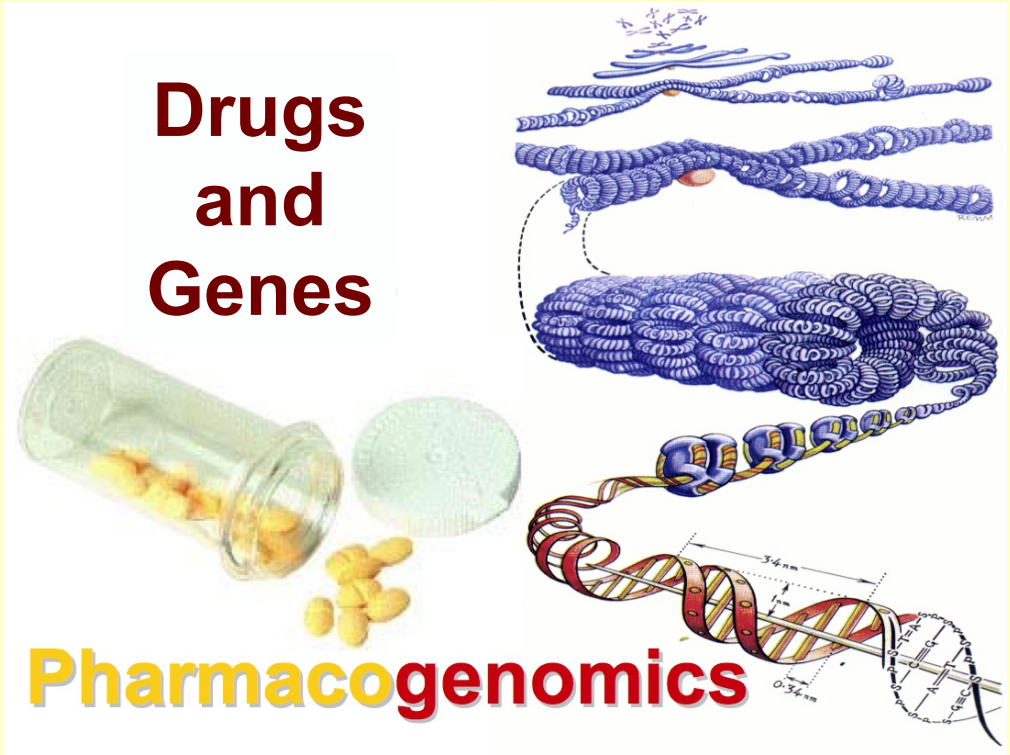
Genomics & Medicine

http://biochem118.stanford.edu/

Pharmacogenomics

http://biochem118.stanford.edu/Drug-Development.html



Doug Brutlag, Professor Emeritus of
Biochemistry and Medicine
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?

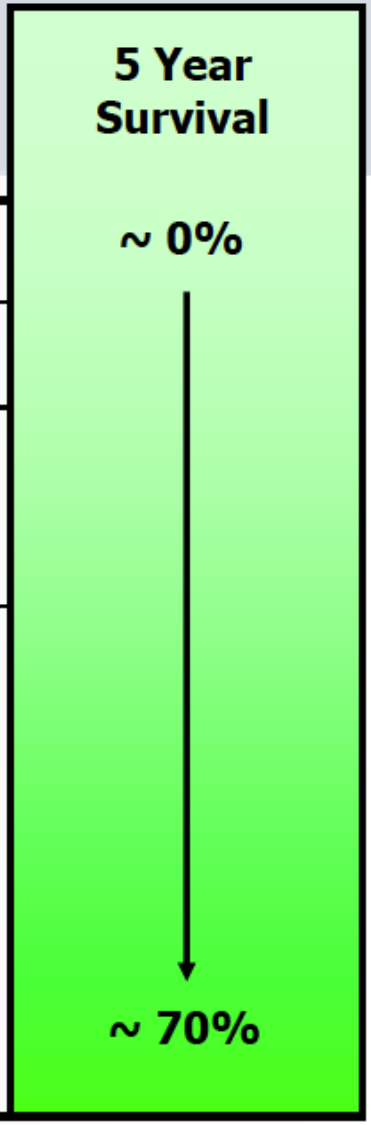
If it were not for the great variability among individuals, medicine might well be a science, not an art.

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

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)

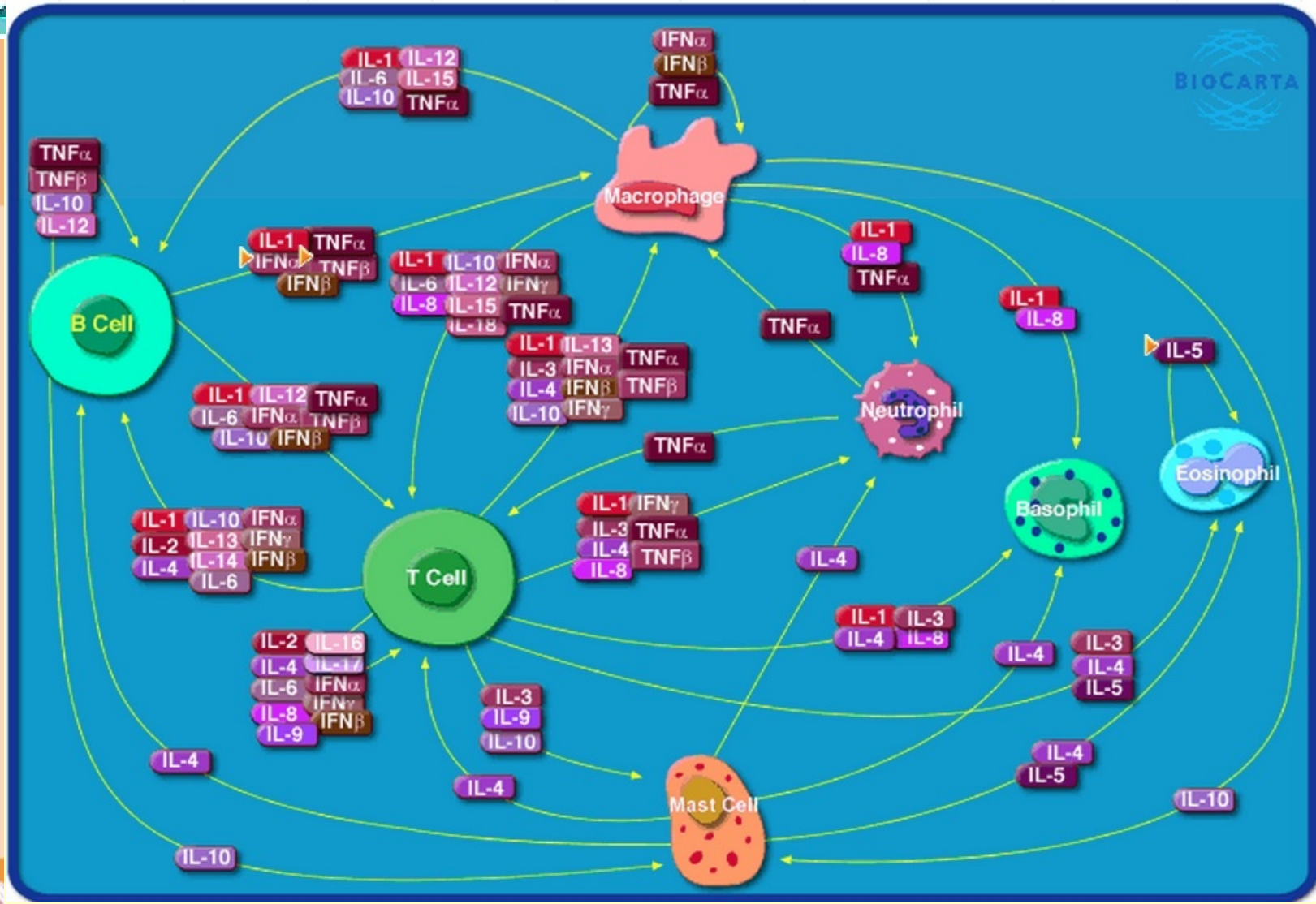


After Mara Aspinall, Genzyme Genetics (modified)

Courtesy Felix W. Frueh

Cytokine Network

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



The Goal of Personalized Medicine

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

Courtesy Felix W. Frueh

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 complete 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)

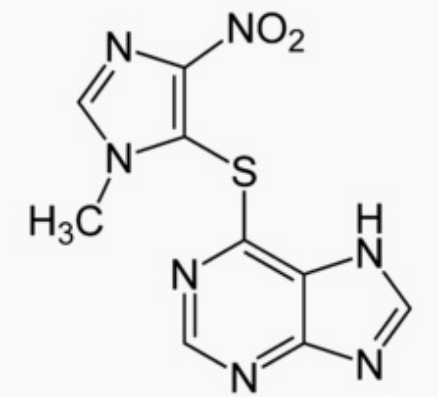
- Pharmacogenomics: study of genomic influence on drug response, often using high-throughput data (sequencing, SNP chip, gene expression, proteomics, epigenetics and complex interactions)

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

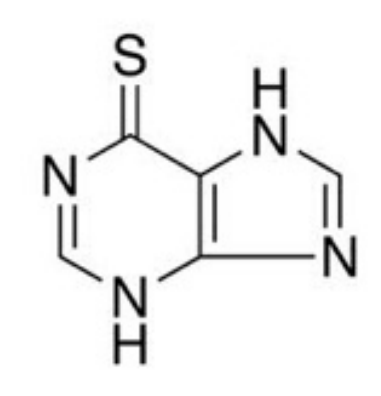
Courtesy of Michelle Whirl-Carillo

Purine Analogs: A Case Study in Pharmacogenetics

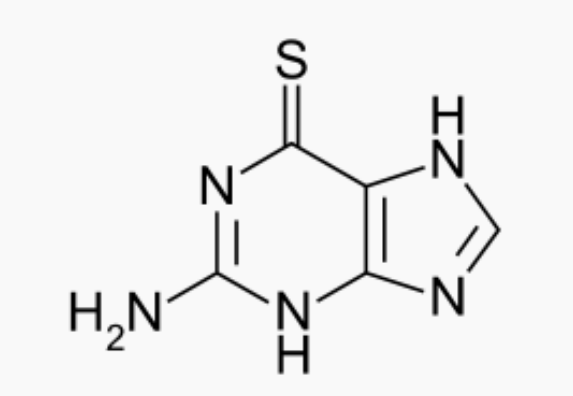
- 6-mercaptopurine, 6-thioguanine, azathioprine
- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, after transplant
- Interferes with nucleic acid synthesis
- Therapeutic index limited by myelosuppression
  (treatment limited by immune suppression side effect)



azathioprine

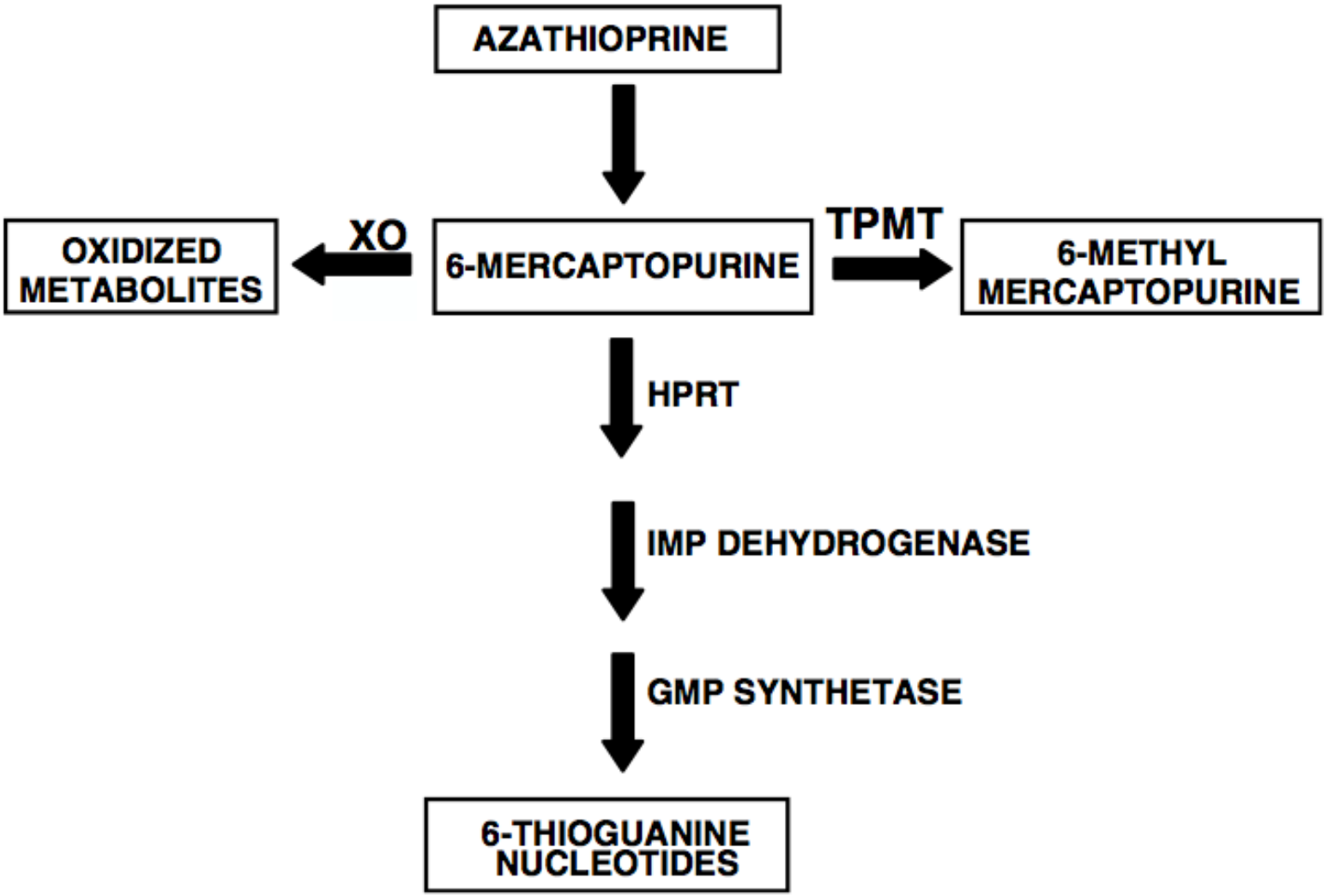


6-mercaptopurine



6-thioguanine

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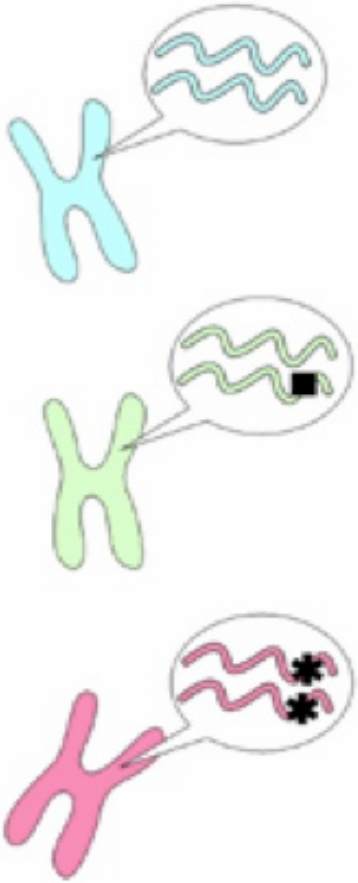
The diversity in responses is due to variations in the gene for an enzyme called TPMT, or thiopurine methyltransferase.



Courtesy of Michelle Whirl-Carillo

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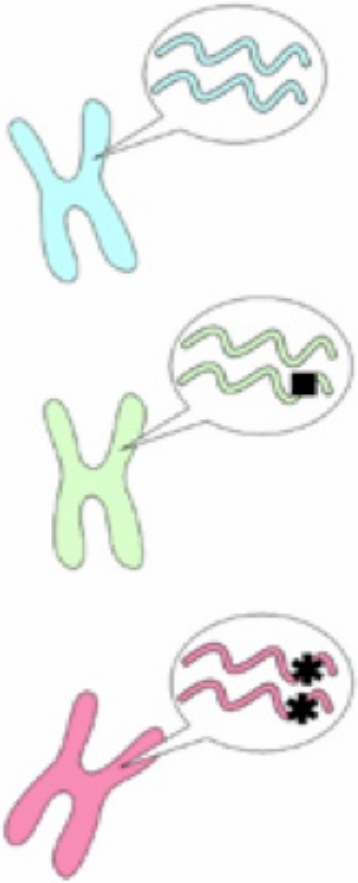
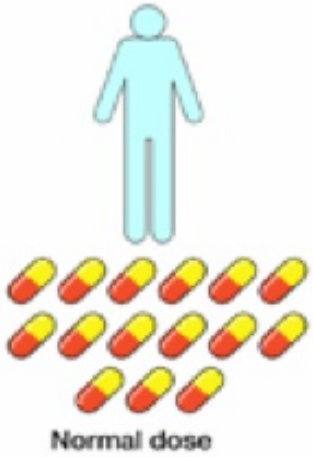


After a simple blood test, individuals can be given doses of medication that are tailored to their genetic profile.

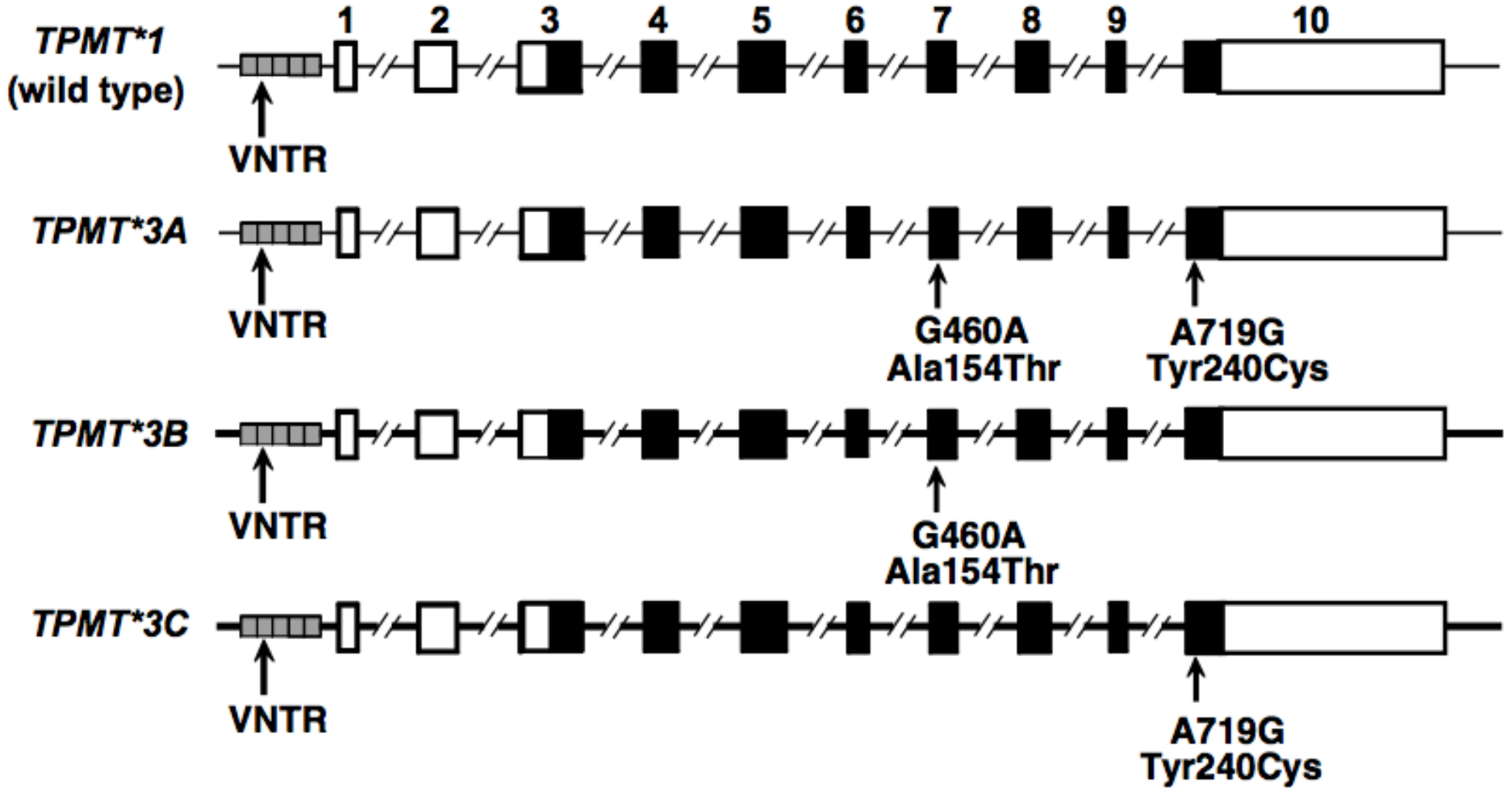


Normal dose

Dose for an extra slow metabolizer (TPMT deficient)

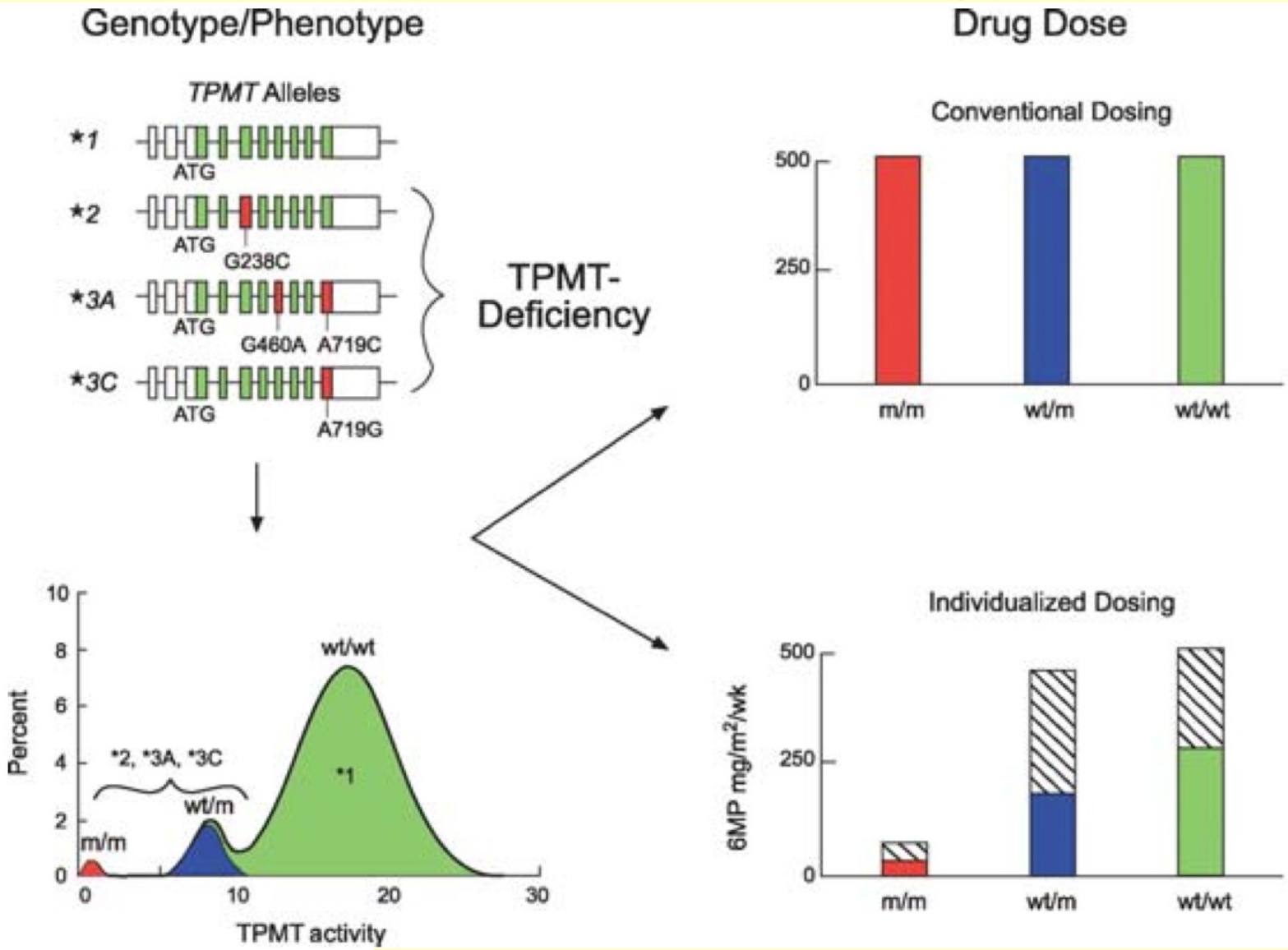
Courtesy of Michelle Whirl-Carillo

Thiopurine Methyl Transferase (TPMT) and Most Common Variant Alleles



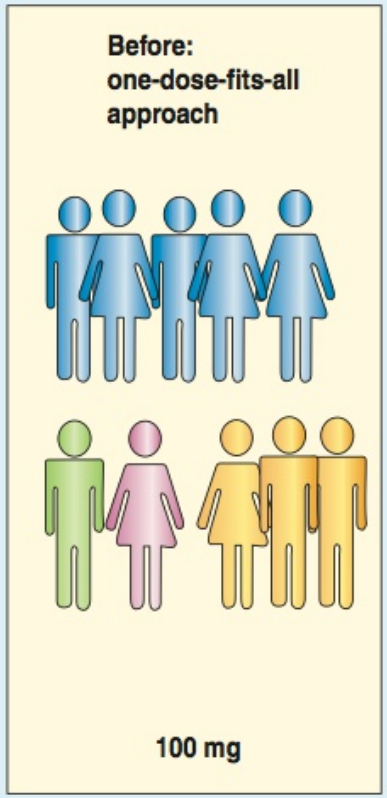
L Wang and R Weinshilboum, Oncogene 25, 1629-1638 (2006)

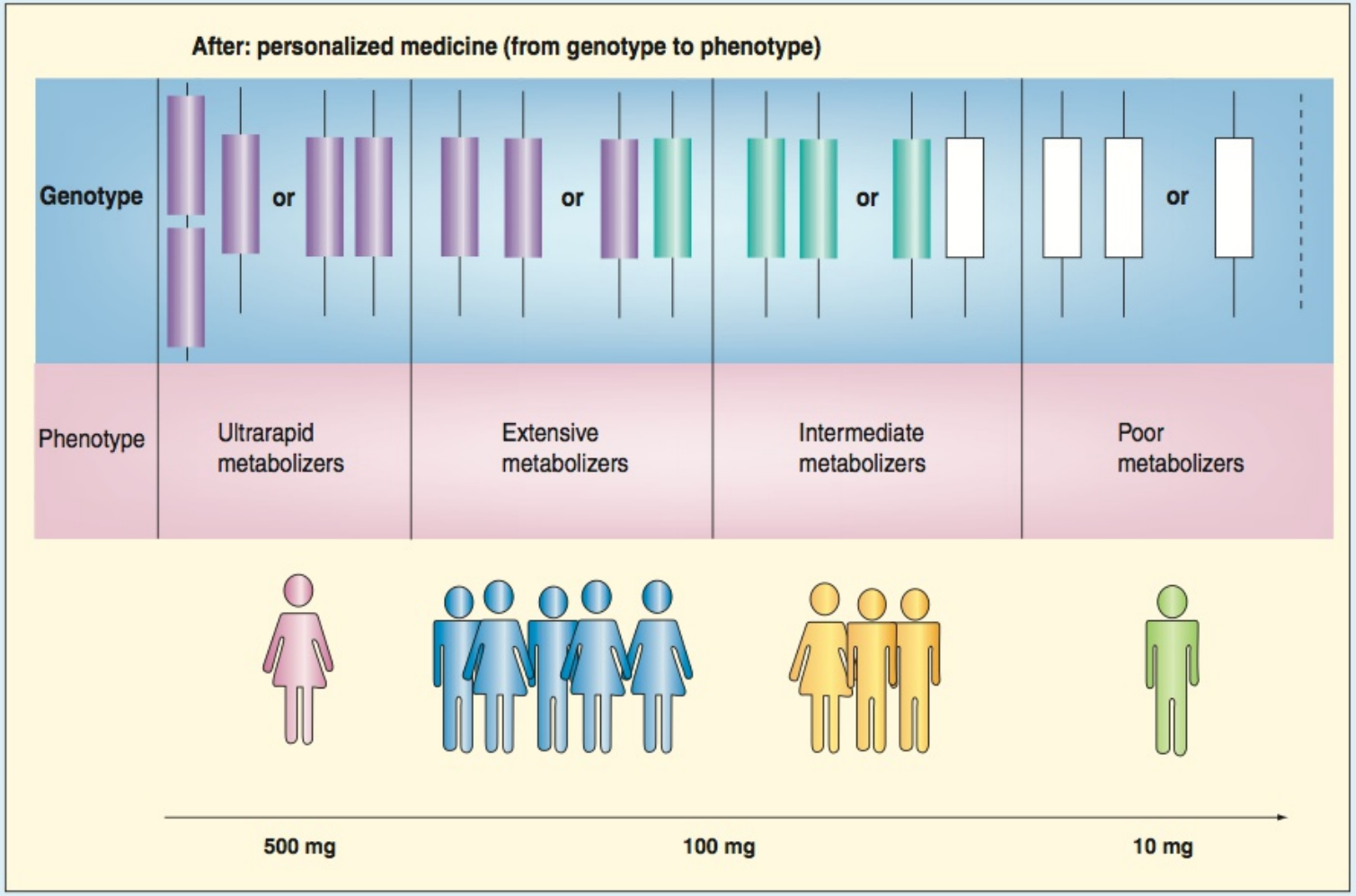
Thiopurine S-methyl Transferase Activity and Personalized Dosage



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

Personalized Medicine





Xie and Frueh, *Personalized Medicine (2005)* ***2(4), 325–337***

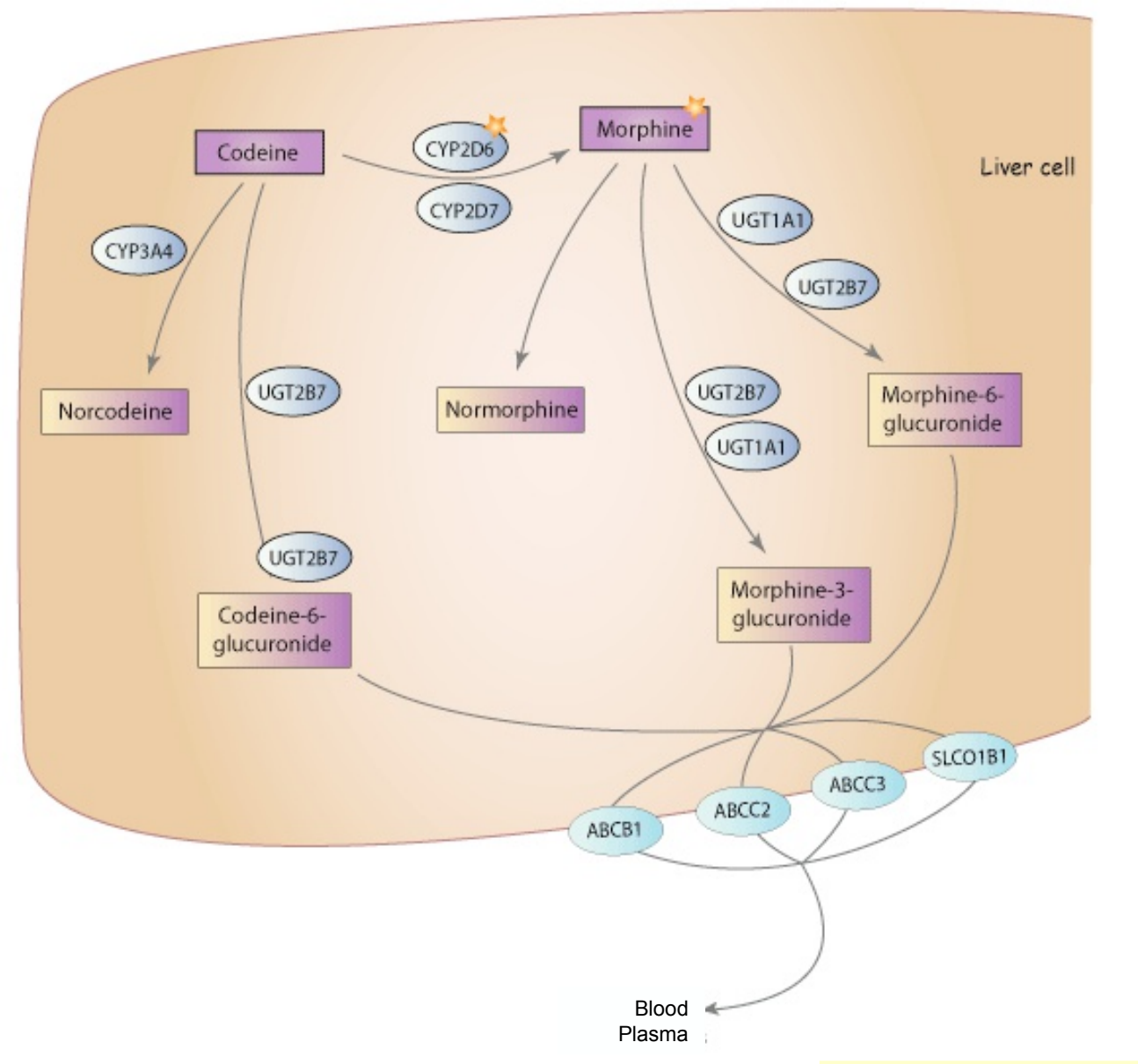
Second Example: Codeine and Cytochrome P450 CYP2D6

- 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

PharmGKB
The Pharmacogenomics Knowledgebase

Codeine and Morphine Metabolism

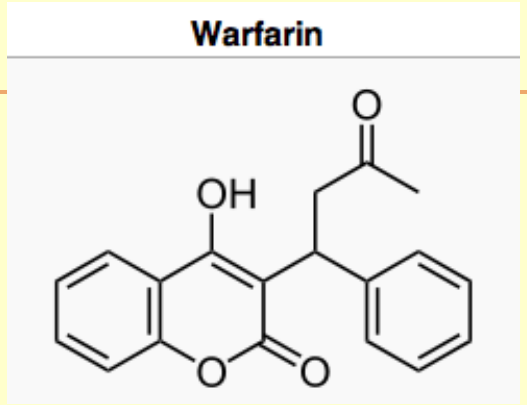


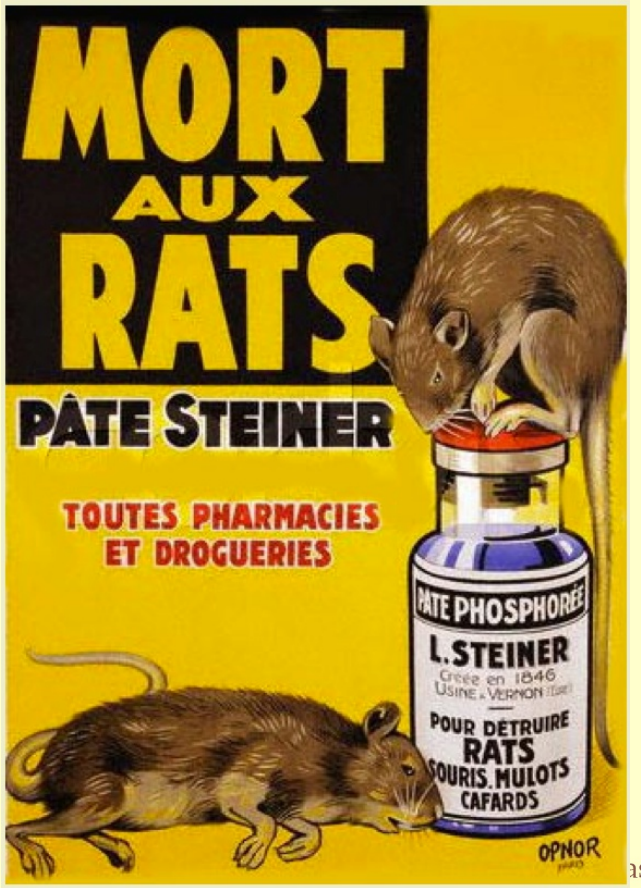
Courtesy of Michelle Whirl-Carillo

Cytochrome Oxidase P450 Enzymes

- 57 Different active genes
- 17 Different families
- 132 variations in different haplotype regions
- 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
- Metabolize 590 different drugs

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.

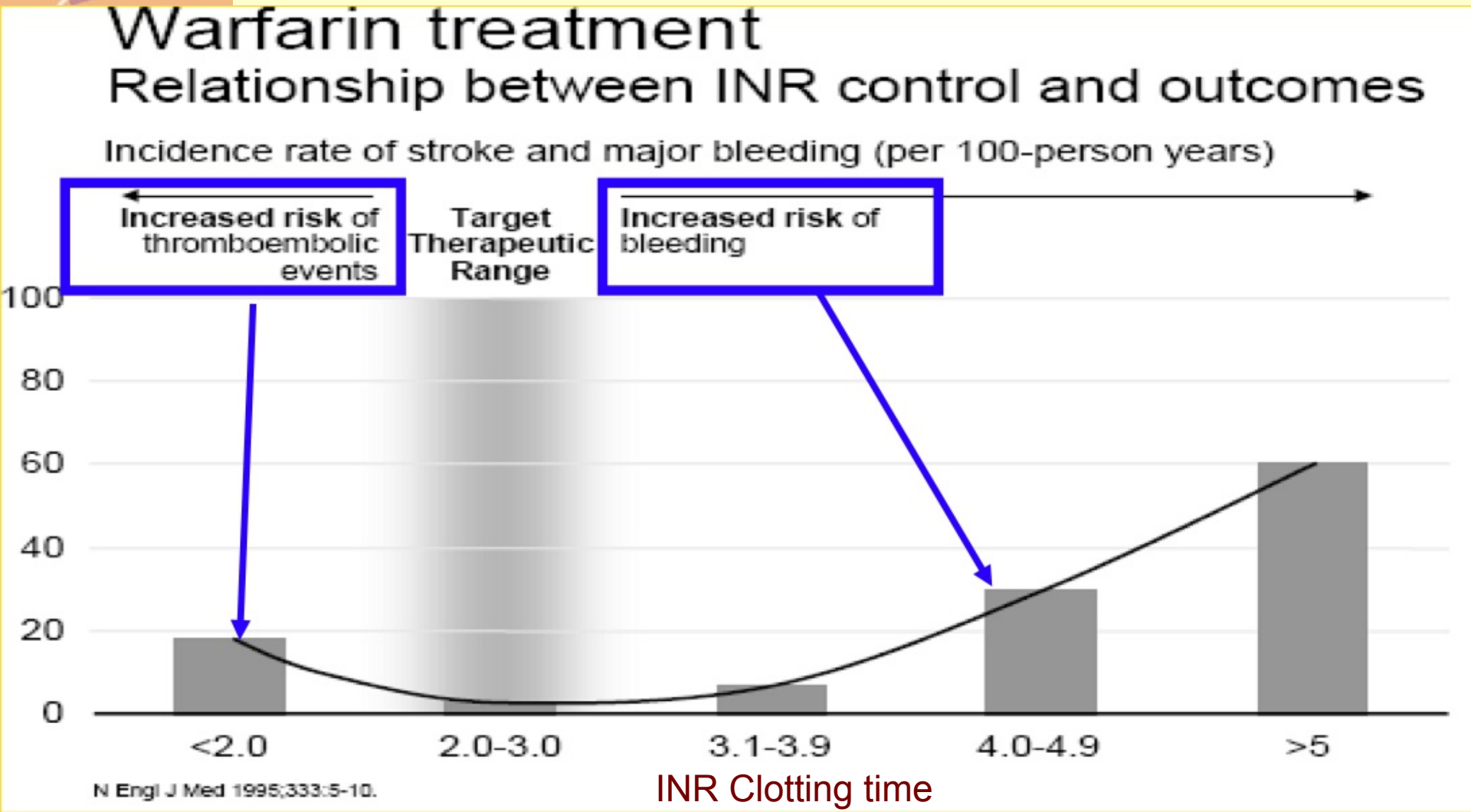
Warfarin: Significant Problems for Humans!

- 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

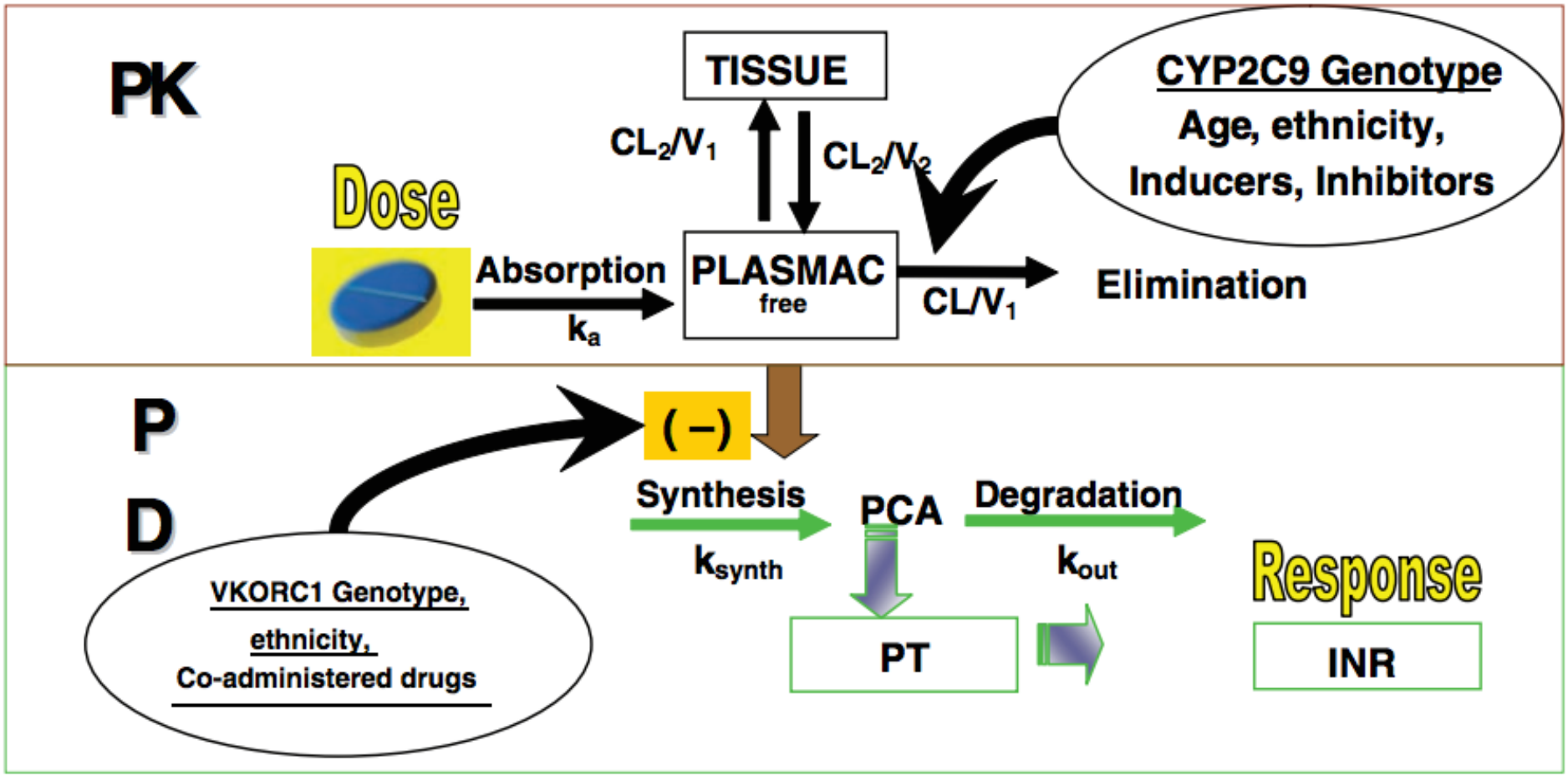
Dedicated: David Belk, who died of a brain haemorrhage brought on in a game of football, loved playing sports

Why Maintaining Warfarin Therapeutic Range is Critical



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

Warfarin Plasma Level Depends on Two Enzymes – CYP2C9 & VKORC1



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

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

http://www.warfarindosing.org/

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

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

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.
- Reduced between 4,500 and 22,000 serious bleeding events annually.
- Genetic testing now required by FDA

Clinical Trials on Genetics of Warfarin Dosing

Update Genetics

A Summary of Recent Published Activity

PERSPECTIVE

Cancer-Drug Discovery and Cardiovascular Surveillance

J.D. Groarke and Others

N Engl J Med 369:1779, November 7, 2013

ORIGINAL ARTICLE

ONLINE FIRST

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

S.E. Kimmel and Others

N Engl J Med, November 19, 2013

Comments

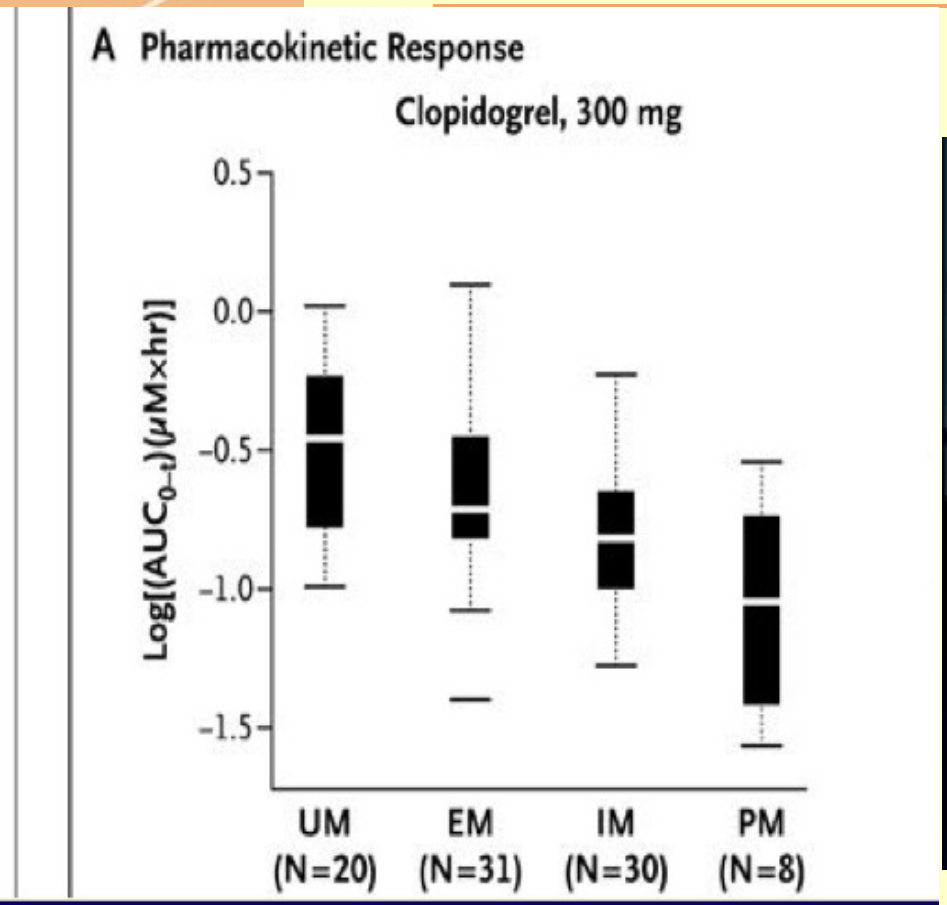
ONLINE FIRST

A Randomized Trial of Genotype-Guided Dosing of Warfarin

M. Pirmohamed and Others

N Engl J Med, November 19, 2013

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

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

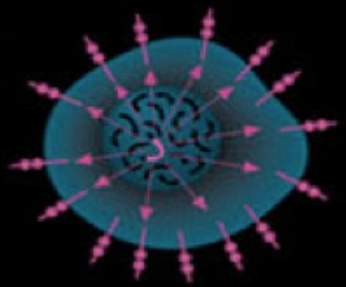
23andMe Drug Response Reports

What are Targeted Drugs?

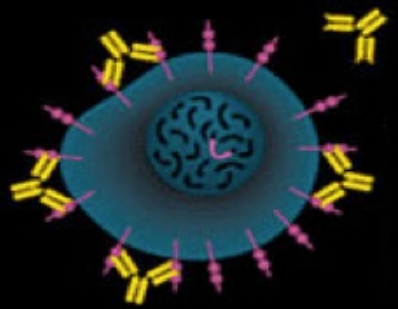
- Often, drugs are only effective in specific "sub-populations" (responders).
- Early identification of responders can have a dramatic effect of treatment success.
- Treatment of non-responders puts these individuals at unnecessary risk of adverse events, while providing no benefit.
- Personalized Medicine 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 and 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 HIV type)

- etc. and the list is growing rapidly …

Antibody therapeutics in cancer Sliwkowski Science 341 1192 (2013)

FDA Requires Genetic Tests

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

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
Aripiprazole	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration
Arsenic Trioxide	Oncology	PML/RARα	Boxed Warning, Clinical Pharmacology, Indications and Usage, Warnings
Atomoxetine	Psychiatry	CYP2D6	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Atorvastatin	Metabolic and Endocrinology	LDL receptor	Indications and Usage, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Azathioprine	Rheumatology	TPMT	Dosage and Administration, Warnings and Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology
Boceprevir	Antivirals	IL28B	Clinical Pharmacology
Brentuximab Vedotin	Oncology	CD30	Indications and Usage, Description, Clinical Pharmacology

394 drugs recommend genetic tests for prescription

71 require genetic tests as of December 3, 2013

Roche Chip for Cytochrome P450 Genes: CYPC19 and CYP2D6

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

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

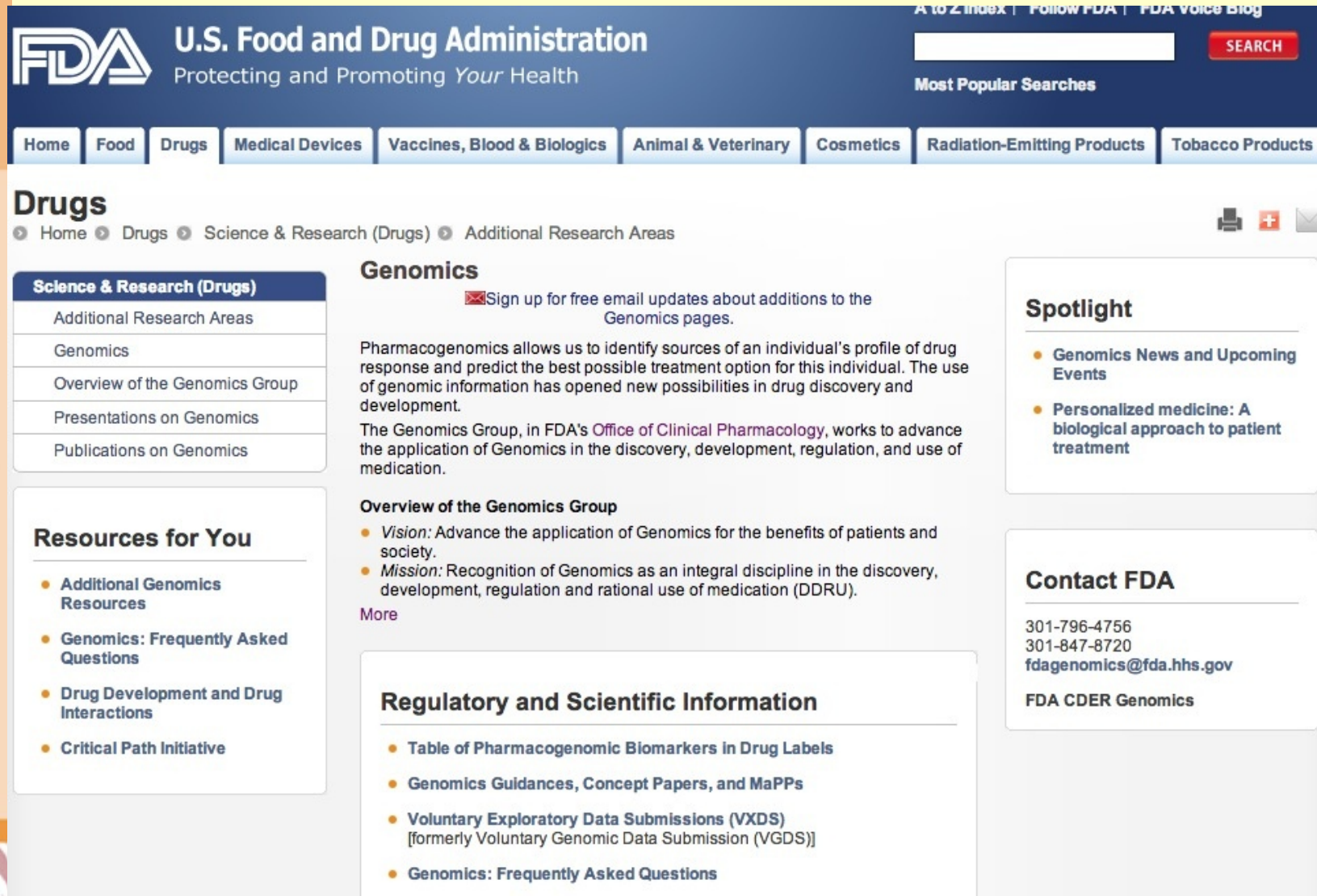
Drug	Ultra-rapid Metabolizer Phenotype
Prodrug, needs metabolism to work (eg. codeine is metabolized by CYP 2D6 to morphine)	Good efficacy, rapid effect
Active drug, inactivated by metabolism (example is omeprazole)	Poor efficacy Need greater dose or slow release formulation

PharmGKB

http://www.pharmgkb.org/

FDA Pharmacogenomics Page

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm



AMA Pharmacogenomics Web Page