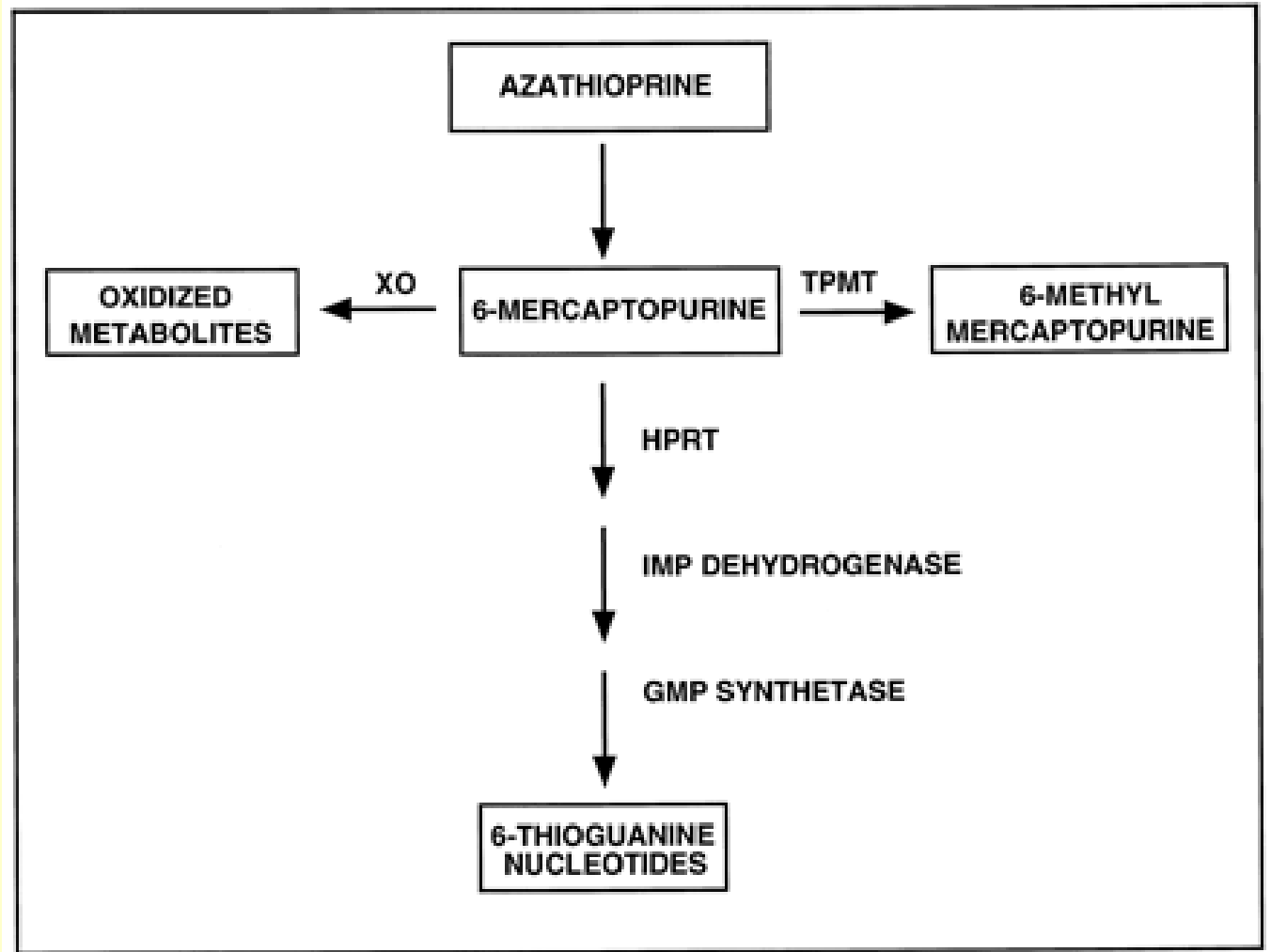


6-thioguanine



azathioprine

# Metabolism of 6-MP



# 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.

# Pharmacogenetics: A Case Study

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

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



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# Pharmacogenetics: A Case Study

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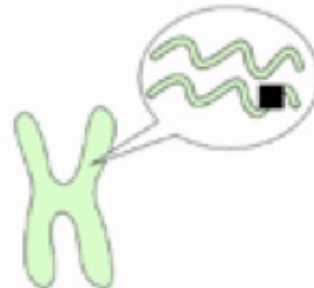


Others metabolize the drug slowly and need lower doses to avoid toxic side effects of the drug.



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



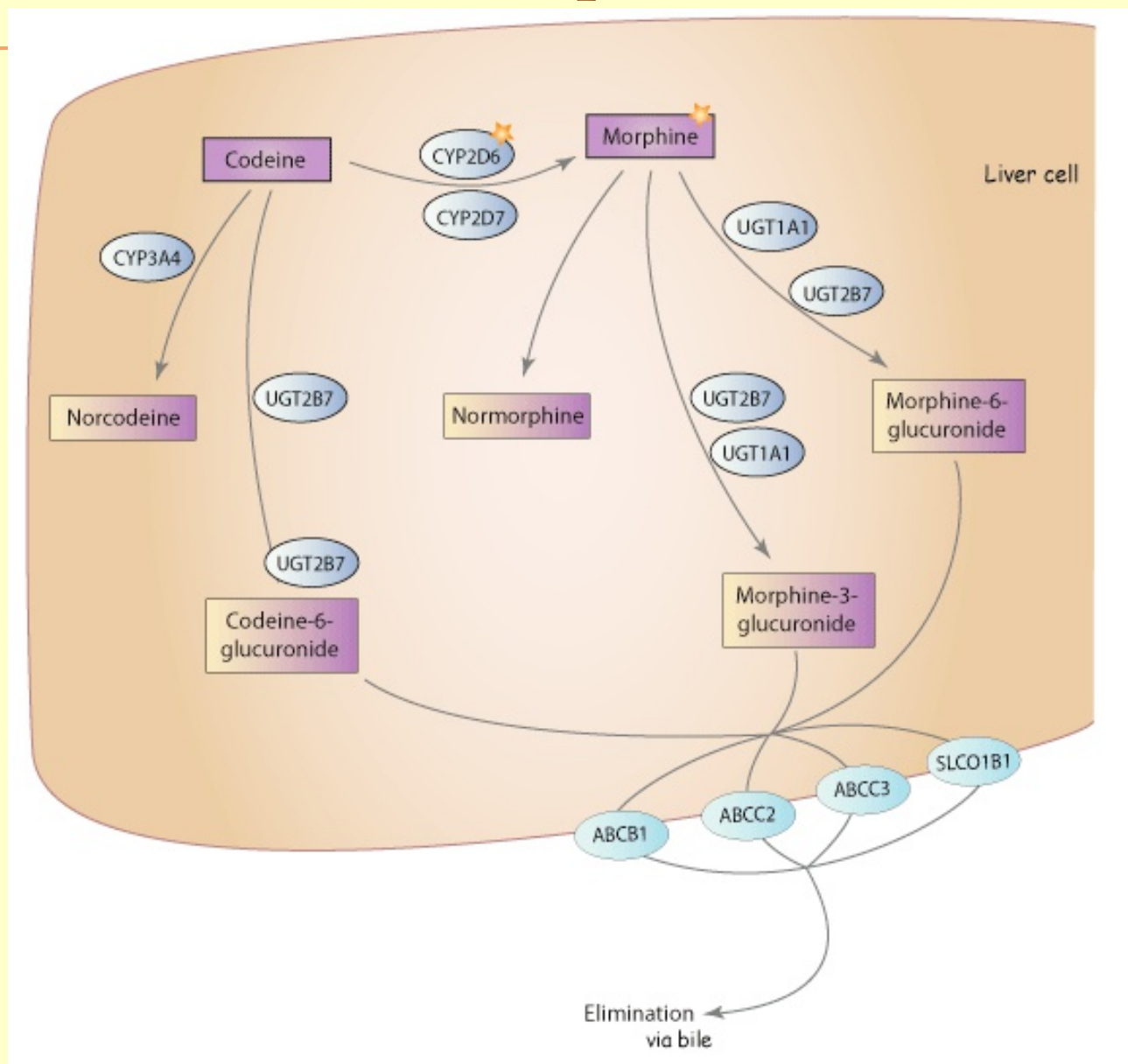
Dose for an extra slow metabolizer (TPMT deficient)

# Second Example: Codeine and Cytochrome P450 CYP2D6

---

- Codeine is a commonly used opioid
  - Codeine is a prodrug
  - It must be metabolized into morphine for activity
- Cytochrome P450 allele CYP2D6 is the metabolizing enzyme in the liver
- 7% of Caucasians are missing one copy of the Cytochrome P450 CYP2D6 gene
  - codeine does not work effectively in these individuals

# Codeine and Morphine Metabolism



# Cytochrome Oxidase P450 Enzymes

[https://en.wikipedia.org/wiki/Cytochrome\\_P450](https://en.wikipedia.org/wiki/Cytochrome_P450)

---

- 57 Different active genes
- 17 Different families
- CYP1, CYP2 and CYP3 are primarily involved in drug metabolism.
- CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 are responsible for metabolizing most clinically important drugs

# Human UDP Glucosyltransferases

<http://en.wikipedia.org/wiki/Glucuronosyltransferase>

---

- 3 Families
- 22 Different alleles
  - B3GAT1, B3GAT2, B3GAT3
  - UGT1A1, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10
  - UGT2A1, UGT2A2, UGT2A3, UGT2B4, UGT2B7, UGT2B10, UGT2B11, UGT2B15, UGT2B17, UGT2B28

# Glutathione- S Transferases

[https://en.wikipedia.org/wiki/Glutathione\\_S-transferase](https://en.wikipedia.org/wiki/Glutathione_S-transferase)

<b>GST Class</b>	<b><i>Homo sapiens</i> GST Class Members (22)</b>
Alpha	GSTA1, GSTA2, GSTA3, GSTA4, GSTA5
Delta	
Kappa	GSTK1
Mu	GSTM1, GSTM1L (RNAi), GSTM2, GSTM3, GSTM4, GSTM5
Omega	GSTO1, GSTO2
Pi	GSTP1
Theta	GSTT1, GSTT2, GSTT4
Zeta	GSTZ1 (aka GSTZ1 MAAI- Maleylacetoacetate isomerase)
Microsomal	MGST1, MGST2, MGST3

# Polymorphic Cytochrome P-450s



## CYP2B6

Selected Substrates	Location	Poor Metabolizer Incidence
bupropion cyclophosphamide efavirenz methadone ifosfamide	Chromosome 19	3-4% of Caucasians

## CYP2C9

Selected Substrates	Location	Poor Metabolizer Incidence
NSAIDs celecoxib diclofenac ibuprofen naproxen piroxicam Oral Hypoglycemic Agents tolbutamide glipizide ARBs irbesartan losartan fluvastatin warfarin phenytoin	Chromosome 10	1-3% Caucasians

## CYP2C19

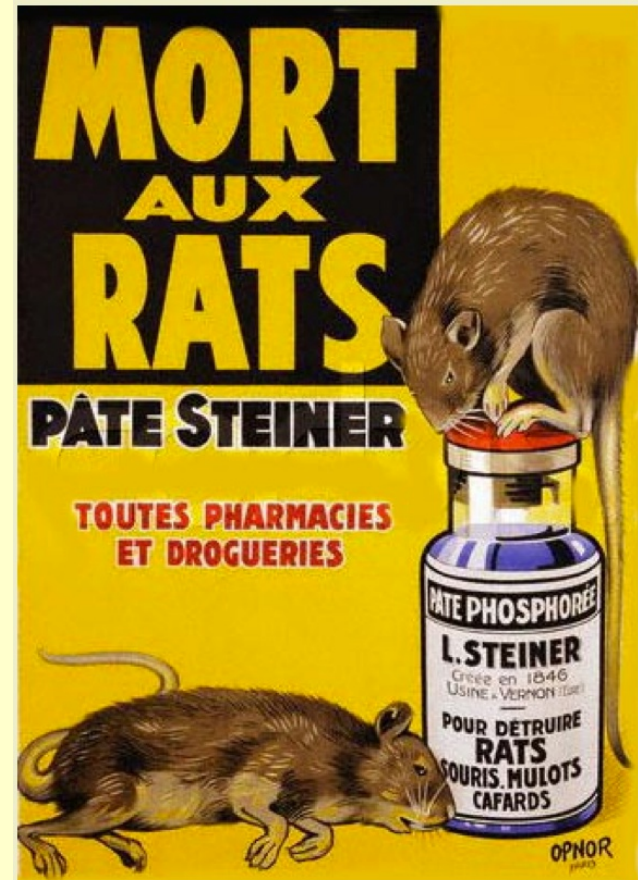
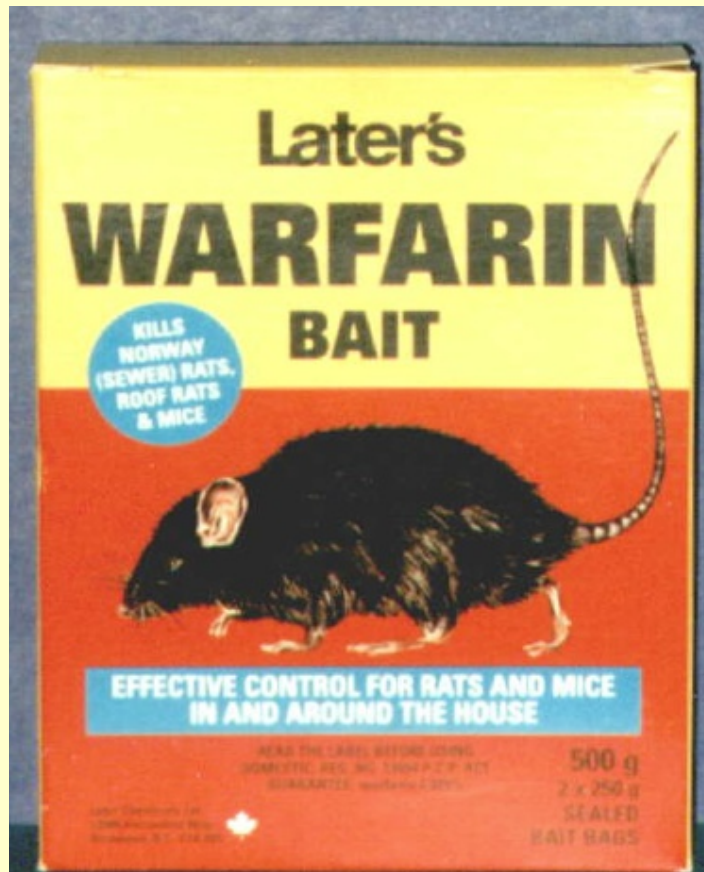
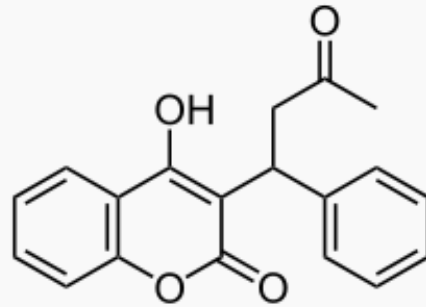
Selected Substrates	Location	Poor Metabolizer Incidence
Proton pump (-) amitriptyline cyclophosphamide diazepam indomethacin phenytoin phenobarbital progesterone voriconazole	Chromosome 10	2-4% African-Americans 3-5% Caucasians 15-20% Asians

## CYP2D6

Selected Substrates	Location	Poor Metabolizer Incidence
antidepressants beta-blockers antipsychotics chlorpheniramine codeine dextromethorphan ondansetron lidocaine promethazine tamoxifen tramadol	Chromosome 22	5-10% Caucasians

# Warfarin: Significant Problems for Rats!

Warfarin



# Warfarin: Significant Problems for Humans!

---

- Ranks #1 in total mentions of deaths for drugs causing adverse events (from death certificates)
- Ranks among the top drugs associated hospital emergency room visits for bleeding
- Overall frequency of major bleeding range from 2% to 16% (versus 0.1% for most drugs)
- Minor bleeding event rates in RCT of new anticoagulants has been as high as 29% (% per year)

# Warfarin: Significant Problems for Humans!

---

- **Case Report July 2, 2008**
  - Company director dies of brain hemorrhage after heading a football
  - Consultant neurosurgeon told the inquest the warfarin effect was probably the cause of the death
  - It can happen to anyone!
- **Other Warfarin Patients**
  - Dwight D. Eisenhower
  - Joseph Stalin



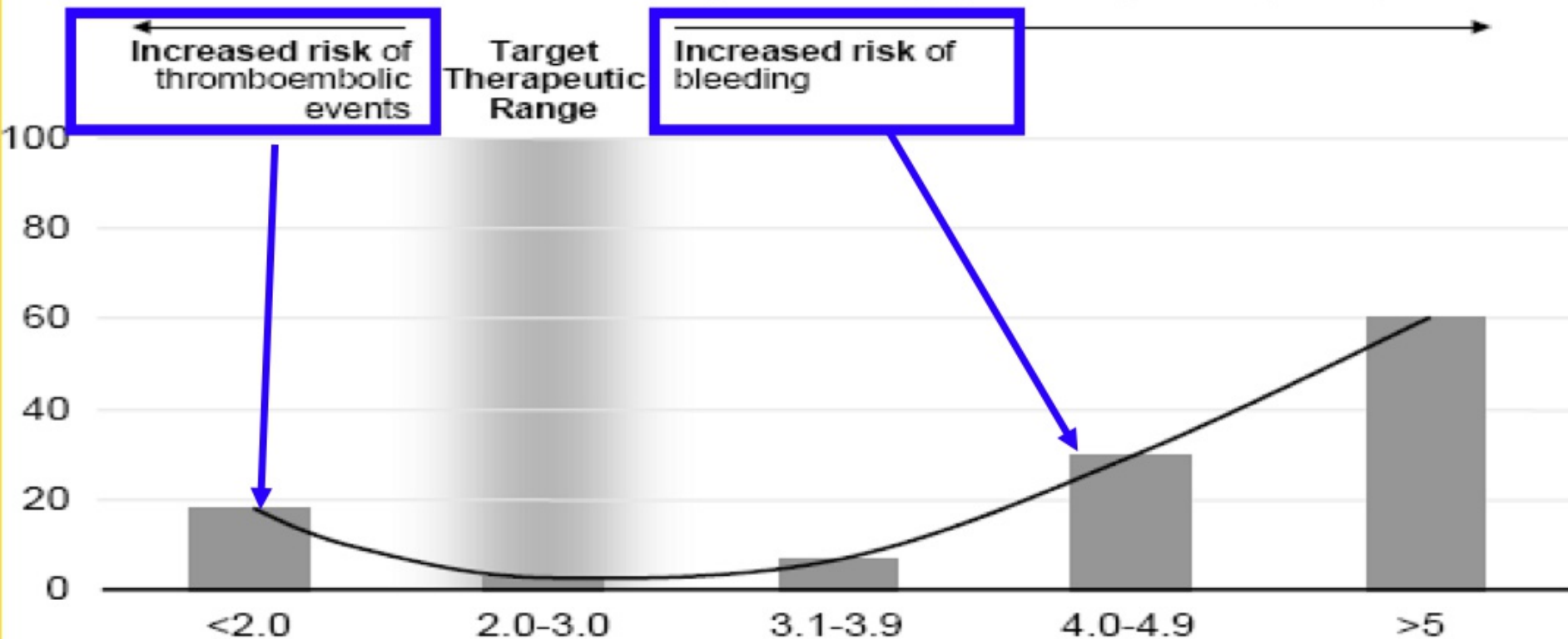
© Copyright Cavendish Press

**Dedicated: David Belk, who died of a brain haemorrhage brought on in a game of football, loved playing sports**

# Why Maintaining Warfarin Therapeutic Range is Critical

## Warfarin treatment

Incidence rate of stroke and major bleeding (per 100-person years)

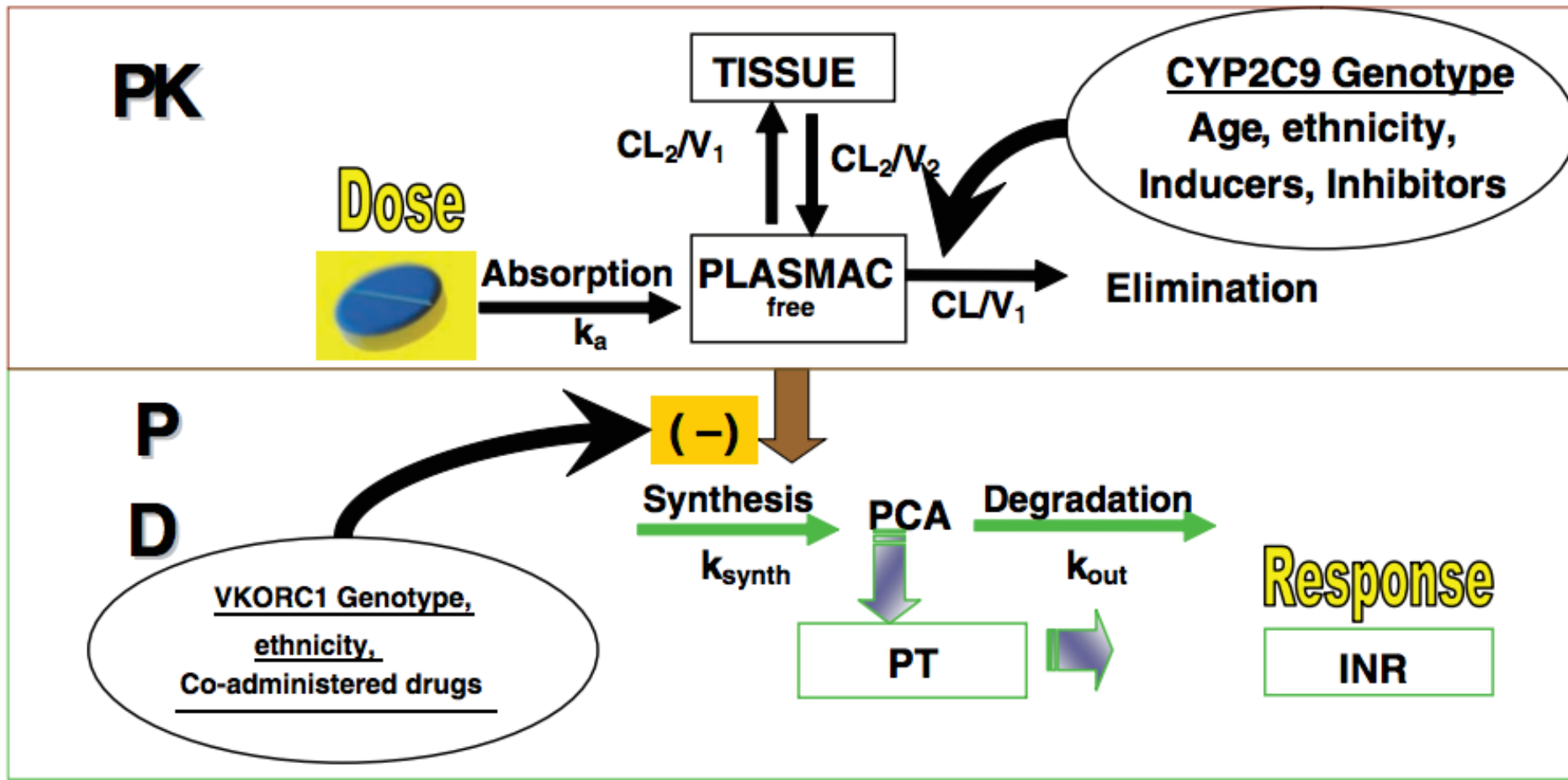


N Engl J Med 1995;333:5-10.

# Home INR measurement using Roche's CoaguChekXS



# Warfarin Levels Depend on Two Enzymes – CYP2C9 & VKORC1





# Warfarin Dosing Washington University

## WARFARIN DOSING

www.WarfarinDosing.org

> [Warfarin Dosing](#)

> [Clinical Trial](#)

> [Outcomes](#)

> [Hemorrhage Risk](#)

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> [About Us](#)

User:

Patient:

[Version 2.34](#)

Build : Jan 30, 2012

Welcome to **WarfarinDosing.org**, a free Web site to help doctors and other clinicians begin warfarin therapy by estimating the therapeutic dose in patients new to warfarin. This site is supported by the Barnes-Jewish Hospital at Washington University Medical Center, the NIH, and donations. Estimates are based on clinical factors and (when available) genotypes of two genes: *cytochrome P450 2C9 (CYP2C9)* and *vitamin K epoxide reductase (VKORC1)*.

Recommendations on this Web site are based on data from over 1000 patients. Once information is entered onto the next page, the initial estimate of therapeutic dose explains 53% of the variability in a warfarin dose. If you return to the Web site and enter an INR value after 3 and/or 4 warfarin doses, the dose refinement is even more accurate.

### Initial Information

Is this patient new to WarfarinDosing.org?

New patient     Existing patient

[Click here](#) to go to Clinical Trial Home.

Warfarin doses taken so far\*:

> CONTINUE

\*Required

Total visitors: 456739  
©Washington University in St. Louis.

# Warfarin Dosing Washington University

## WARFARIN DOSING

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User:  
Patient:  
[Version 2.34](#)  
Build : Jan 30, 2012

### Required Patient Information

Age:  Sex:  Ethnicity:

Race:

Weight:  lbs or  kgs

Height: ( feet and  inches) or ( cms)

Smokes:  Liver Disease:

Indication:

Baseline INR:  Target INR:   Randomize & Blind

Amiodarone/Cordarone® Dose:  mg/day

Statin/HMG CoA Reductase Inhibitor:

Any azole (eg. Fluconazole):

Sulfamethoxazole/Septtra/Bactrim/Cotrim/Sulfatrim:

### Genetic Information

VKORC1-1639/3673:

CYP4F2 V433M:

GGCX rs11676382:

CYP2C9\*2:

CYP2C9\*3:

CYP2C9\*5:

CYP2C9\*6:

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> ESTIMATE WARFARIN DOSE

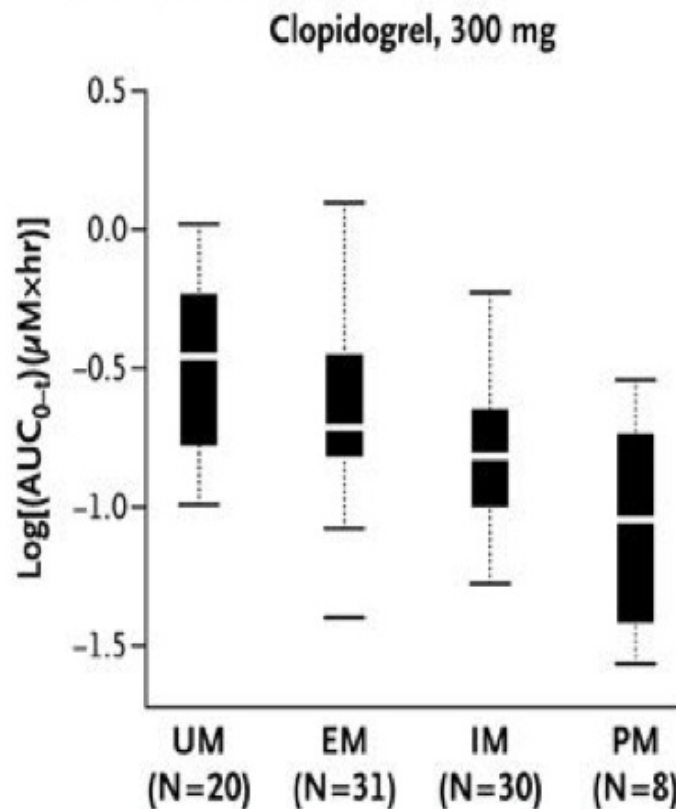
# Genetic Analysis Permits

---

- More rapid determination of stable therapeutic dose.
- Better prediction of dose than clinical methods alone.
- Applicable to the 70-75% of patients not in controlled anticoagulation centers.
- Reduces between 4,500 and 22,000 serious bleeding events annually.
- Genetic testing now required by FDA

# Another Anticoagulant Clopidogrel (Plavix) and CYP2C19 Alleles

## A Pharmacokinetic Response



**PM: with two reduced function alleles**

**IM: one reduced function allele**

**EM: no variant alleles;**

**UM: one or two \*17**

# Plavix Ad with Genetic Disclaimers



Show results for

[See new and recently updated reports »](#)

23andMe Discoveries were made possible by 23andMe members who took surveys.

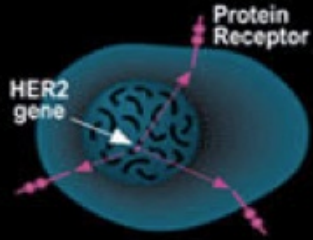
Name	Confidence ▾	Status
Clopidogrel (Plavix®) Efficacy	★★★★★	Greatly Reduced
Abacavir Hypersensitivity	★★★★★	Typical
Alcohol Consumption, Smoking and Risk of Esophageal Cancer	★★★★★	Typical
Fluorouracil Toxicity	★★★★★	Typical
Response to Hepatitis C Treatment	★★★★★	Typical
Pseudocholinesterase Deficiency	★★★★★	Typical
Warfarin (Coumadin®) Sensitivity	★★★★★	Typical
Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism ♀	★★★★★	Not Applicable
Caffeine Metabolism	★★★	Fast Metabolizer
Metformin Response <span style="background-color: #f4a460; padding: 2px;">new</span>	★★★	Typical Odds of Positive Response
Antidepressant Response	★★	See Report
Beta-Blocker Response	★★	See Report
Floxacin Toxicity	★★	Typical Odds
Heroin Addiction	★★	Typical Odds
Lumiracoxib (Prexige®) Side Effects	★★	Typical Odds
Naltrexone Treatment Response	★★	See Report
Postoperative Nausea and Vomiting (PONV)	★★	Higher Odds
Response to Interferon Beta Therapy	★★	Increased Odds of Responding
Statin Response	★★	See Report

# What are Targeted Drugs?

---

- Often, drugs are only effective in specific “sub-populations” (responders).
- Early identification of responders can have a dramatic effect of treatment success.
- Treatment of non-responders puts these individuals at unnecessary risk of adverse events, while providing no benefit.
- Personalized Medicine allows the identification of responders and non-responders for targeted therapies.
- This is happening today!

# Trastuzumab (Herceptin®)

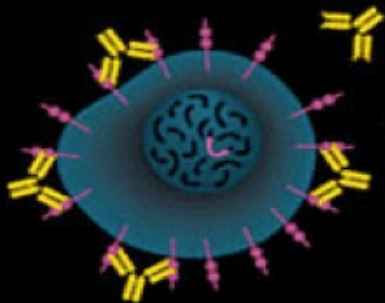


In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.



In certain types of breast cancers, the Her-2 gene is **over-expressing** this cell surface receptor, contributing to cancerous cell growth.

This is the case in ~30% of breast cancers.



**Herceptin (trastuzumab) is an antibody** that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.

# Targeted Drugs

---

- Herceptin (breast cancer, target: Her2 / neu)
- Erbitux (colorectal cancer, target: EGFR)
- Tarceva (lung cancer, target: EGFR)
- Strattera (attention-deficit / hyperactivity disorder, Metabolism: P4502D6)
- 6-MP (leukemia, Metabolism: TPMT)
- Antivirals (i.e. resistance based on form of HIV)
- etc. and the list is growing rapidly ...



## Overview of the Genomics and Targeted Therapy Group

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The Genomics and Targeted Therapy Group, in FDA's [Office of Clinical Pharmacology](#), works to advance the application of genomic technologies in the discovery, development, regulation, and use of medications.

Through pre-market review of therapeutics, policy development, regulatory research, and education, the Group ensures that pharmacogenomic and targeted development strategies are appropriately promoted and proactively applied in all phases of drug development.

### More in Genomics

▶ [Overview of the Genomics and Targeted Therapy Group](#)

[Publications on Genomics](#)



# FDA Requires Genetic Tests for 165 Therapies



U.S. Food and Drug Administration  
Protecting and Promoting *Your* Health

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## Drugs

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- Additional Research Areas



Science & Research (Drugs)
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<a href="#">Genomics</a>
<a href="#">Overview of the Genomics Group</a>
<a href="#">Presentations on Genomics</a>
<a href="#">Publications on Genomics</a>

### Table of Pharmacogenomic Biomarkers in Drug Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labels may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labels. Some, but not all, of the labels include specific actions to be taken based on genetic information. Relevant sections of the label with such information are noted in the last column of the table. Biomarkers may include gene variants, functional deficiencies, expression changes, chromosomal abnormalities, and others. Microbial variants that influence sensitivity to anti-infectives are not included in the table. Please note that the table columns can be sorted.

Pharmacogenomic information can appear in different sections of the label. For more information on the relevance of information in various parts of the drug label (e.g. Indications and Usage, Dosage and Administration, Boxed Warning, etc.), please go to the relevant labeling guidance. For information on the FDA's initiative to improve prescription drug labels, visit the FDA/CDER Learn website.

### Pharmacogenomic Biomarkers in Drug Labels

Drug	Therapeutic Area	Biomarker	Label Sections
<b>Abacavir</b>	Antivirals	HLA-B*5701	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information
<b>Ado-Trastuzumab Emtansine</b>	Oncology	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
<b>Aripiprazole</b>	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration
<b>Arsenic Trioxide</b>	Oncology	PML/RAR $\alpha$	Boxed Warning, Clinical Pharmacology, Indications and Usage, Warnings

# Roche Chip for Cytochrome P450 Genes: CYP2C19 and CYP2D6

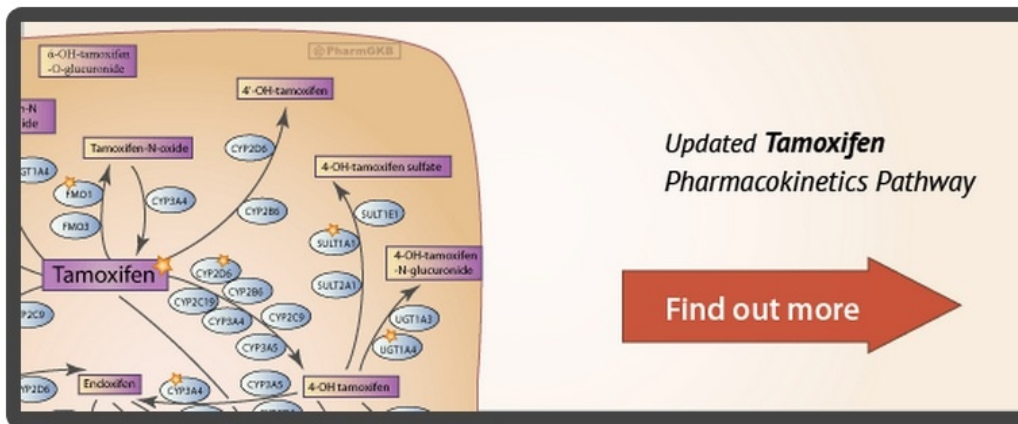
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**Pharmacogenomics. Knowledge. Implementation.**  
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

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[New Methylene Blue PD Pathway](#)

[TPMT allele nomenclature](#)

[Updated Tamoxifen PK Pathway](#)

[CPIC Allopurinol/HLA-B Guideline](#)

[PharmGKB Knowledge Pyramid](#)

### Clinically-Relevant PGx

- [Well-known PGx associations](#)
- [Clinically relevant PGx summaries](#)
- [PGx drug dosing guidelines](#)
- [Drug labels with PGx info](#)
- [Genetic tests for PGx](#)
- [Star \(\\*\) allele translations](#)

### PGx-Based Drug Dosing Guidelines

- [HLA-B/allopurinol:](#) [article](#) and [supplement](#)
- [SLCO1B1/simvastatin:](#) [article](#) and [supplement](#)
- [more guidelines...](#)

[CPIC Gene-Drug Pairs](#)

[TPP Gene Tables](#)

### PGx Research

- **VIP:** [Very Important PGx gene summaries](#)
- [View PharmGKB pathways](#)
  - [Alphabetically](#)
  - [By therapeutic category](#)
- [Annotated SNPs by gene](#)
- [Drugs with genetic information](#)

## Well-Known Pharmacogenomic Associations

The following icons indicate that data of a certain type is available:

- DG** Dosing Guideline information is available
- DL** Drug Label information is available
- CA** High-level Clinical Annotation is available
- VA** Variant Annotation is available
- VIP** VIP information is available
- PW** Pathway is available

[ [close](#) ]

Drug	Gene	Types of data
<a href="#">abacavir</a>	<a href="#">HLA-B</a>	<b>DG</b> <b>DL</b> <b>CA</b> <b>VA</b>
<a href="#">acenocoumarol</a>	<a href="#">CYP2C9</a>	<b>DG</b> <b>CA</b> <b>VA</b>
<a href="#">acenocoumarol</a>	<a href="#">VKORC1</a>	<b>DG</b> <b>CA</b> <b>VA</b> <b>VIP</b>
<a href="#">acetaminophen</a>	<a href="#">CYP2D6</a>	<b>DL</b> <b>PW</b>
<a href="#">allopurinol</a>	<a href="#">HLA-B</a>	<b>DG</b> <b>CA</b> <b>VA</b>
<a href="#">amitriptyline</a>	<a href="#">CYP2D6</a>	<b>DG</b> <b>DL</b> <b>VA</b> <b>VIP</b>
<a href="#">aripiprazole</a>	<a href="#">CYP2D6</a>	<b>DG</b> <b>DL</b>
<a href="#">aripiprazole</a>	<a href="#">CYP3A4</a>	<b>DL</b> <b>VIP</b>
<a href="#">arsenic trioxide</a>	<a href="#">PML</a>	<b>DL</b>
<a href="#">arsenic trioxide</a>	<a href="#">RARA</a>	<b>DL</b>
<a href="#">atomoxetine</a>	<a href="#">CYP2D6</a>	<b>DG</b> <b>DL</b> <b>VIP</b>

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## Dosing Guidelines

These dosing guidelines take into consideration patient genotype and have been published by the [Clinical Pharmacogenetics Implementation Consortium](#), [Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group \(DPWG\)](#) (manually curated by PharmGKB), or other professional society ([PRO](#)).

Title	Drug - Gene Pair
<a href="#">Dosing Guidelines for abacavir</a>	<a href="#">CPIC</a> <a href="#">abacavir HLA-B</a> <a href="#">DPWG</a> <a href="#">abacavir HLA-B</a>
<a href="#">Dosing Guidelines for acenocoumarol</a>	<a href="#">DPWG</a> <a href="#">acenocoumarol CYP2C9</a> <a href="#">DPWG</a> <a href="#">acenocoumarol VKORC1</a>
<a href="#">Dosing Guidelines for allopurinol</a>	<a href="#">CPIC</a> <a href="#">allopurinol HLA-B</a> <a href="#">PRO</a> <a href="#">allopurinol HLA-B</a>
<a href="#">Dosing Guidelines for amitriptyline</a>	<a href="#">DPWG</a> <a href="#">amitriptyline CYP2D6</a>
<a href="#">Dosing Guidelines for aripiprazole</a>	<a href="#">DPWG</a> <a href="#">aripiprazole CYP2D6</a>
<a href="#">Dosing Guidelines for atomoxetine</a>	<a href="#">DPWG</a> <a href="#">atomoxetine CYP2D6</a>
<a href="#">Dosing Guidelines for azathioprine</a>	<a href="#">CPIC</a> <a href="#">azathioprine TPMT</a> <a href="#">DPWG</a> <a href="#">azathioprine TPMT</a>
<a href="#">Dosing Guidelines for capecitabine</a>	<a href="#">DPWG</a> <a href="#">capecitabine DPYD</a>
<a href="#">Dosing Guidelines for carvedilol</a>	<a href="#">DPWG</a> <a href="#">carvedilol CYP2D6</a>
<a href="#">Dosing Guidelines for citalopram</a>	<a href="#">DPWG</a> <a href="#">citalopram CYP2C19</a>
<a href="#">Dosing Guidelines for clomipramine</a>	<a href="#">DPWG</a> <a href="#">clomipramine CYP2D6</a>
<a href="#">Dosing Guidelines for clopidogrel</a>	<a href="#">CPIC</a> <a href="#">clopidogrel CYP2C19</a> <a href="#">DPWG</a> <a href="#">clopidogrel CYP2C19</a>
<a href="#">Dosing Guidelines for clozapine</a>	<a href="#">DPWG</a> <a href="#">clozapine CYP2D6</a>
<a href="#">Dosing Guidelines for codeine</a>	<a href="#">CPIC</a> <a href="#">codeine CYP2D6</a> <a href="#">DPWG</a> <a href="#">codeine CYP2D6</a>
<a href="#">Dosing Guidelines for doxepin</a>	<a href="#">DPWG</a> <a href="#">doxepin CYP2D6</a>

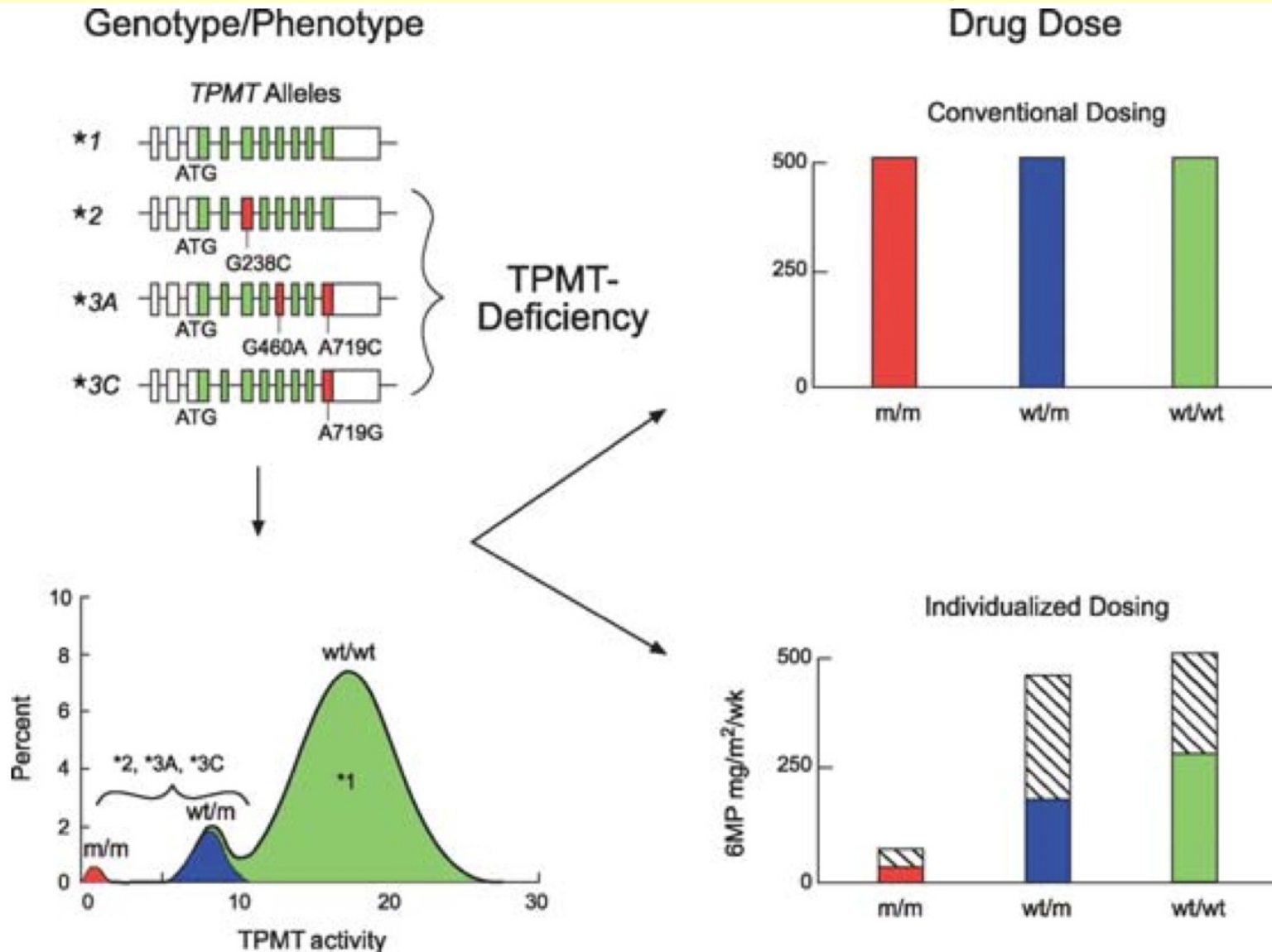
# Genetic Tests from PharmGKB

## Genetic Tests

This is a **non-comprehensive** list of genetic tests with pharmacogenetics relevance (manually curated by PharmGKB). The information listed is provided for educational purposes only and **does not** constitute an endorsement of any listed test or manufacturer. If you would like to suggest a test to add, please [email us](#).

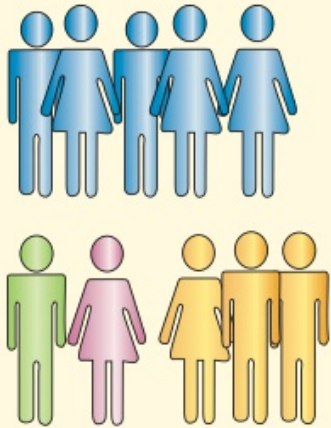
Genetic Test	Genes	Related Drugs
<a href="#"><u>Roche AmpliChip CYP450 Test</u></a>	<a href="#"><u>CYP2C19</u></a> <a href="#"><u>CYP2D6</u></a>	<a href="#"><u>amitriptyline</u></a> , <a href="#"><u>clomipramine</u></a> , <a href="#"><u>clopidogrel</u></a> , <a href="#"><u>codeine</u></a> , <a href="#"><u>desipramine</u></a> , <a href="#"><u>doxepin</u></a> , <a href="#"><u>esomeprazole</u></a> , <a href="#"><u>fluoxetine</u></a> , <a href="#"><u>imipramine</u></a> , <a href="#"><u>metoprolol</u></a> , <a href="#"><u>nortriptyline</u></a> , <a href="#"><u>omeprazole</u></a> , <a href="#"><u>paroxetine</u></a> , <a href="#"><u>phenytoin</u></a> , <a href="#"><u>risperidone</u></a> , <a href="#"><u>tamoxifen</u></a> , <a href="#"><u>trimipramine</u></a>
<a href="#"><u>DMET Plus (Affymetrix, Inc)</u></a>	<a href="#"><u>CYP2C19</u></a> <a href="#"><u>CYP2C9</u></a> <a href="#"><u>CYP2D6</u></a> <a href="#"><u>SLCO1B1</u></a> <a href="#"><u>VKORC1</u></a>	<a href="#"><u>amitriptyline</u></a> , <a href="#"><u>clomipramine</u></a> , <a href="#"><u>clopidogrel</u></a> , <a href="#"><u>codeine</u></a> , <a href="#"><u>desipramine</u></a> , <a href="#"><u>doxepin</u></a> , <a href="#"><u>fluoxetine</u></a> , <a href="#"><u>imipramine</u></a> , <a href="#"><u>nortriptyline</u></a> , <a href="#"><u>paroxetine</u></a> , <a href="#"><u>simvastatin</u></a> , <a href="#"><u>trimipramine</u></a> , <a href="#"><u>warfarin</u></a>
<a href="#"><u>VeraCode ADME Core Panel (Illumina, Inc)</u></a>	<a href="#"><u>CYP2C19</u></a> <a href="#"><u>CYP2C9</u></a> <a href="#"><u>CYP2D6</u></a> <a href="#"><u>SLCO1B1</u></a> <a href="#"><u>VKORC1</u></a>	<a href="#"><u>amitriptyline</u></a> , <a href="#"><u>clomipramine</u></a> , <a href="#"><u>clopidogrel</u></a> , <a href="#"><u>codeine</u></a> , <a href="#"><u>desipramine</u></a> , <a href="#"><u>doxepin</u></a> , <a href="#"><u>fluoxetine</u></a> , <a href="#"><u>imipramine</u></a> , <a href="#"><u>nortriptyline</u></a> , <a href="#"><u>paroxetine</u></a> , <a href="#"><u>simvastatin</u></a> , <a href="#"><u>trimipramine</u></a> , <a href="#"><u>warfarin</u></a>
<a href="#"><u>TaqMan Drug Metabolism Genotyping Assay Sets (Applied Biosystems, Inc)</u></a>	<a href="#"><u>CYP2C19</u></a> <a href="#"><u>CYP2C9</u></a> <a href="#"><u>CYP2D6</u></a> <a href="#"><u>VKORC1</u></a>	<a href="#"><u>amitriptyline</u></a> , <a href="#"><u>clomipramine</u></a> , <a href="#"><u>clopidogrel</u></a> , <a href="#"><u>codeine</u></a> , <a href="#"><u>desipramine</u></a> , <a href="#"><u>doxepin</u></a> , <a href="#"><u>fluoxetine</u></a> , <a href="#"><u>imipramine</u></a> , <a href="#"><u>nortriptyline</u></a> , <a href="#"><u>paroxetine</u></a> , <a href="#"><u>trimipramine</u></a> , <a href="#"><u>warfarin</u></a>
<a href="#"><u>Laboratory Corporation of America</u></a>	<a href="#"><u>CYP2C19</u></a> <a href="#"><u>CYP2D6</u></a>	<a href="#"><u>amitriptyline</u></a> , <a href="#"><u>clomipramine</u></a> , <a href="#"><u>clopidogrel</u></a> , <a href="#"><u>codeine</u></a> , <a href="#"><u>desipramine</u></a> , <a href="#"><u>doxepin</u></a> , <a href="#"><u>fluoxetine</u></a> , <a href="#"><u>imipramine</u></a> , <a href="#"><u>nortriptyline</u></a> , <a href="#"><u>paroxetine</u></a> , <a href="#"><u>trimipramine</u></a>
<a href="#"><u>Quest Diagnostics, Inc</u></a>	<a href="#"><u>CYP2D6</u></a>	<a href="#"><u>amitriptyline</u></a> , <a href="#"><u>clomipramine</u></a> , <a href="#"><u>codeine</u></a> , <a href="#"><u>desipramine</u></a> , <a href="#"><u>doxepin</u></a> , <a href="#"><u>fluoxetine</u></a> ,

# Thiopurine S-methyl Transferase Activity and Personalized Dosage



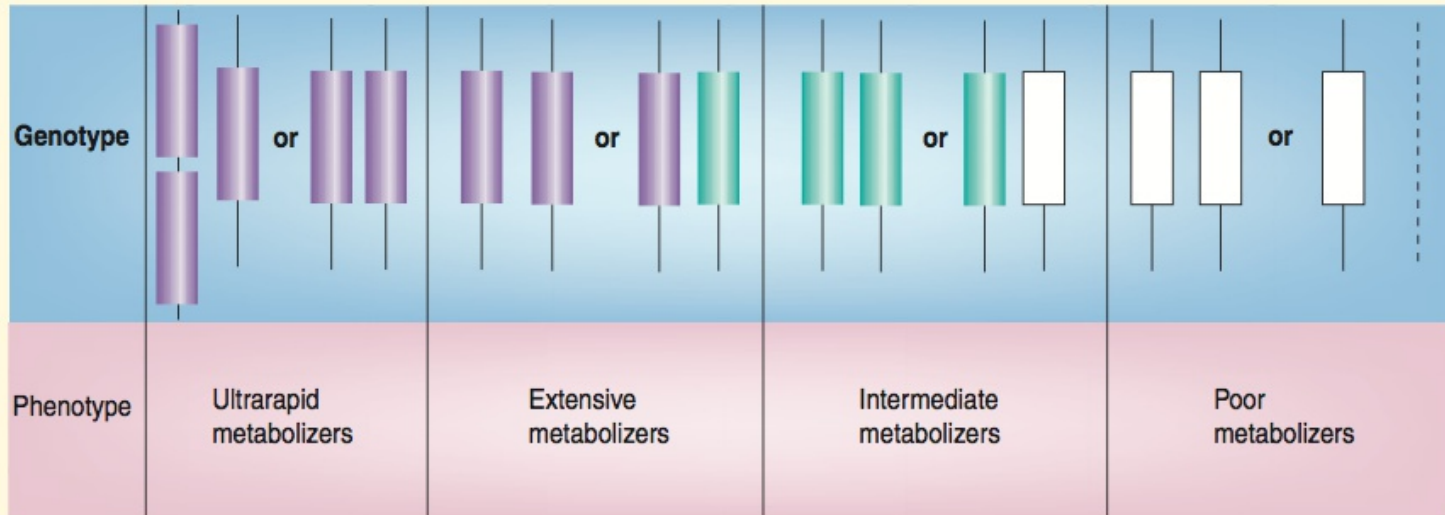
# Personalized Medicine

Before:  
one-dose-fits-all  
approach



100 mg

After: personalized medicine (from genotype to phenotype)



500 mg

100 mg

10 mg

# Effect of Metabolic Rate on Drug Dosage

Drug	Poor Metabolizer Phenotype
<b>Prodrug, needs metabolism to work (eg. codeine is metabolized by CYP 2D6 to morphine)</b>	<b>Poor efficacy</b> <b>Possible accumulation of prodrug</b>
<b>Active drug, inactivated by metabolism (example is omeprazole)</b>	<b>Good efficacy</b> <b>Accumulation of active drug can produce adverse reactions</b> <b>May need lower dose</b>

Drug	Ultra-rapid Metabolizer Phenotype
<b>Prodrug, needs metabolism to work (eg. codeine is metabolized by CYP 2D6 to morphine)</b>	<b>Good efficacy, rapid effect</b>
<b>Active drug, inactivated by metabolism (example is omeprazole)</b>	<b>Poor efficacy</b> <b>Need greater dose or slow release formulation</b>