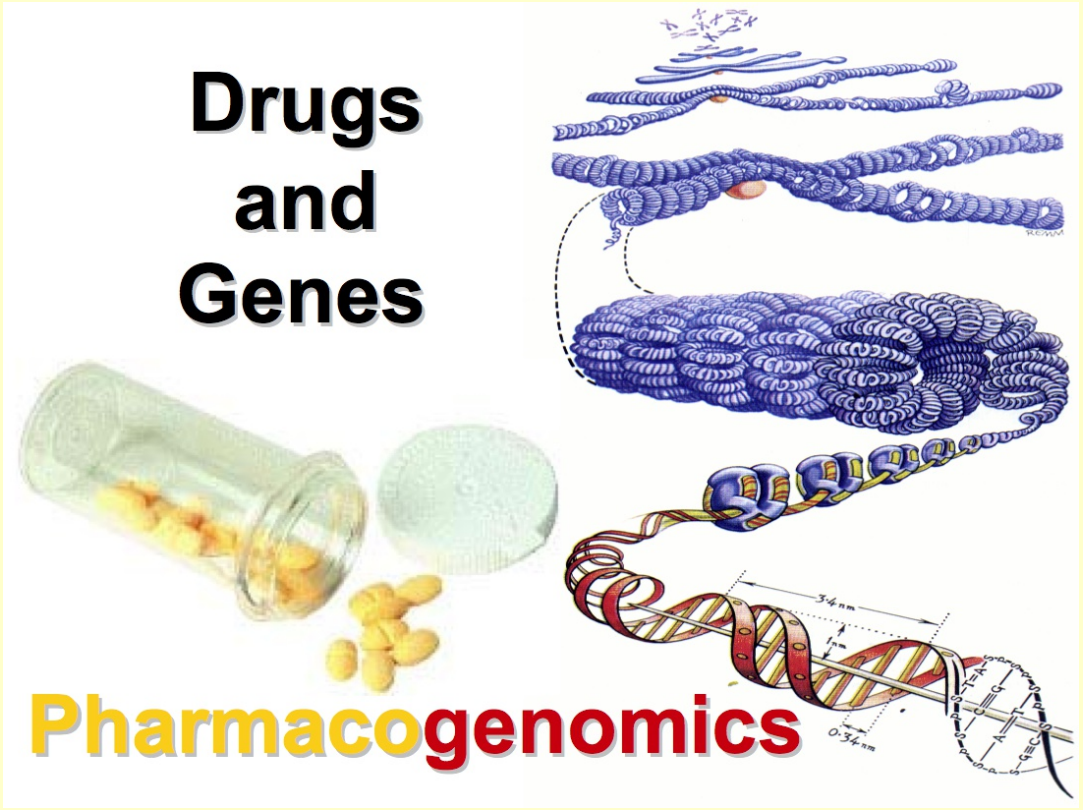
Genomics, Bioinformatics & Medicine

http://biochem158.stanford.edu/

Pharmacogenomics

http://biochem158.stanford.edu/Drug-Development.html



Doug Brutlag
Professor Emeritus of Biochemistry and Medicine
Stanford University School of Medicine
brutlag@stanford.edu

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 well be a science, not an art.

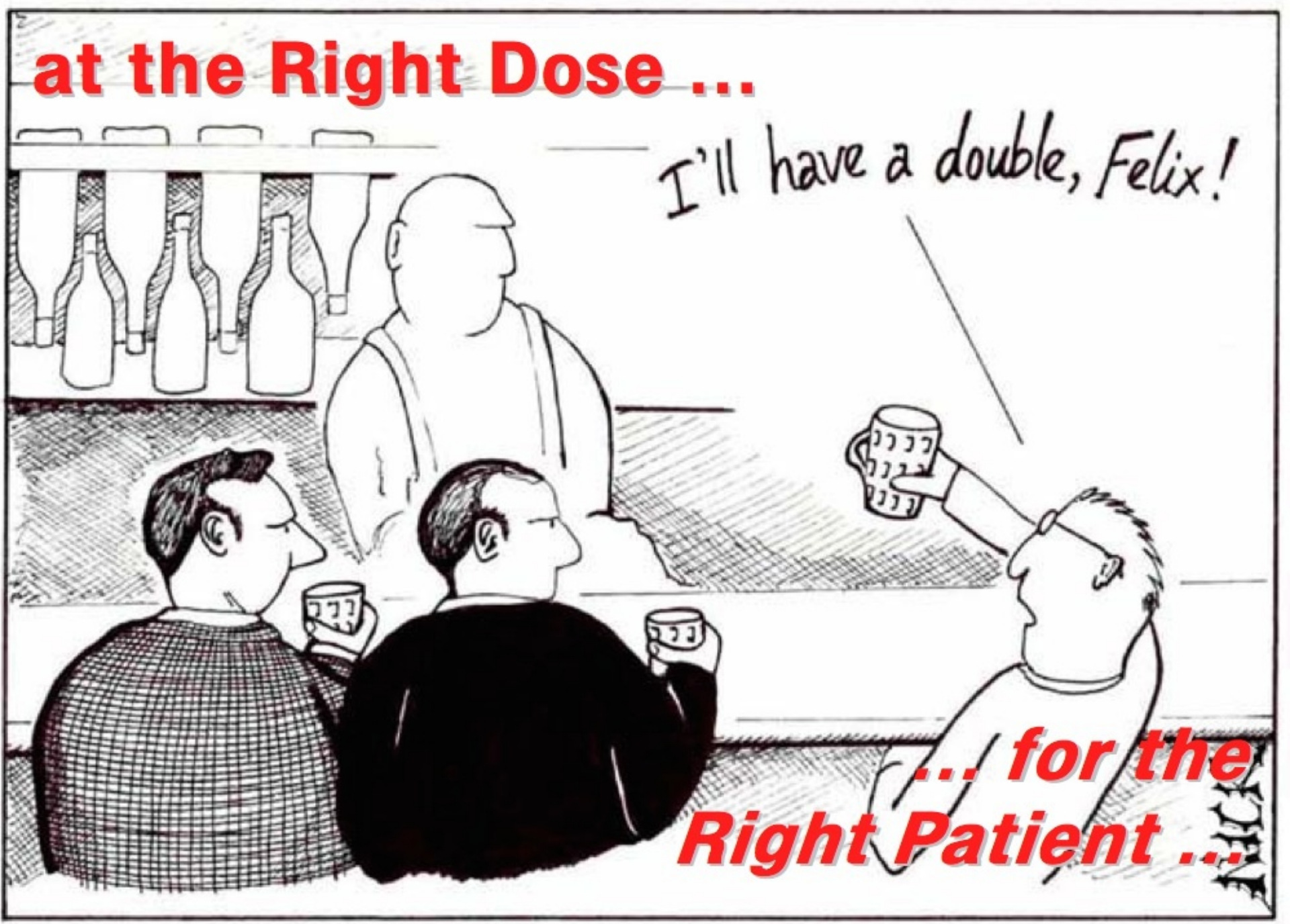
- Sir William Osler, Physician 1892
- Johns Hopkins School of Medicine
- Johns Hopkins Hospital
- Father of modern medicine

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.

Courtesy Felix W. Frueh

at the Right Dose …



Courtesy Felix W. Frueh

Variability of Disease

Example: Leukemia and Lymphoma

1950	"Disease of the Blood"	
1960	Leukemia	Lymphoma
1970	Chronic Leukemia Acute Leukemia Preleukemia	Indolent Lymphoma Aggressive Lymphoma
2007	~38 Leukemia types identified: Acute myeloid leukemia (~12 types) Acute lymphoblastic leukemia (2 types) Acute promyelocytic leukemia (2 types) Acute monocytic leukemia (2 types) Acute erythroid leukemia (2 types) Acute megakaryoblastic leukemia Acute myelomonocytic leukemia (2 types) Chronic myeloid leukemia Chronic myeloproliferative disorders (5 types) Myelodysplastic syndromes (6 types) Mixed myeloproliferative/myelodysplastic syndromes (3 types)	~51 Lymphomas identified: Mature B-cell lymphomas (~14 types) Mature T-cell lymphomas (15 types) Plasma cell neoplasm (3 types) Immature (precursor) lymphomas (2 types) Hodgkin's lymphoma (5 types) Immunodeficiency associated lymphomas (~5 types) Other hematolymphoid neoplasms (~7 types)

5 Year Survival

~ 0%

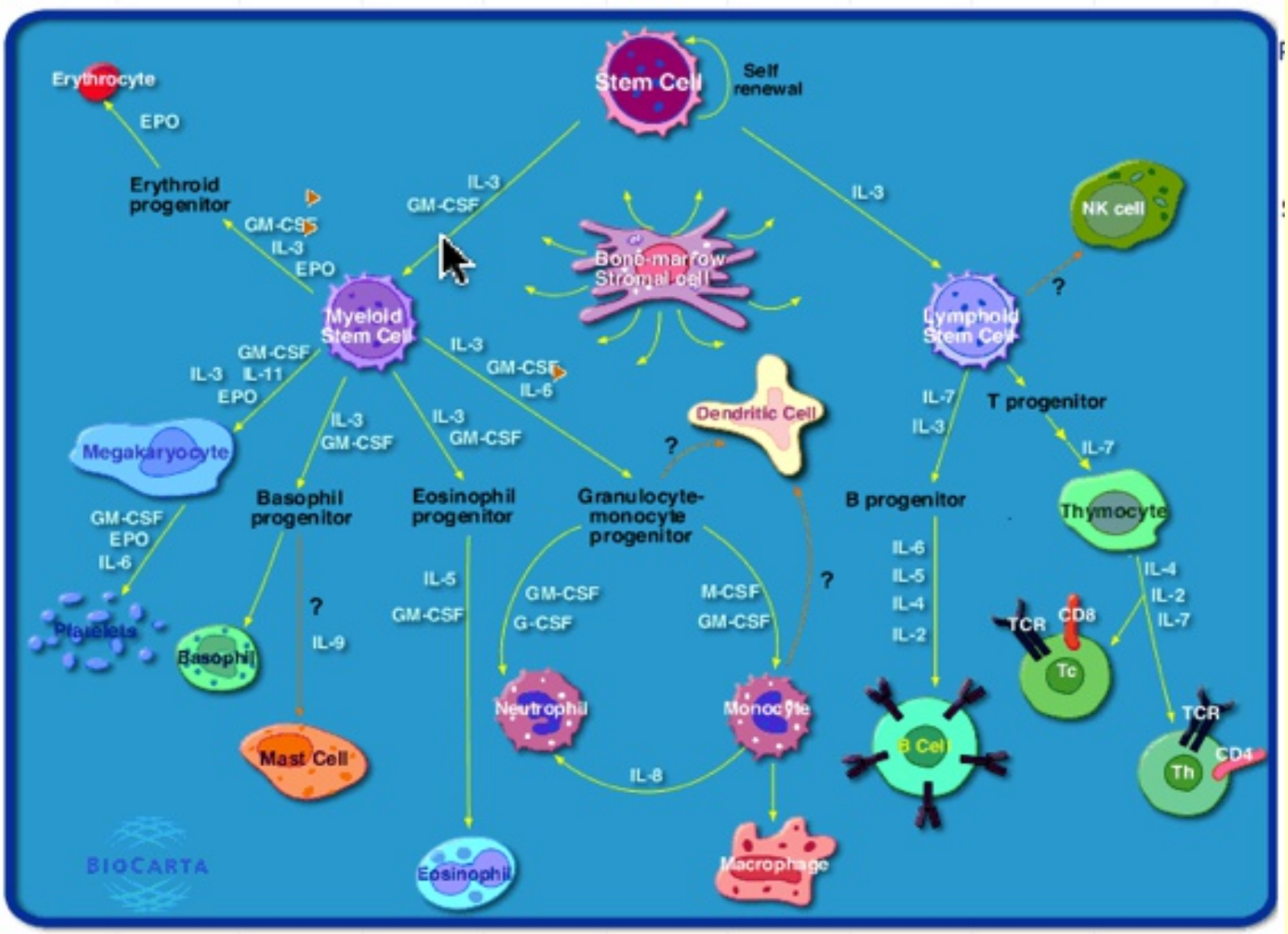
~ 70%

After Mara Aspinall, Genzyme Genetics (modified)

Courtesy Felix W. Frueh

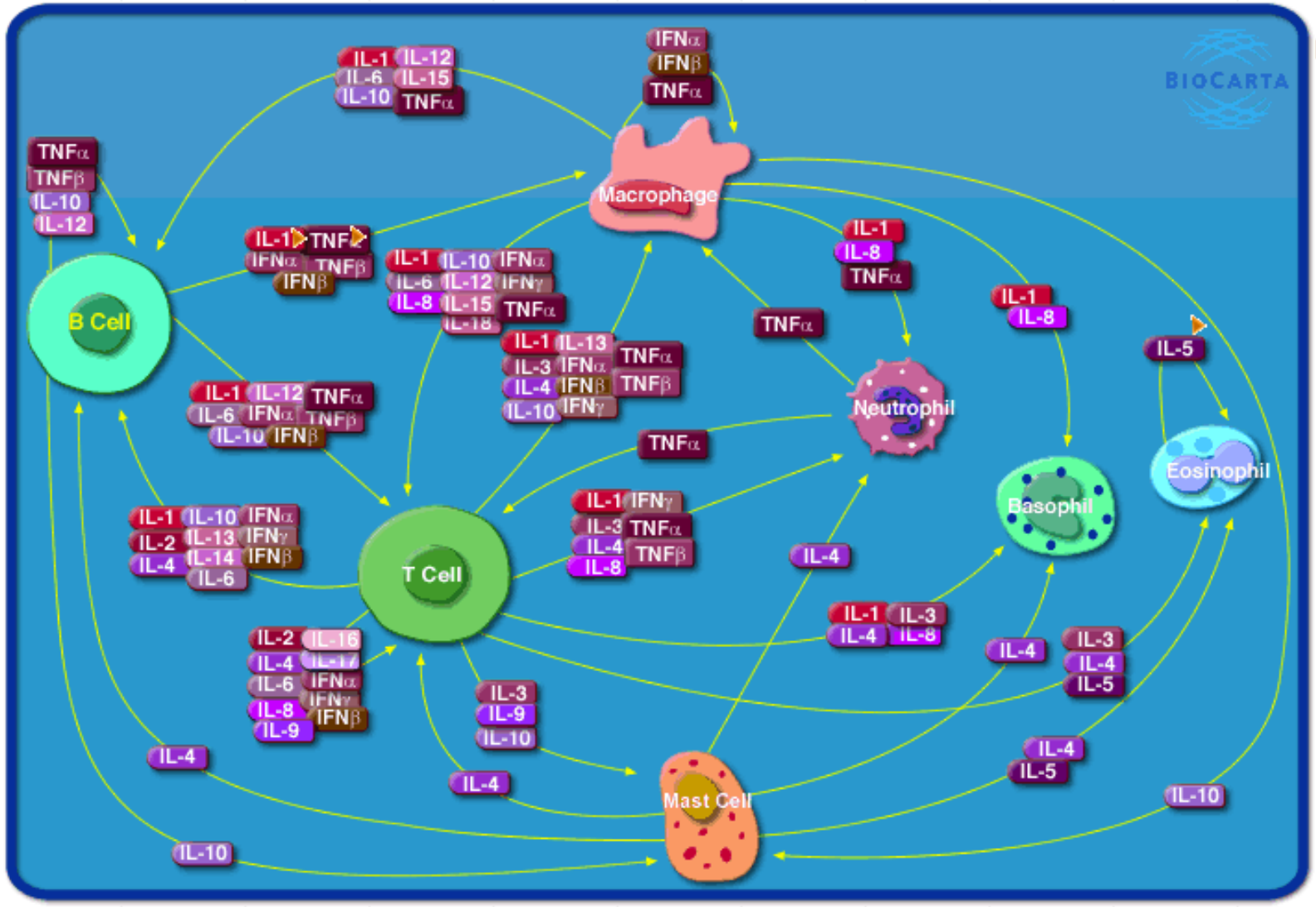
Hematopoiesis

http://www.biocarta.com/pathfiles/h_stemPathway.asp



Cytokine Network

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.
- "Molecular Targeted Therapy"[Majr]
  - "Molecular Targeted Therapy"[Majr]
- FDA Fast Tracks Approval of Targeted Drug Therapies
  - http://p.nytimes.com/email/re?location=InCMR7g4BCKC2wiZPk
    0

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

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 individuals entire genetic makeup.
  - Felix Frueh, Associate Director of Genomics, FDA

Courtesy Felix W. Frueh

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)

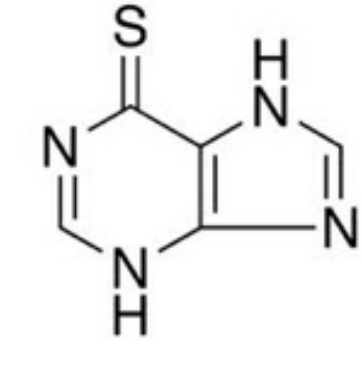
- Pharmacogenomics: study of genomic influence on drug response, often using high-throughput data (sequencing, SNP chip, expression, proteomics - COMPLEX interactions)

  - PharmGKB Website: http://www.pharmgkb.org/

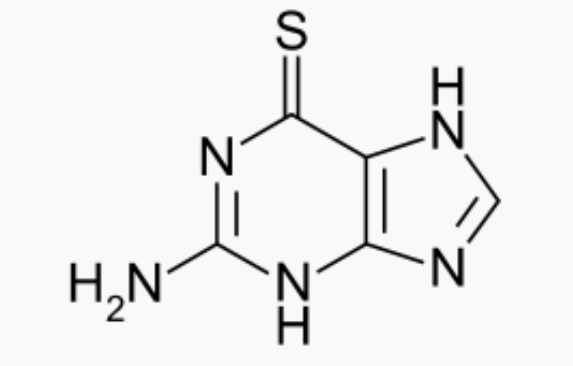
Courtesy of PharmGKB Web Site

Purine Analogs: A Case Study in Pharmacogenetics

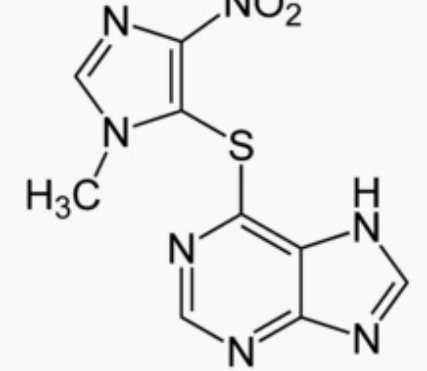
- 6-mercaptopurine, 6-thioguanine, azathioprine
- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, immune supression after organ transplants
- Interferes with nucleic acid synthesis
- Therapeutic index limited by myelosuppression



6-mercaptopurine

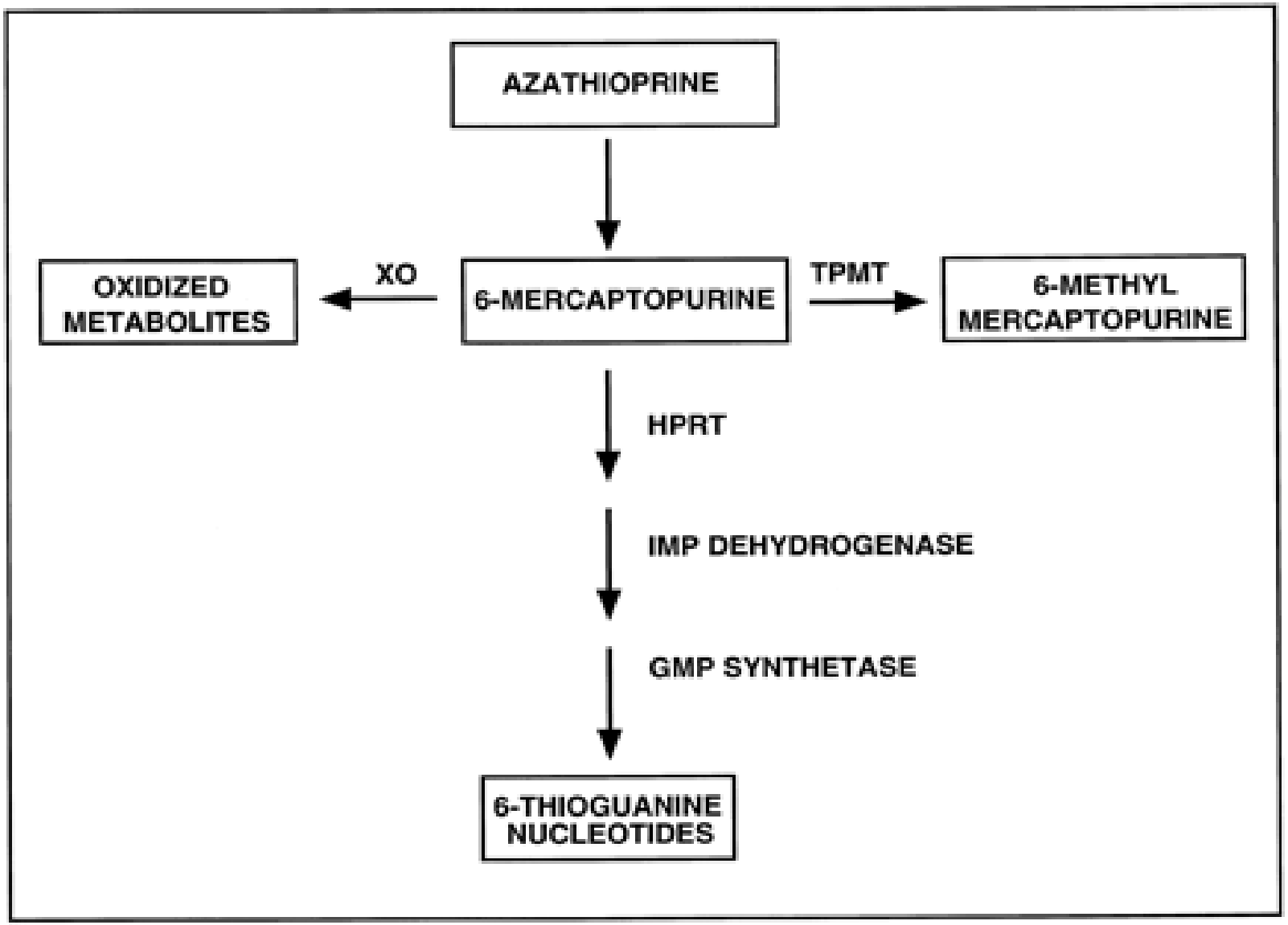


6-thioguanine



azathioprine

Metabolism of 6-MP



L Wang and R Weinshilboum, Oncogene 25, 1629-1638 (2006)

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.

Courtesy of Michelle Whirl-Carillo

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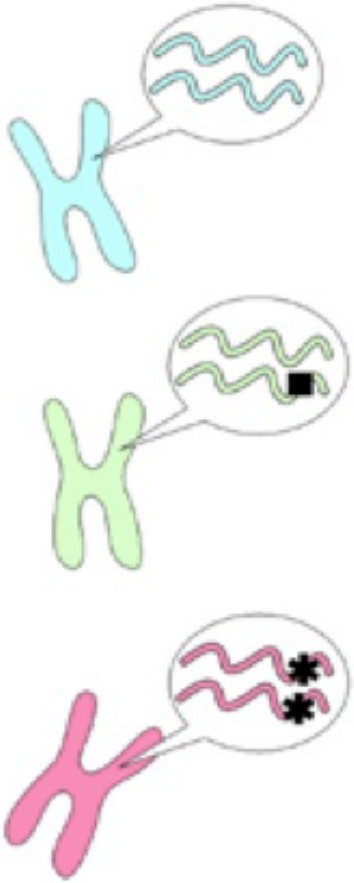
The diversity in responses is due to variations in the gene for an enzyme called TPMT, or thiopurine methyltransferase.



Courtesy of Michelle Whirl-Carillo

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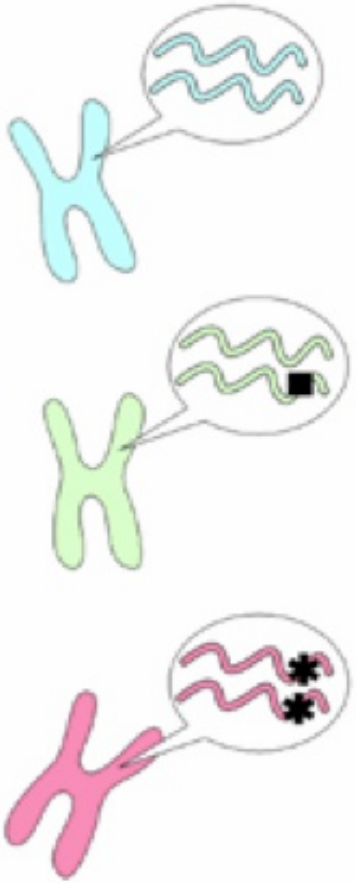
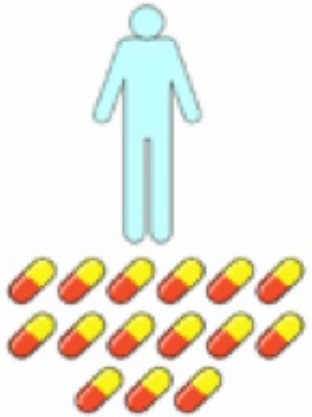


After a simple blood test, individuals can be given doses of medication that are tailored to their genetic profile.

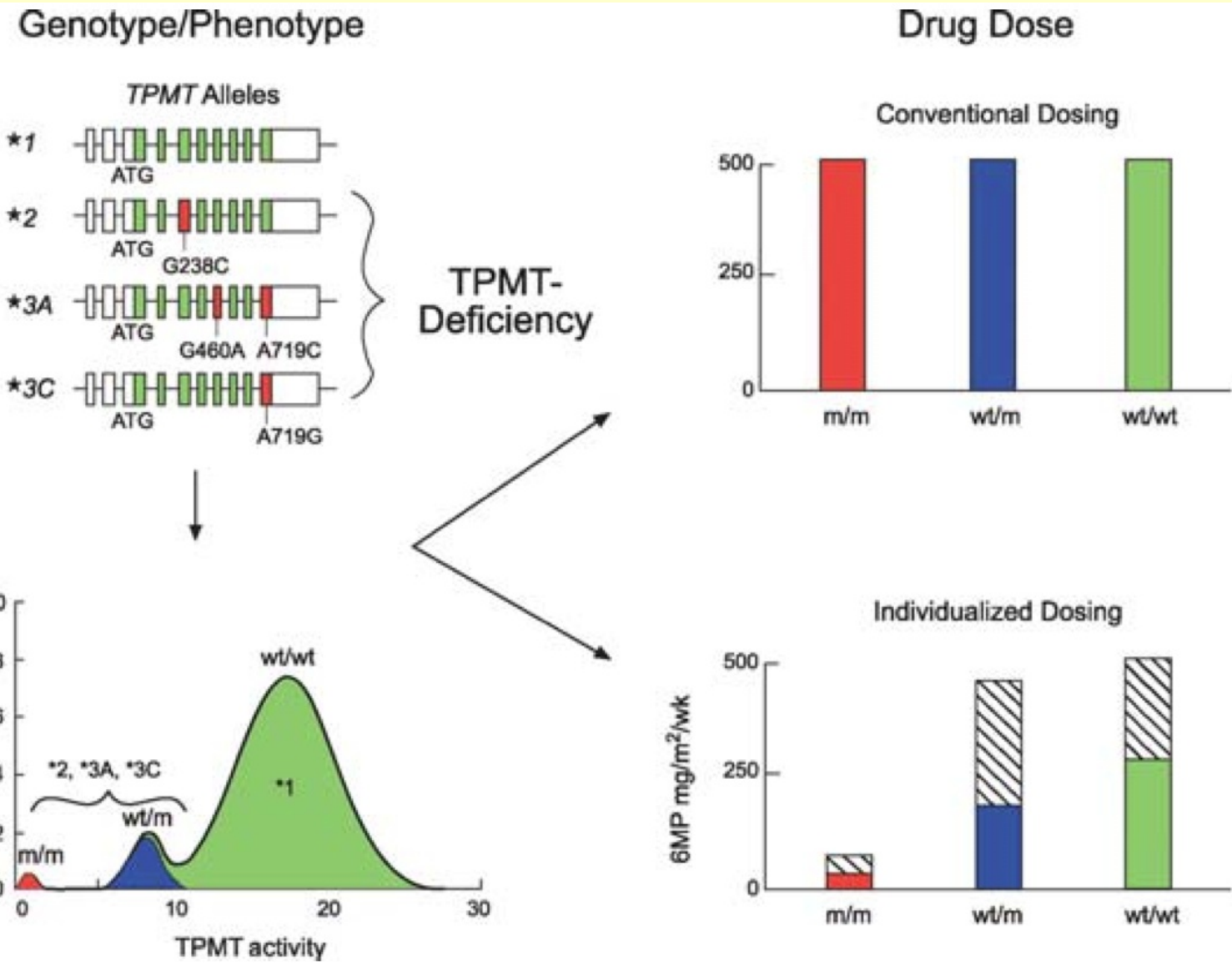


Normal dose

Dose for an extra slow metabolizer (TPMT deficient)

Courtesy of Michelle Whirl-Carillo

Thiopurine S-methyl Transferase Activity and Personalized Dosage



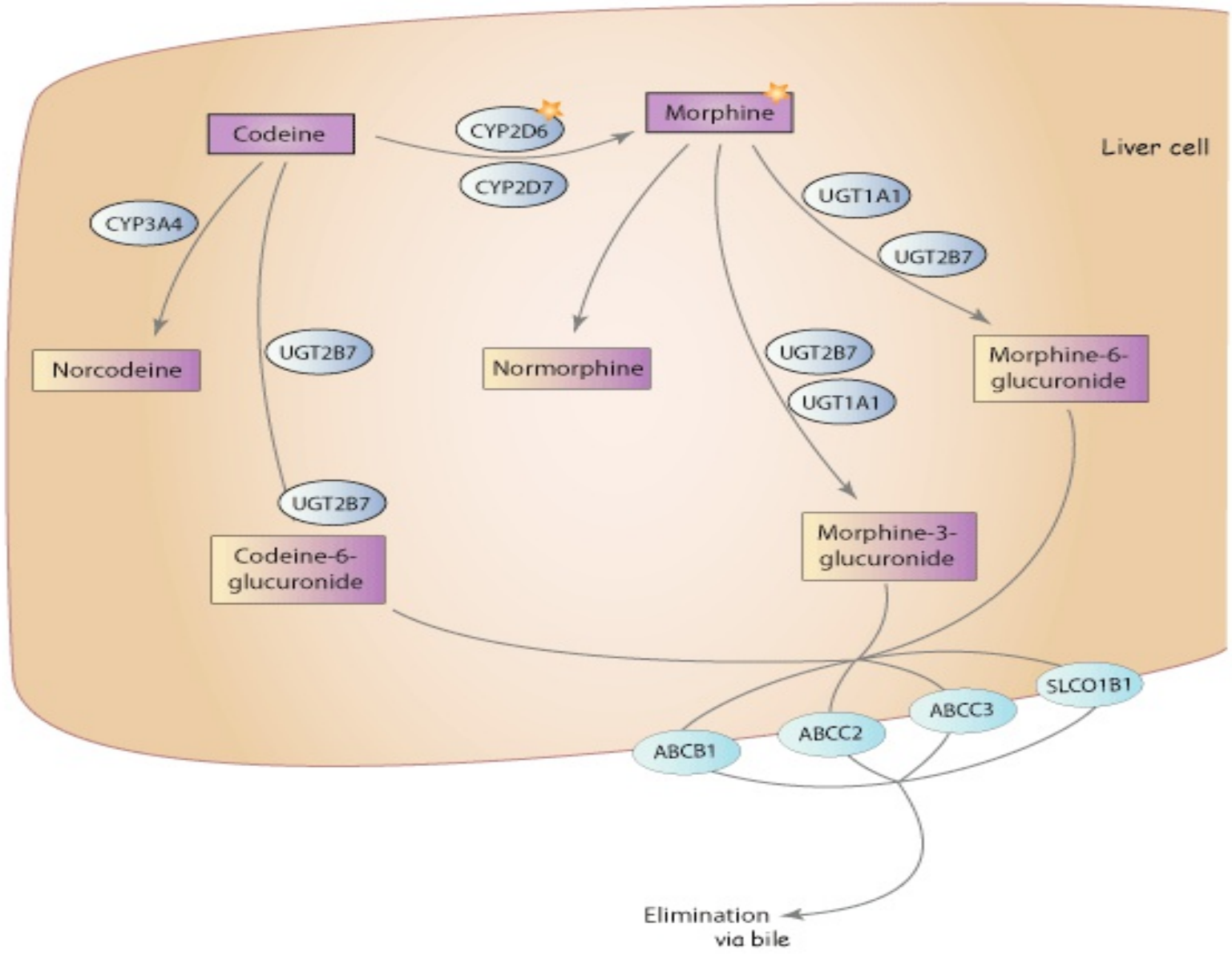
Eichelbaum et al., Annu. Rev. Med. 2006.57:119-137.

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

Courtesy of Michelle Whirl-Carillo

Codeine and Morphine Metabolism



Courtesy of PharmGKB

Human Cytochrome Oxidase P450 Enzymes

http://en.wikipedia.org/wiki/Cytochrome_P450#P450s_in_humans

- 57 Different active genes
- 18 Different families
- 43 subfamilies
- 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

Human Glutathione S Transferases

http://en.wikipedia.org/wiki/Glutathione_S-transferase

GST Class	*Homo sapiens* GST Class Members (22)
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

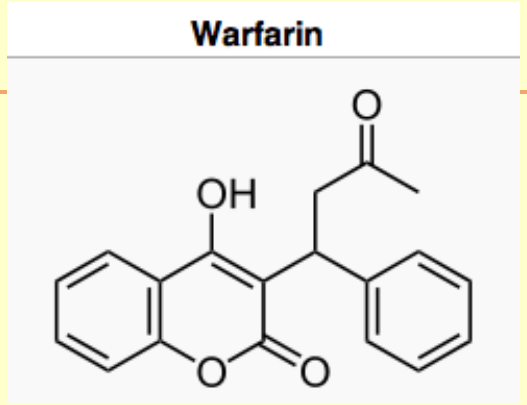
Selected Substrates	Location	Poor Metabolizer Incidence
antidepressants beta-blockers antipsychotics chlorpheniramine codeine dextromethorphan ondansetron lidocaine promethazine tamoxifen tramadol	Chromosome 22	5-10% Caucasians

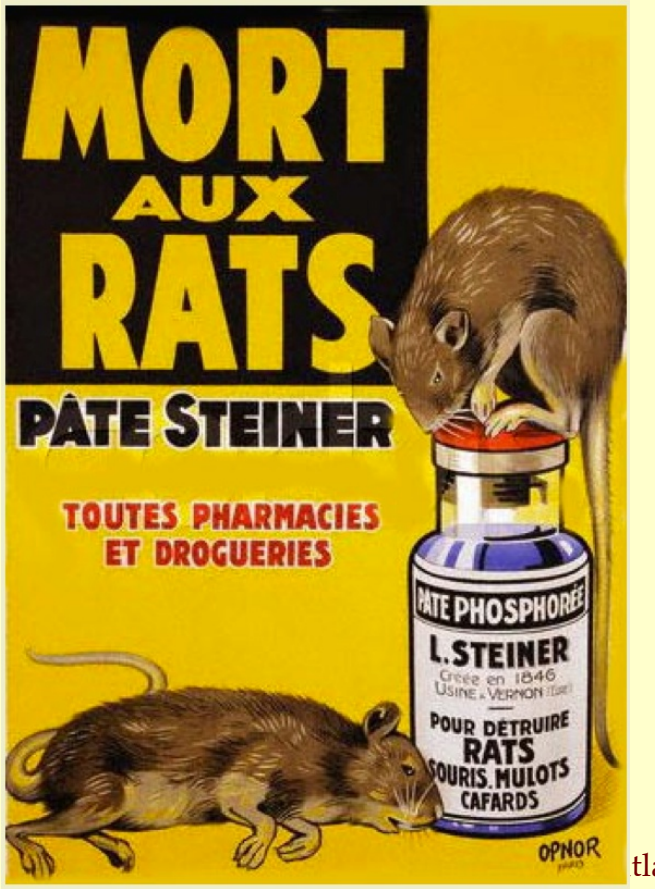
Effect of Metabolic Rate on Drug Dosage

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

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

Warfarin: Significant Problems for Rats!





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 randomized control trials of new anticoagulants has been as high as 29% per year.

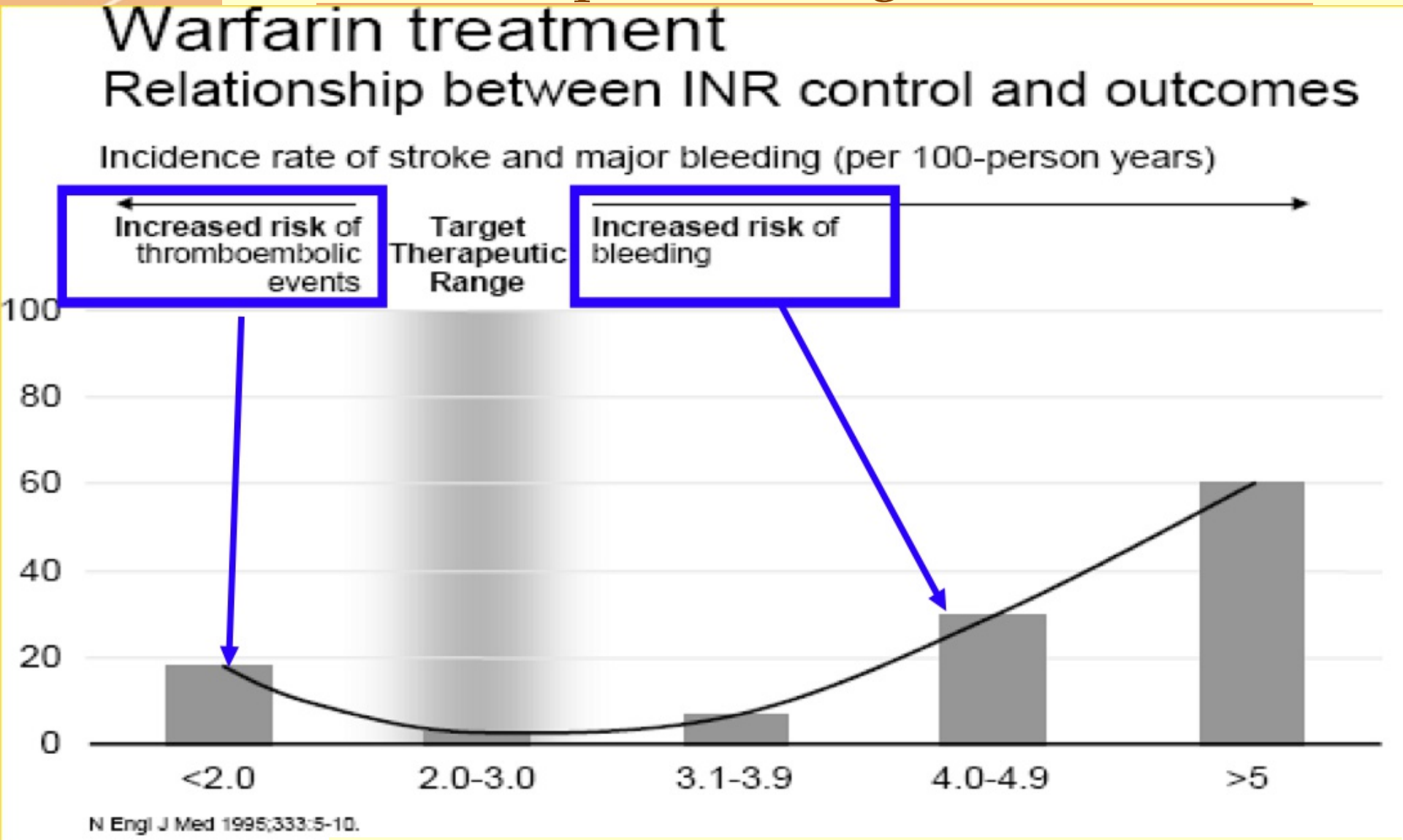
Warfarin: Significant Problems for Humans!

- 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

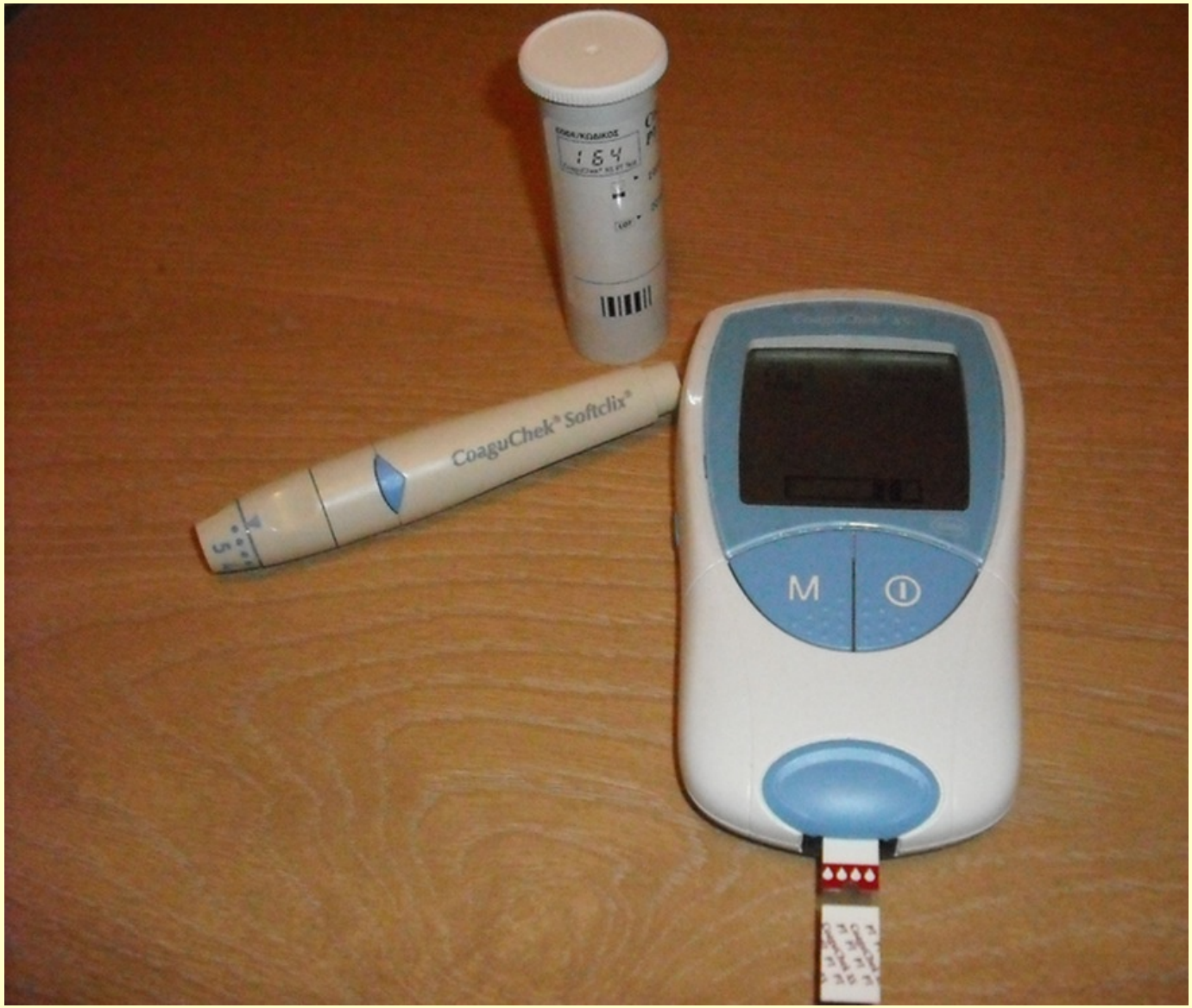
Dedicated: David Belk, who died of a brain haemorrhage brought on in a game of football, loved playing sports

Why Maintaining Warfarin Therapeutic Range is Critical

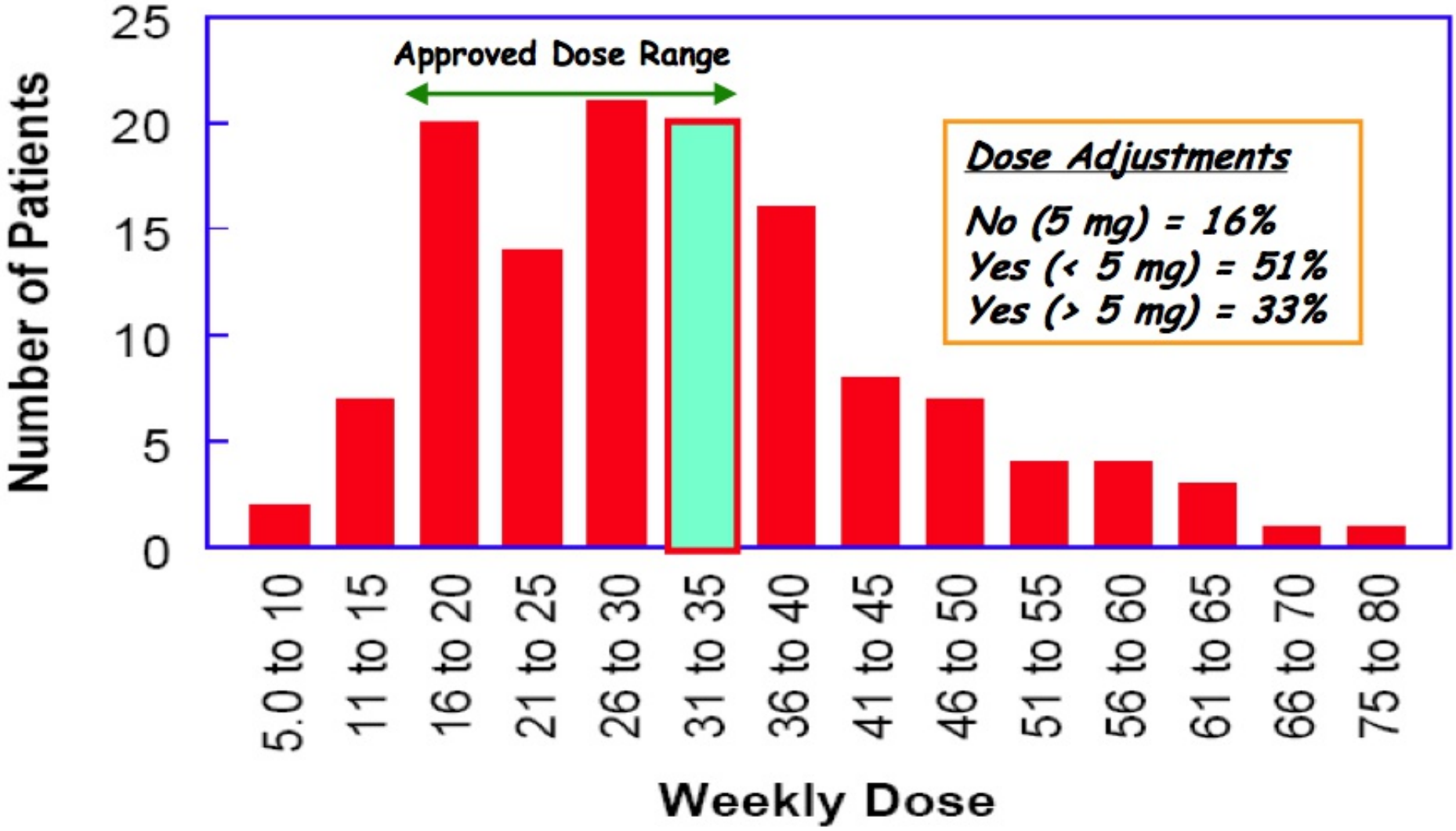


European Atrial Fibrillation Trial Study Group, N Engl J Med 1995;333:5-10.

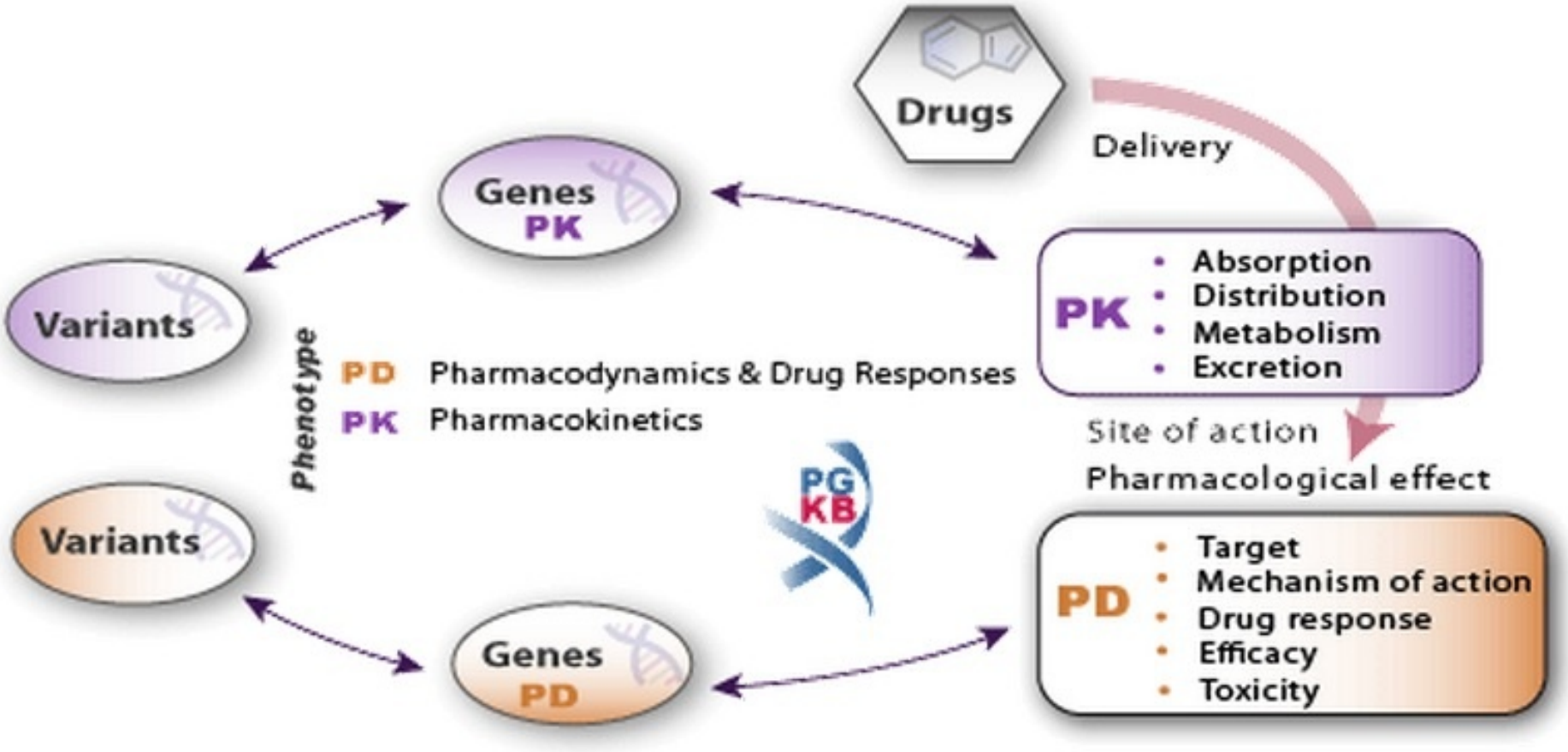
Home INR measurement using Roche's CoaguChekXS



Finding Doses to Maintain Therapeutic Anticoagulation is Largely Trial and Error

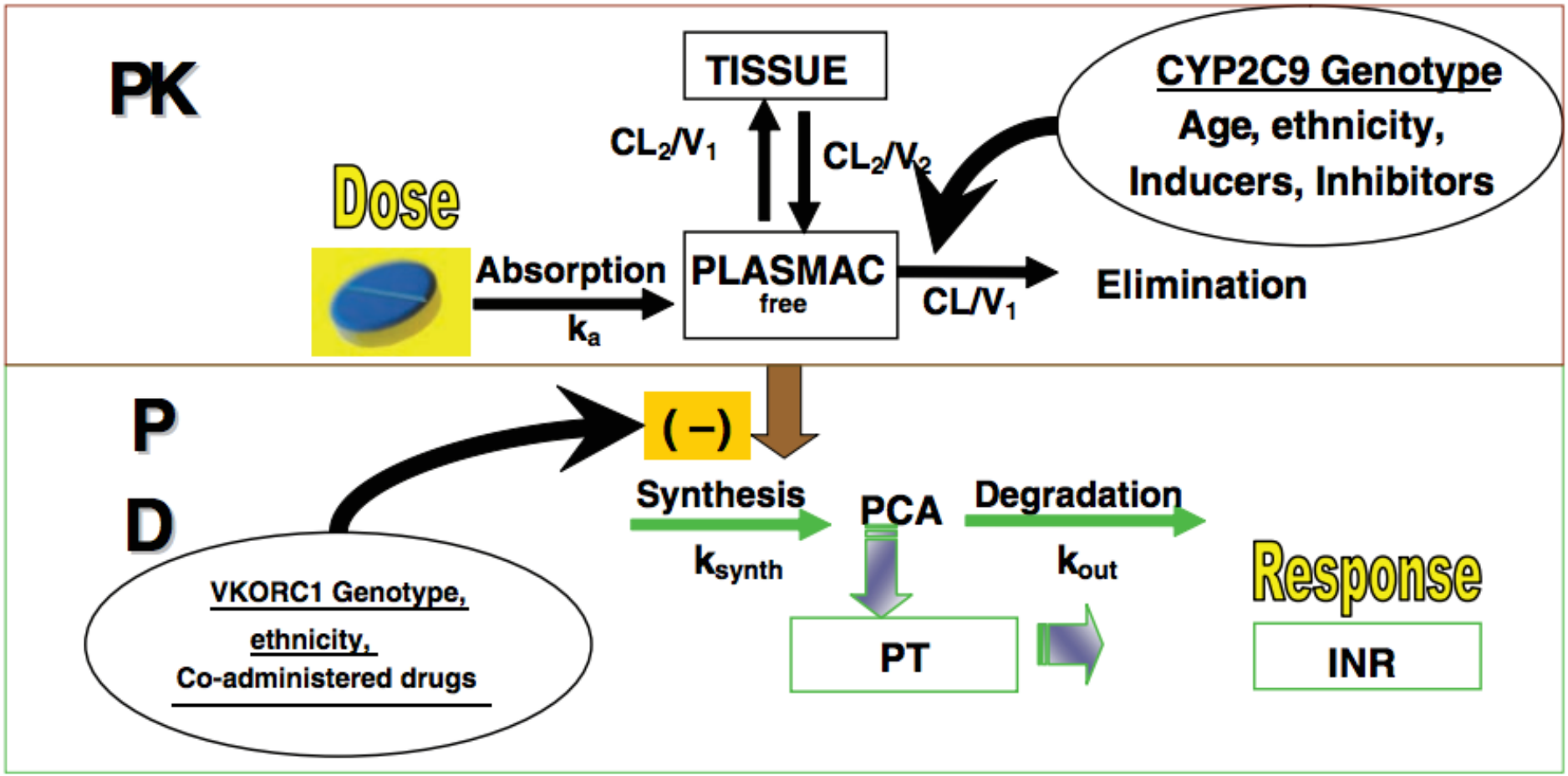


Pharmacokinetics versus Pharmacodynamics



Courtesy of PharmGKB

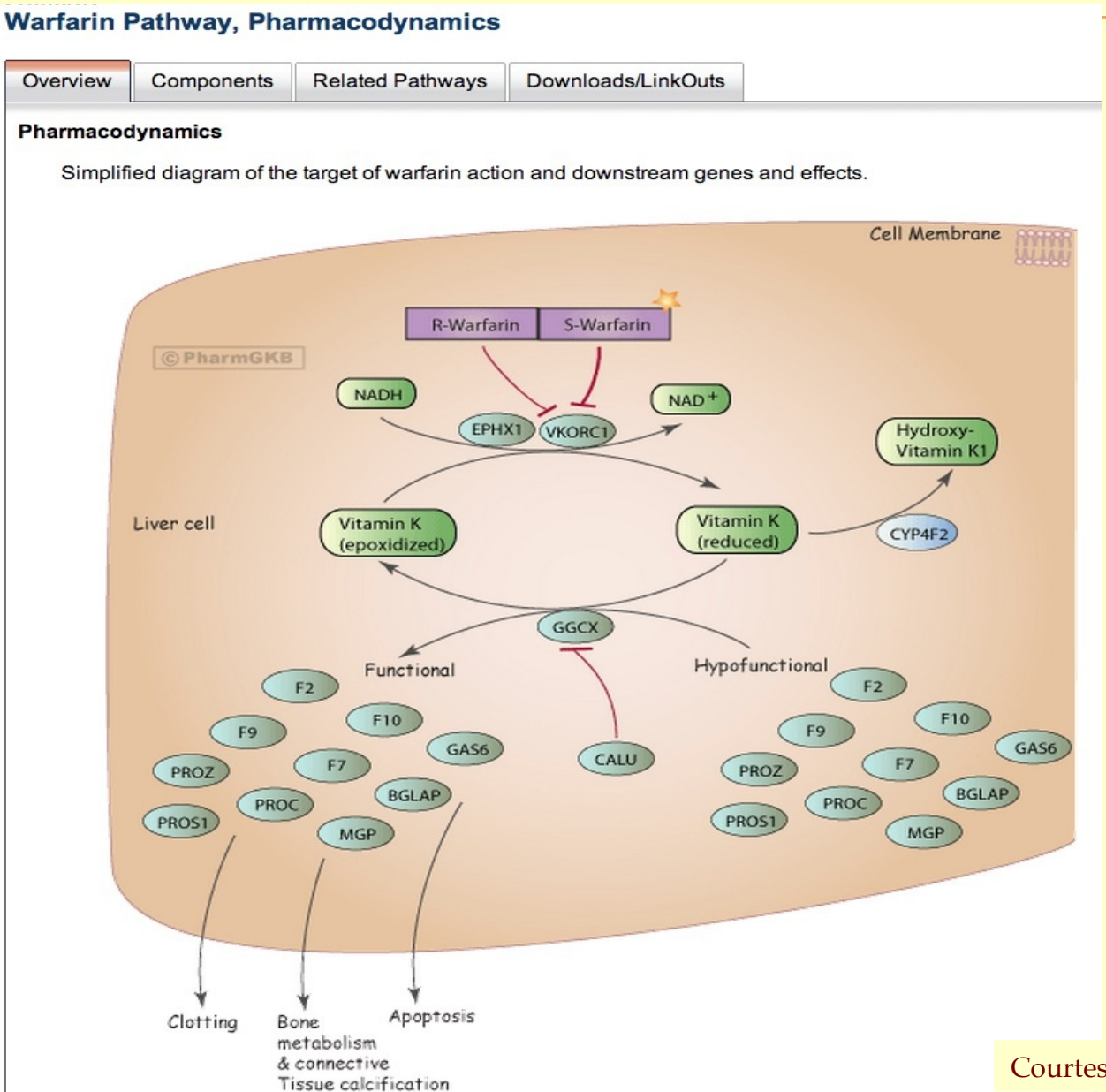
Warfarin Levels Depend on Two Enzymes – CYP2C9 & VKORC1



Kim et al.J. 2009 Clinical Pharmacology 49 138-46.

Warafarin Pathway on PharmaGKB

https://www.pharmgkb.org/pathway/PA145011114



Courtesy of PharmGKB

Estimated Warfarin Dose (mg/day) Based on Genotypes

VKORC1 genotype \ CYP2C9 genotype	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	6	5	4	4	3.5	3
GA	5	4	3	3	2.5	2
AA	3	2.5	2	2	2	1.5

<Kim MJ, Huang S-M, Meyer U, Rahman, A, Lesko LJ,

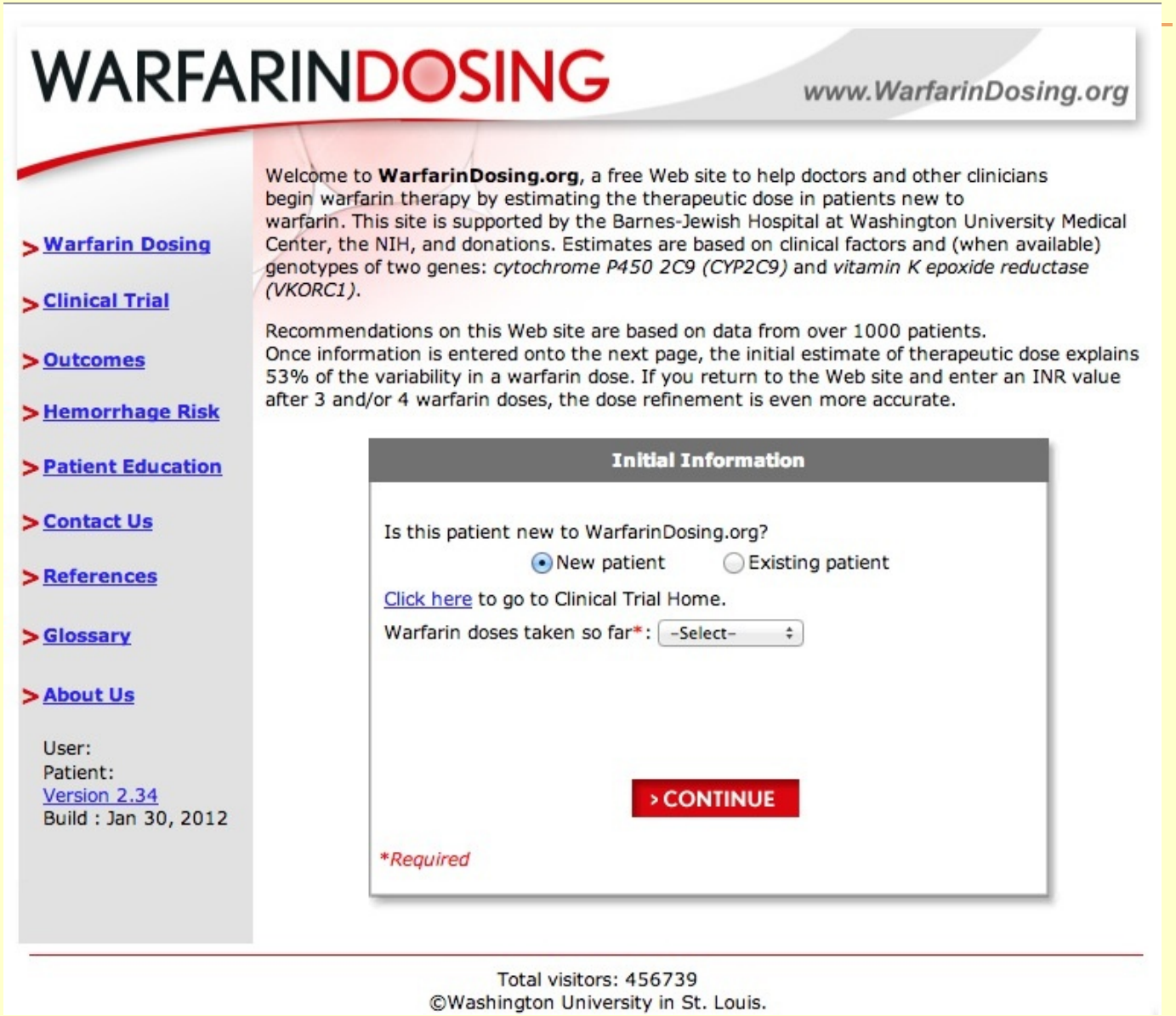
Frequency of VKORC1 Alleles in Various Populations

-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%

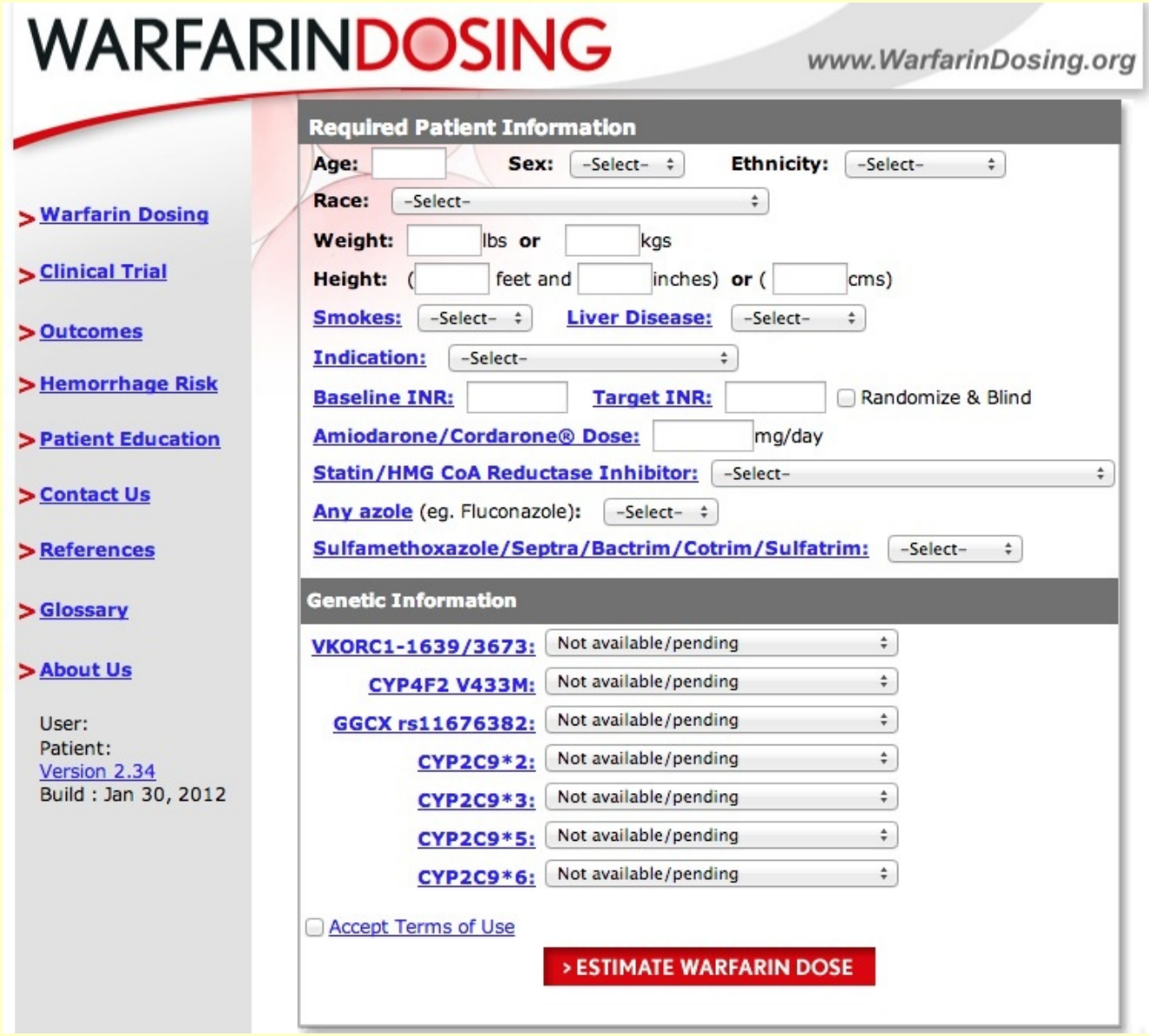
Asians may need a lower dose

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

Warfarin Dosing: Washington University
http://warfarindosing.org/



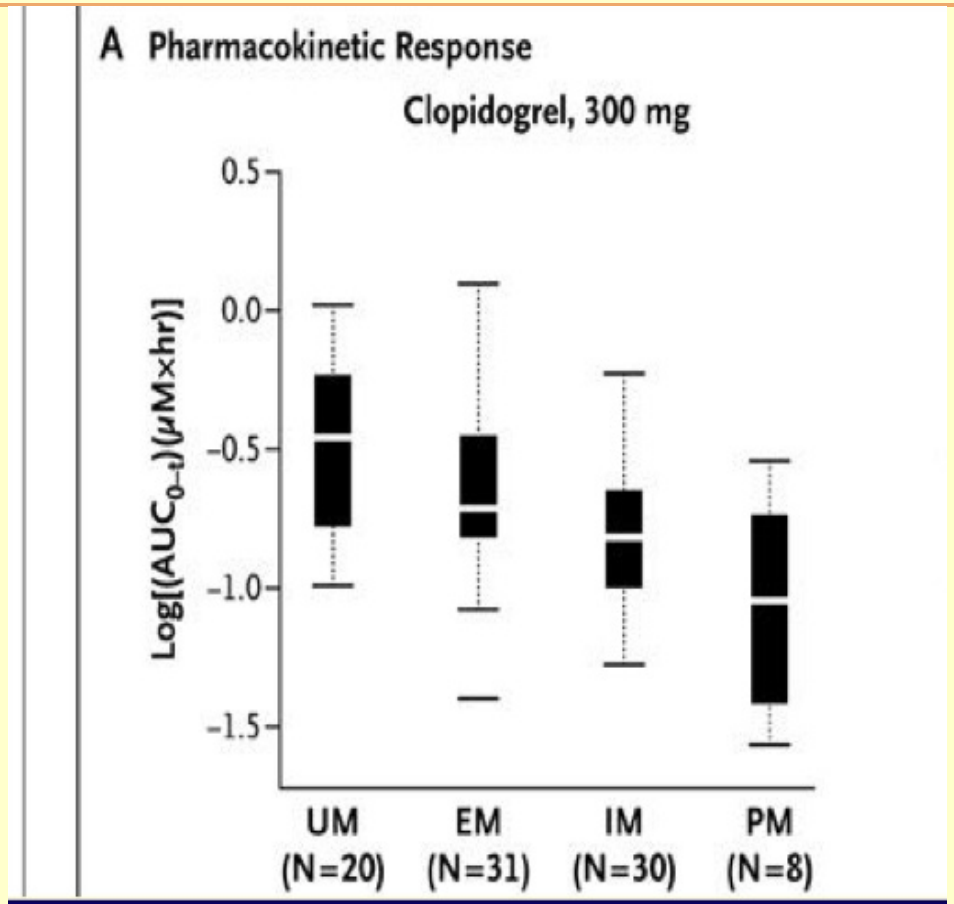
Warfarin Dosing Washington University



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 controled anticoagulation centers.
- Reduces between 4,500 and 22,000 serious bleeding events annually.
- Genetic testing now recommended by FDA

Another Anticoagulant Clopidogrel (Plavix) and CYP2C19 Alleles



PM: with two reduced function alleles
IM: one reduced function allele
EM: no variant alleles;
UM: one or two *17

Bristol-Myers Squibb

Plavix Ad with Genetic Disclaimers

drug response

Share my health results with family and friends

Show results for Douglas Brutlag

See new and recently updated reports »

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

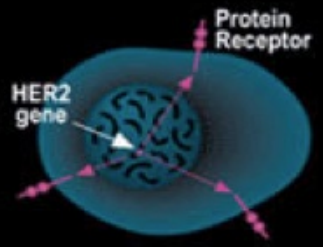
Name	Confidence	Status
Clopidogrel (Plavix®) Efficacy	★★★★	Greatly Reduced
Abacavir Hypersensitivity	★★★★	Typical
Alcohol Consumption, Smoking and Risk of Esophageal Cancer	★★★★	Typical
Fluorouracil Toxicity	★★★★	Typical
Response to Hepatitis C Treatment	★★★★	Typical
Pseudocholinesterase Deficiency	★★★★	Typical
Warfarin (Coumadin®) Sensitivity	★★★★	Typical
Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism ♀	★★★★	Not Applicable
Caffeine Metabolism	★★★	Fast Metabolizer
Metformin Response new	★★★	Typical Odds of Positive Response
Antidepressant Response	★★	See Report
Beta-Blocker Response	★★	See Report
Floxacillin 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

23andMe Drug Response Reports

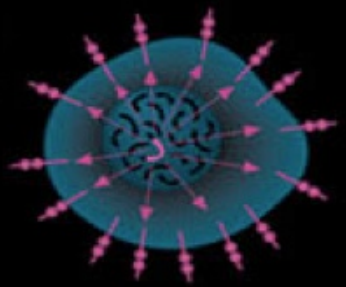
What are Targeted Drugs?

- 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!

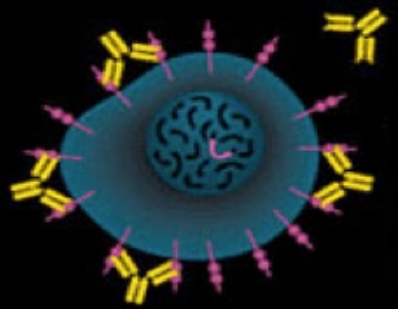
Trastuzumab (Herceptin®)



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.

Personalized 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 …

FDA Requires Genetic Tests for Certain Th

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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
Abacavir	Antivirals	HLA-B*5701	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information
Ado-Trastuzumab Emtansine	Oncology	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Aripiprazole	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration
Arsenic Trioxide	Oncology	PML/RARα	Boxed Warning, Clinical Pharmacology, Indications and Usage, Warnings

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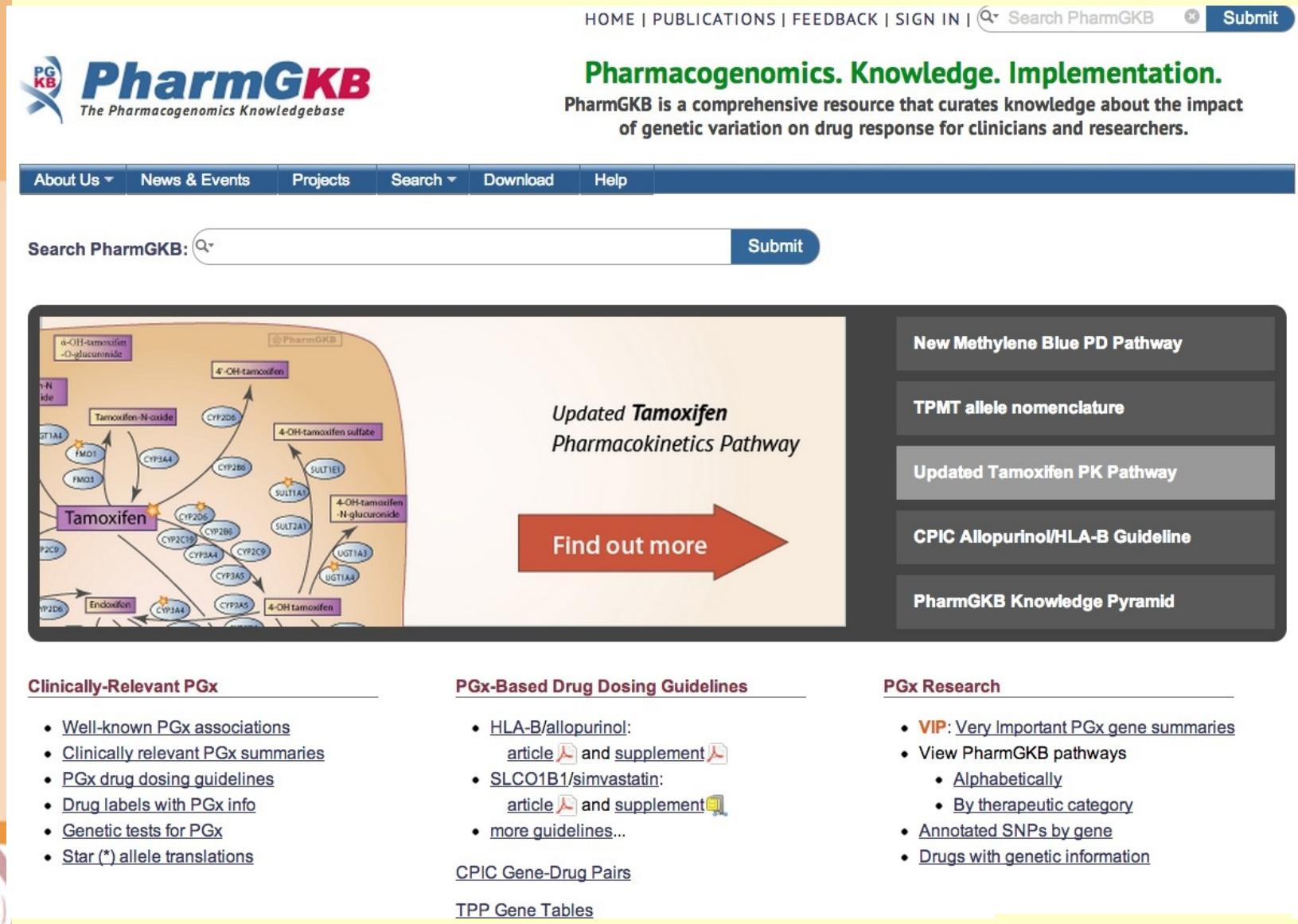
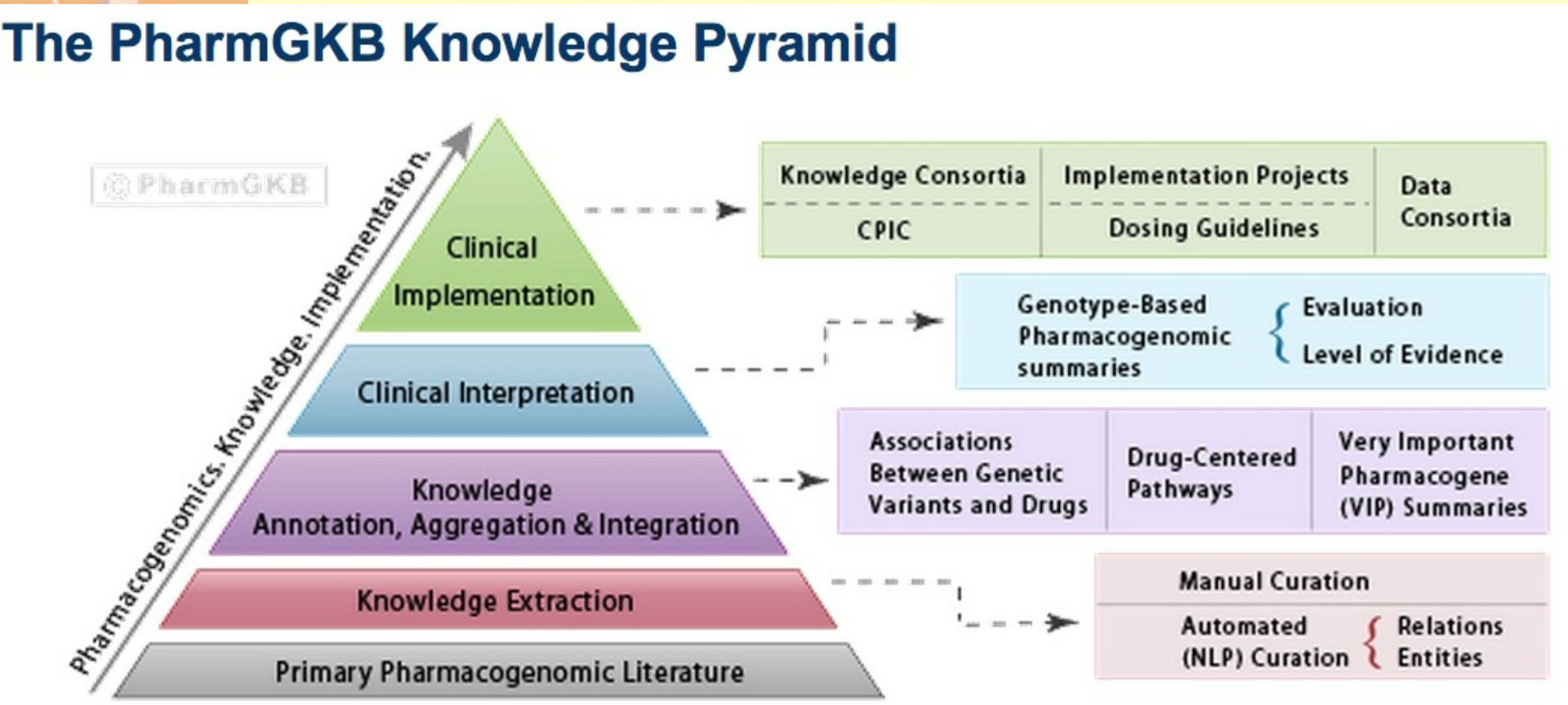


Courtesy of PharmGKB

PharmGKB Knowledge Base



Courtesy of PharmGKB

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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
abacavir	HLA-B	DG DL CA VA
acenocoumarol	CYP2C9	DG CA VA
acenocoumarol	VKORC1	DG CA VA VIP
acetaminophen	CYP2D6	DL PW
allopurinol	HLA-B	DG CA VA
amitriptyline	CYP2D6	DG DL VA VIP
aripiprazole	CYP2D6	DG DL
aripiprazole	CYP3A4	DL VIP
arsenic trioxide	PML	DL
arsenic trioxide	RARA	DL
atomoxetine	CYP2D6	DG DL

Courtesy of PharmGKB

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 profes society (PRO).

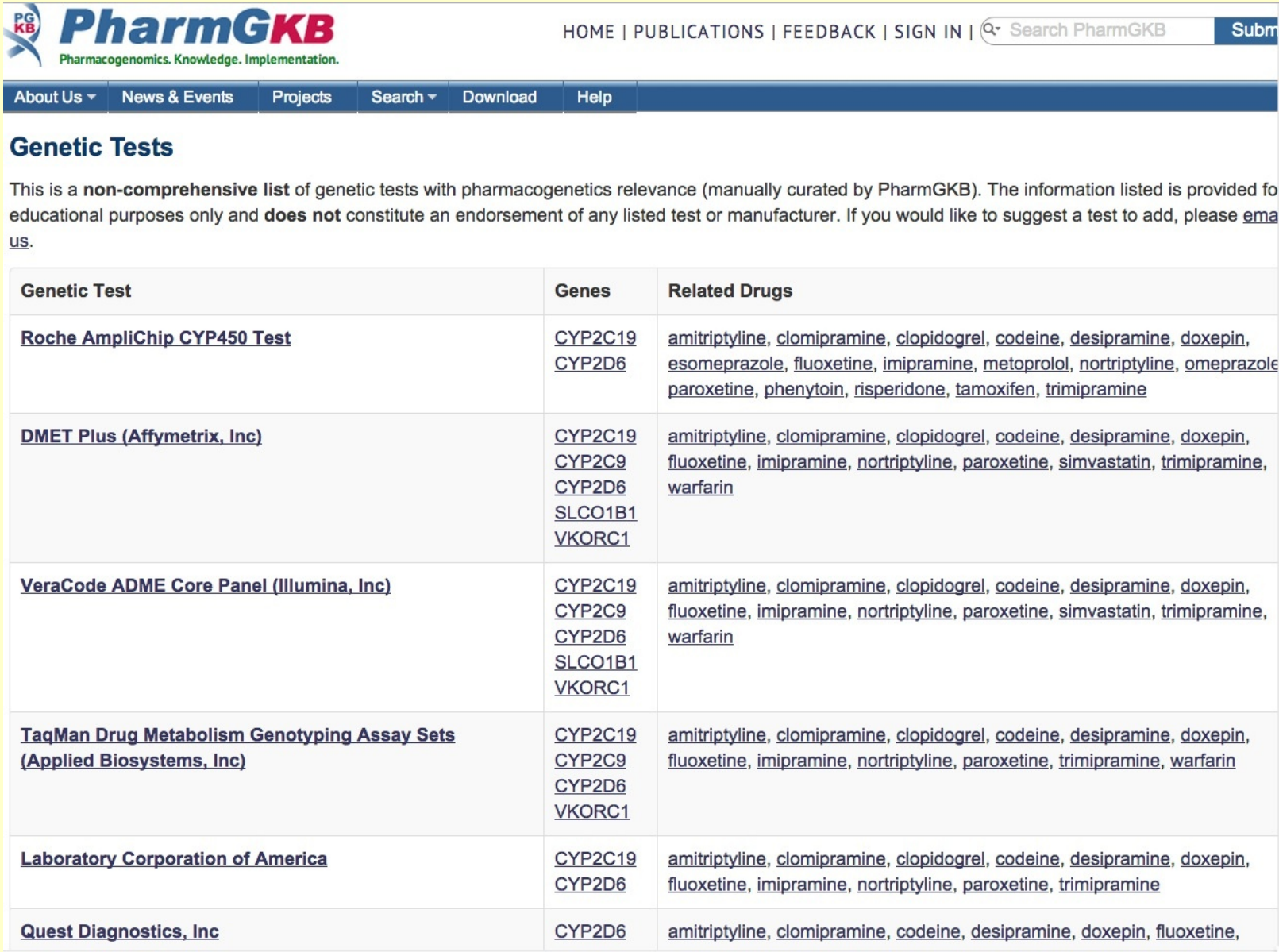
Title	Drug - Gene Pair
Dosing Guidelines for abacavir	CPIC abacavir HLA-B DPWG abacavir HLA-B
Dosing Guidelines for acenocoumarol	DPWG acenocoumarol CYP2C9 DPWG acenocoumarol VKORC1
Dosing Guidelines for allopurinol	CPIC allopurinol HLA-B PRO allopurinol HLA-B
Dosing Guidelines for amitriptyline	DPWG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

Courtesy of PharmGKB

Roche Chip for Cytochrome P450 Genes: CYPC19 and CYP2D6

Xie and Frueh, Pharmacogenomics steps toward Personalized Medicine, Personalized Medicine 2005, 2, 325-337

Genetic Tests from PharmGKB



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Genetic Tests

This is a **non-comprehensive list** of genetic tests with pharmacogenetics relevance (manually curated by PharmGKB). The information listed is provided fo
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 ema
us.

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