Personalized Medicine
The Genetic-Kinetic Interface and Beyond

GTAACGTAGTACCTACGGATTACAGTTCAGTCGAATCGATG

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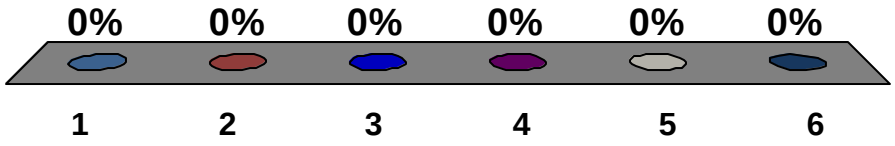
Department of Pharmaceutical and Biomedical Sciences

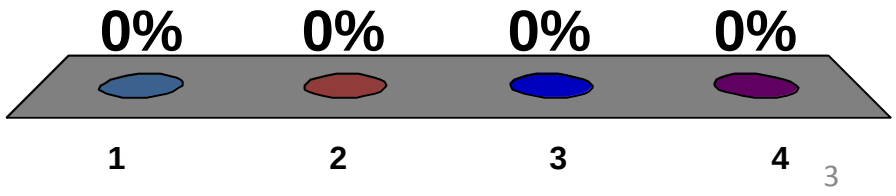
Clicker Practice:
I graduated from pharmacy school:

1. 1960-1969
2. 1970-1979
3. 1980-1989
4. 1990-1999
5. 2000-2010
6. 2011



With respect to pharmacogenetics:

1. I have minimal knowledge.
2. I have moderate knowledge.
3. I have extensive knowledge.
4. I have no knowledge.



Personalized Medicine
The Genetic-Kinetic Interface and Beyond

Goals

Upon completion of this CE program, participants will be able to:

-Define “personalized medicine (pharmacogenomics)” and distinguish pharmacogenomics from pharmacogenetics.

-Recognize the genetic basis for pharmacokinetic differences in how a drug is “handled” by a given patient.

- Understand the genetic basis of therapy with clopidogrel, warfarin, and other drugs.

Describe the current state of “personalized medicine” relative to:

-Medical/Pharmacy education

-Healthcare information technology

-Regulation

-Technology and tools

-Insurance coverage and reimbursement

-Genetic privacy and legal protections

What does it mean?

Personalized Medicine

- “In the not too distant future, our DNA will determine everything about us.”-GATTACA

Personalized medicine is the tailoring of medical treatment to the individual characteristics of each patient.

What does it mean?

Pharmacogenomics: The general study of all of the many different genes that determine drug behavior.

Pharmacogenetics: The study of inherited differences (variation) in drug metabolism and response.

The distinction between the two terms is considered arbitrary, however, and now the two terms are used interchangeably.

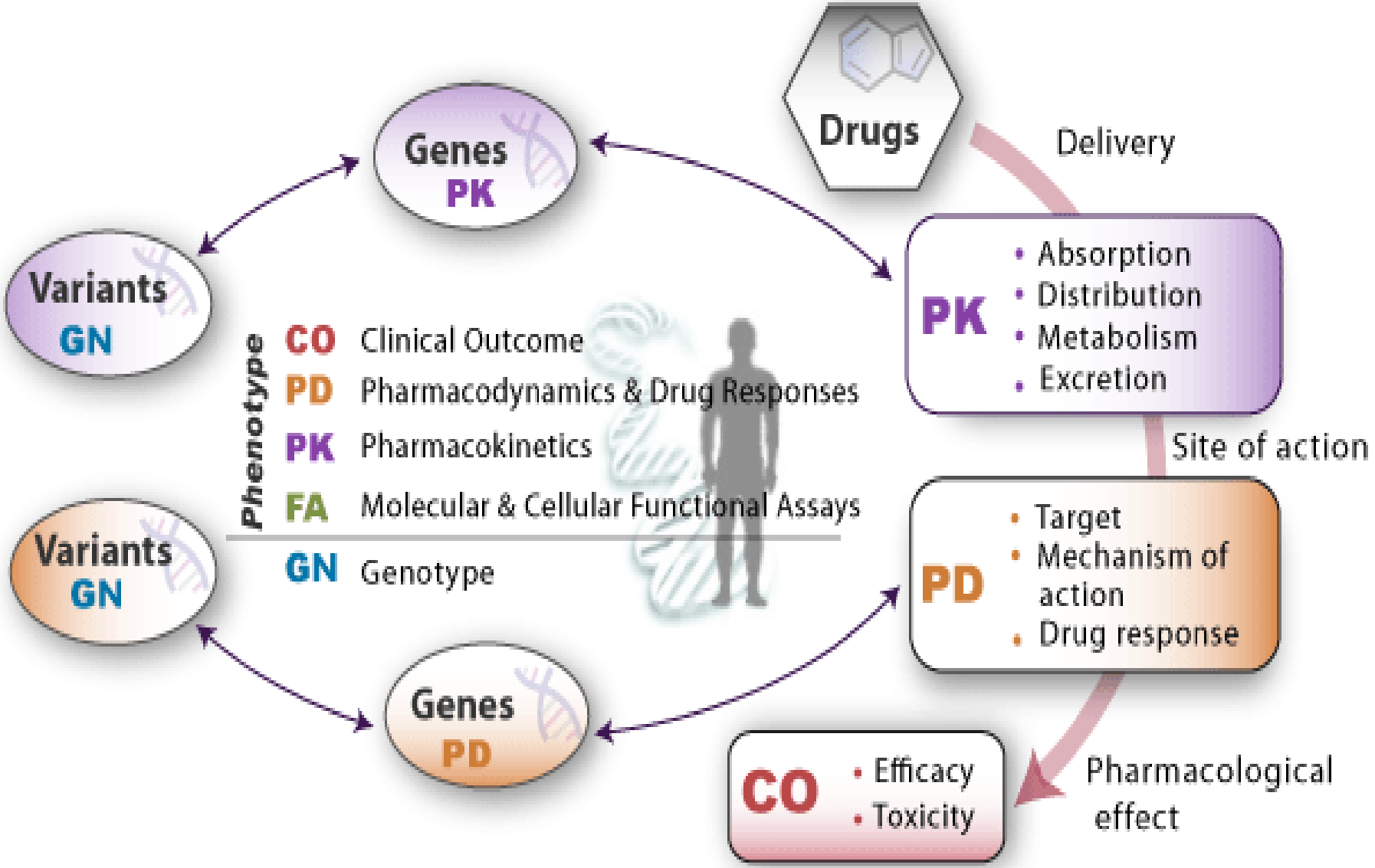
http://www.ncbi.nlm.nih.gov/About/primer/pharm.html; Accessed 13 Sep 2011.

What does it mean?

Pharmacogenomics: Analyzing entire genomes, across groups of individuals, to identify the genetic factors influencing responses to a drug.

Pharmacogenetics: Studying an individual's genetic make up in order to predict responses to a drug and guide prescription.

http://www.yourgenome.org/help/; Accessed 13 Sep 2011.



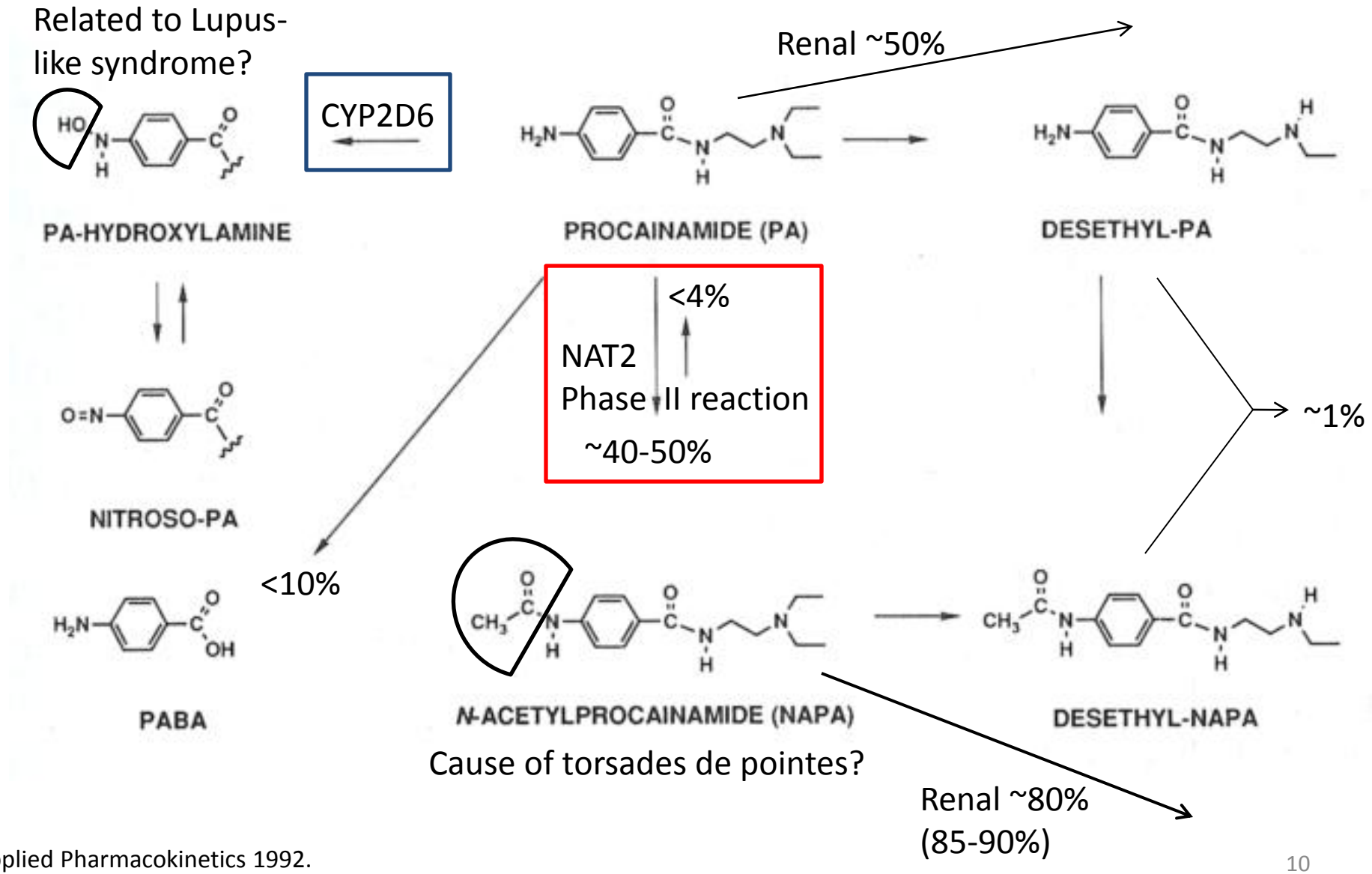
PharmGKB (pharmgkb.org) supported by the NIGMS, NHLBI, NHGRI, NIEHS, NCI, and NLM within the NIH, HHS. Accessed 09/2011.

Procainamide – Old Drug – Good Example

- The N-acetyltransferase 2 (NAT2) enzyme N-acetylates procainamide to form the active metabolite N-acetylprocainamide (NAPA).

- Both procainamide and N-acetylprocainamide have antiarrhythmic and pro-arrhythmic activity.

Procainamide Metabolism



Applied Pharmacokinetics 1992.

Applied Pharmacokinetics & Pharmacodynamics. Clinical Pharmacokinetics of Oral Antiarrhythmic Drugs 2006; 440-462.

The "Evolution" of Drug Dosing

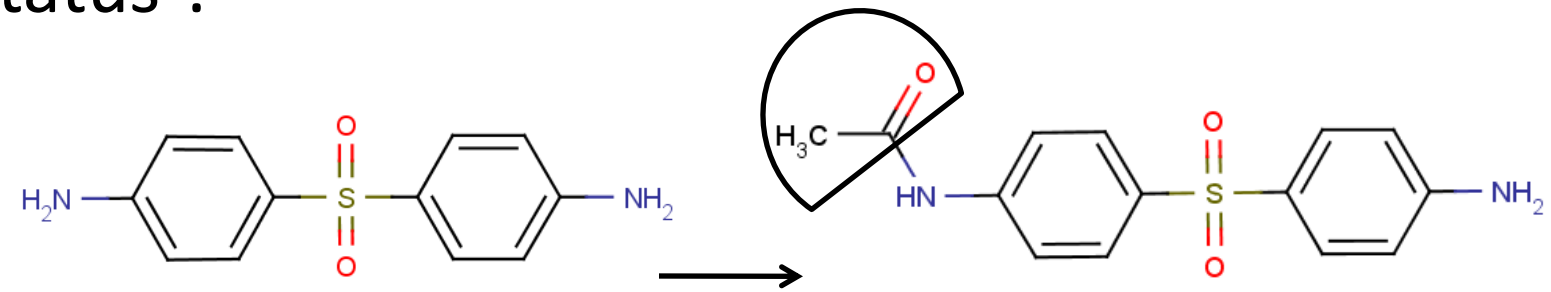
Standard Dosing → **Empirical Dosing** → **Pharmacokinetic Dosing** → PGx

Standard Dosing	Empirical Dosing	Pharmacokinetic Dosing
Assumes the same dose will produce the same pharmacologic response in all patients.	Based on clinician's experience with specific drugs.	Assumes the same (or very similar) drug concentration will produce the same pharmacologic response in all patients.
Easy to teach – use of reference drug doses (e.g., PDR, package labeling, other).	Difficult to teach – requires years of experience.	Somewhat difficult to teach – requires some complex mathematical computations.
Does not account for differences among individual patients.	Accounts for some differences between patients.	Accounts for differences based on "population estimates".
No guidelines for adjustment of doses.	No guidelines for adjustment of doses.	Individualization of dose based on drug concentration.

Postgrad Med 1990; 87(4): 239-241, 244, 246.

Determining Acetylation Status - Exogenous Probe of Acetylation

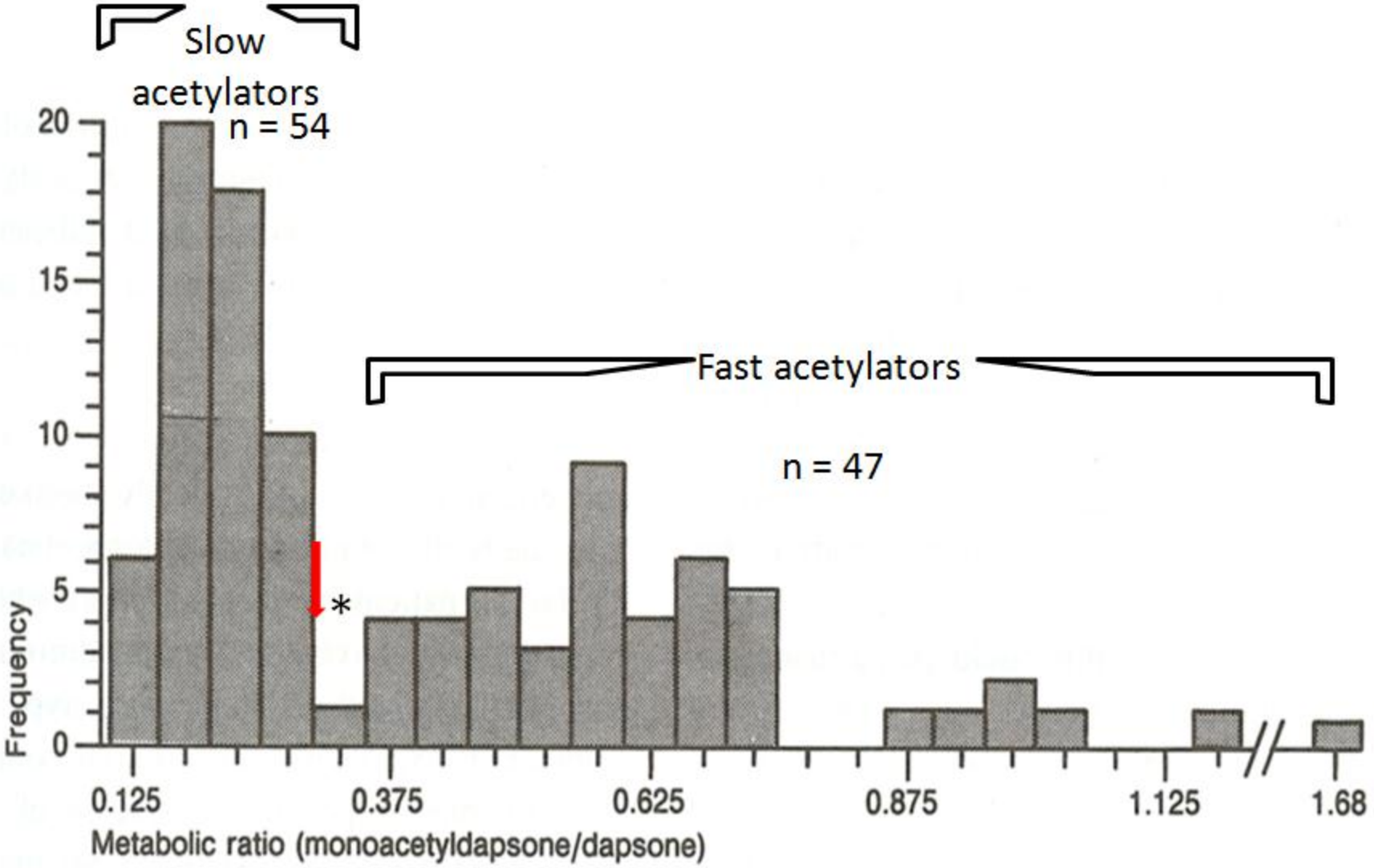
- Following a dose of dapsone (50 to 100 mg), the ratio of monoacetyldapsone to dapsone in plasma remains stable from approximately three to forty-eight hours. A blood sample at three hours, with subsequent plasma analysis of dapsone and monoacetyldapsone allows for relatively rapid determination of “acetylator status”.



Dapsone Monoacetyldapsone

Clin Pharmacol Ther 1977: 22; 251-258.
Pharmacology 1981: 22; 162-171.

Acetylation Metabolic Ratios



Clin Exp Pharm Physiol 1984: 8; 67.
Drugs 1985: 29; 342-375.

Pharmacokinetic Dosing

Procainamide

Therapeutic range (mg/L)	4 – 10
V (L/kg)	2
CL (L/hr/kg) CL renal (L/hr/kg) CL acetylation (L/hr/kg): **Average** Fast Slow CL other (L/hr/kg)	 3 x CLcr **0.13** **Intermediate "Average" 1%** 0.19 Fast 46% 0.07 Slow 53% 0.1

Basic Clinical Pharmacokinetics. Procainamide 2004; 364-387.
Applied Clinical Pharmacokinetics. Procainamide 2008; 398-447.

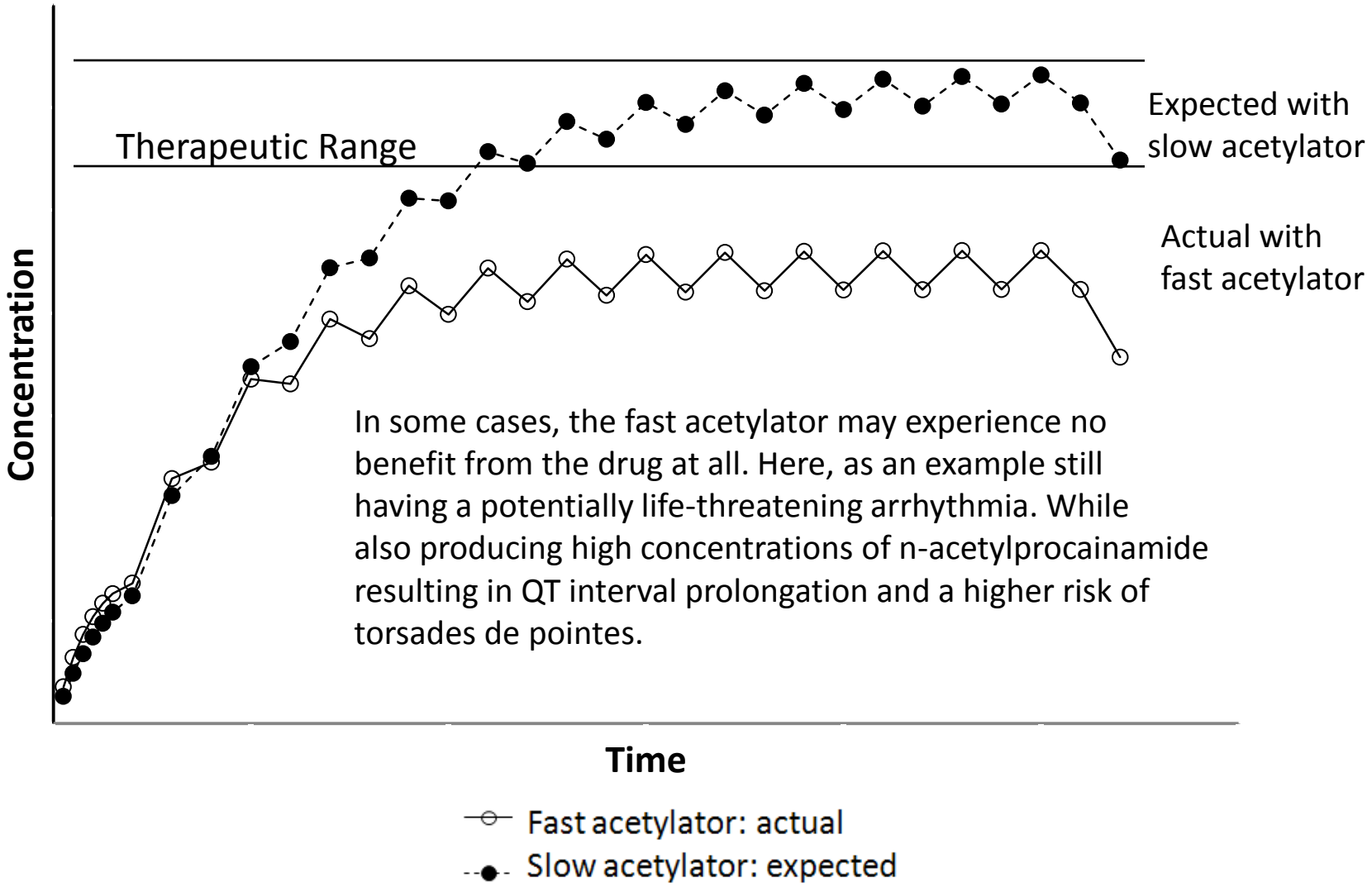
Procainamide Pharmacokinetic Dosing

Scenario:
Patient: Fast Acetylator *
- Dosed as a Slow Acetylator
Patient: 70 kg, CLcr 50 mL/min (3 L/hr), CLother (7 L/hr)

	Expected Value (for slow)	*Actual Value (for fast)
V (L)	140	140
CL (L/hr)	20.9	29.3
t½ (hr)	4.6	3.3
Cave (mg/L)	6	4.3 – low end of therapeutic range
Cmax (mg/L)	7.9	6.3 – OK but “short-lived”
Cmin (mg/L)	4.3	2.7 – likely sub-therapeutic

Calculated based on data from Basic Clinical Pharmacokinetics. Procainamide 2004; 364-387.

Procainamide Pharmacokinetic Dosing



Procainamide and the NAT2 Polymorphism

- 13 polymorphisms in the coding region.
  - Contribute to 26 alleles accounting for the fast, intermediate, and slow acetylator phenotypes.

Population	%Slow Acetylator Phenotype
Caucasian	~50
African American	~40
Asian	~10

Pharmacogenomics: Applications to Patient Care. Cardiovascular Diseases 2004; 495-528.

NAT2 Alleles With Mutations

		Position in the Coding Region				
Allele[a]	Phenotype	191	341	481	590	857
*NAT2*4 (WT)*	Fast	G	T	C	G	G
*NAT2*5D*	Slow		C			
[*NAT2*6A*]	Slow				A	
*NAT2*7A*	Slow					A
[*NAT2*11A*]	Fast			T		
*NAT2*14A*	Slow	A				
*NAT2*14G*	Slow	A				

Examples from the currently known (May 2008) total of 53 alleles.
[a]Brackets = incomplete typing

Clin Chem 2003: 50; 1264-1266.
Molecular Biology 2004: 38; 383-387.

Ethnic Population Acetylator Status

Population	% Fast Acetylators	NAT2 Genotype(s)
Chinese	**78 - 85**	***NAT2*4/*4 (F), *4/*5 (F), *4/*6 (F), *4/*7 (F), *5/*5 (S), *5/*6 (S), *5/*7 (S), *6/*6 (S), *6/*7 (S), *7/*7 (S) (83.3% F; 16.7% S)***
Japanese	**88 - 90**	
Korean	**89**	
African American	49 - 58	
African	43 - 51	*NAT2*14 (S)*
Caucasian (USA)	43 - 48	*NAT2*4 (F), NAT2*5 (S), NAT2*6 (S)*
Canadian	30 - 41	
Israeli	25 – 33	
Egyptian	18	*NAT2*4* (F), *NAT2*5* (S), *NAT2*6* (S), *NAT2*7* (S) (21.5% F; 78.5% S)

Eur J Clin Pharmacol 2006: 62; 355-359.
Br J Clin Pharmacol 2003: 55; 560-569.
Drug Treatment. Pharmacological Basis for Adverse Drug Reactions 1980; 202-235.
Drugs 1985: 29; 342-375.

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

Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	References (PubMed ID)
	Representative Label	Test[a]	Drug		
NAT Variants	N-acetyltransferase slow and fast acetylators and toxicity- "slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions."	3	Rifampin, isoniazid, pyrazinamide	Isosorbide dinitrate, Hydralazine hydrochloride	12669770 12715953 2224079 12271964 11259359 11677864 15951616

[a]Reference is made to the requirement of testing for the biomarker:
1 = test required;
2 = test recommended; 2* test for at risk populations
3 = information only

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm; Accessed 12/2008.

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

Pharmacogenomic Biomarkers in Drug Labels

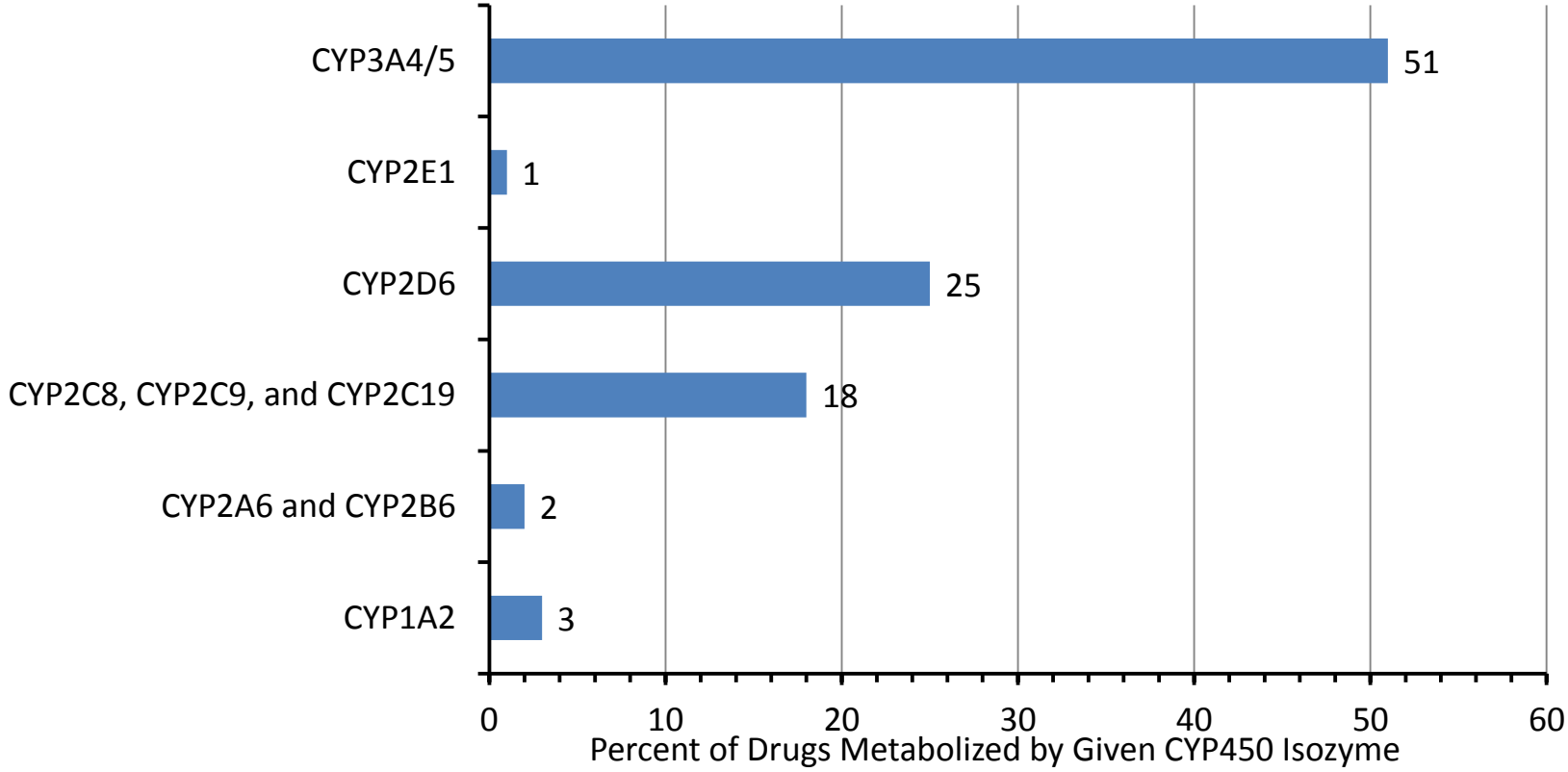
Drug	Therapeutic Area	Biomarker	Label Sections
Isosorbide and Hydralazine	Cardiovascular	NAT1; NAT2	Clinical Pharmacology
Rifampin, Isoniazid and Pyrazinamide	Antiinfectives	NAT1; NAT2	Adverse Reactions, Clinical Pharmacology

New format: Less information. Must “drill down” to package label to see information.

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm; Accessed 09/2011.

Cytochrome P450 Isozymes

The CYP enzyme superfamily is a major drug metabolizing system in the human body and for many drugs is the major “driver” of the drugs clearance. Alterations or differences in CYP enzyme activity can dictate certain pharmacokinetic characteristics.



Pharmacogenomics: Applications to Patient care. 2004; 273-308.

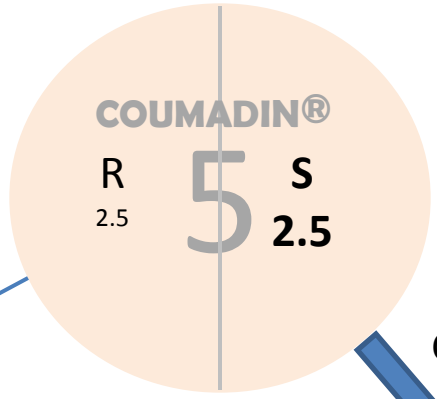
Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	References (PubMed ID)
	Representative Label	Test[a]	Drug		
CYP2C9 Variants	**CYP2C9 Variant genotypes and drug dose** "The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles."	2*	Warfarin		18034618 17989110 17955230

[a] Reference is made to the requirement of testing for the biomarker:
2 = test recommended; 2* test for at risk populations

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm; Accessed 12/2008.

Warfarin- Genetics - Kinetics



CYP1A1
CYP1A2
CYP2C19
CYP3A4

10-hydroxywarfarin
6-hydroxywarfarin
8-hydroxywarfarin

Wild-type "normal"; Dose = 5 mg

CYP2C9

Genetic Allele	Kinetic Concept Equations	Clearance	Equivalent Dose (mg)
CYP2C9*1/*2	$\downarrow Dose = \frac{C_{AVE} \cdot \downarrow CL \cdot \tau}{F}$	↓20%	4
CYP2C9*1/*3		↓40%	3
CYP2C9*2/*2		↓50%	2.5
CYP2C9*2/*3		↓60%	2
CYP2C9*3/*3		↓85%	0.75

7-hydroxywarfarin

Note: CYP4F2
-CC variant lower dose
-TT variant higher dose

www.aacc.org ; Accessed 12/2008
Clin Pharmacol Ther 2008: 83; 460-470.

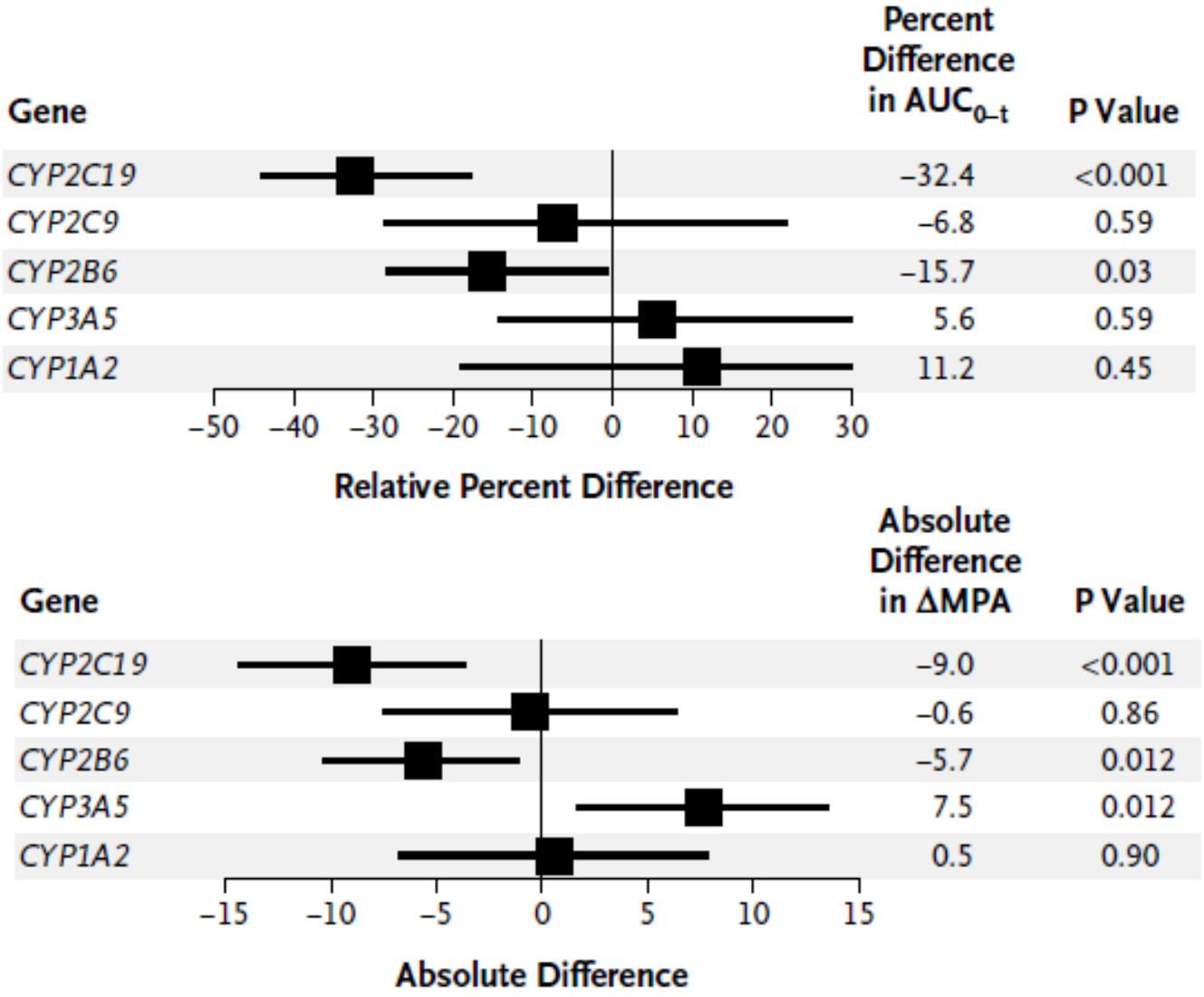
Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

What might we see for clopidogrel?

Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	References
	Representative Label	Test[a]	Drug		
CYP2C19 Variants	**CYP2C19 Variant genotypes and drug dose ""**"The analysis suggested a risk of lack of efficacy and a risk of adverse events for patients carrying either of the CYP2C19 PM's"	1? 2? 3?	Clopidogrel		-N Engl J Med 2009; 360 -Lancet 2008 12/23/08

[a]Reference is made to the requirement of testing for the biomarker:
1 = test required;
2 = test recommended; 2* test for at risk populations
3 = information only

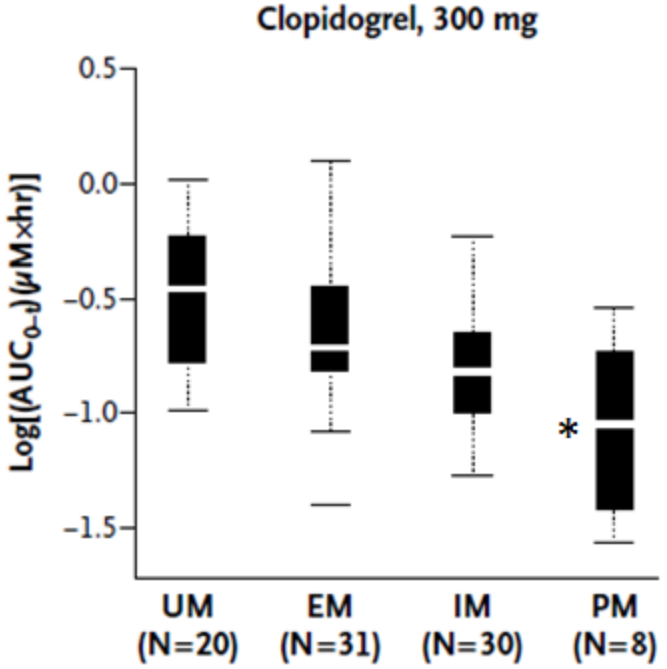
Clopidogrel- Genetics - Kinetics - Dynamics



Significant at a p-value of < 0.01

N Engl J Med 2009: 360

Clopidogrel- Genetics - Kinetics



$$\downarrow C_{AVE} = \frac{(\sim\downarrow F \cdot Dose)}{V \cdot ke \cdot \tau}$$

N Engl J Med 2009: 360

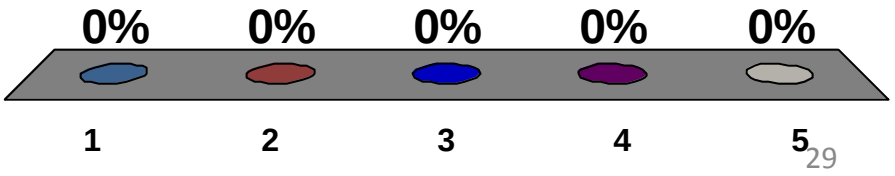
Genetic – Kinetic Interface

Genetic Effect on Kinetic Parameter	Genetic Cause/ Phenotypic Expression	Effect on other PK parameters	Consequences/Response
↓CL	PM	↑ t½, ↑Cmax	Longer time to Css. If toxicity occurs and drug is discontinued, longer time to be removed from the body (5 x longer t½)/Decrease dose likely with less frequent dosing/Use another drug.
↑CL	UM	↓ t½, ↓Cmax	Shorter time to Css. Potential inefficacy/Increase dose and like give the dose more frequently/Use another drug.
↓ Bioactivation	PM	↓F, ↓C, ↓AUC	Lack of efficacy/Increase dose/Use another drug.

All relative to the “normal” extensive metabolizer.

My pharmacy education adequately prepared me to apply pharmacogenetics in my practice:

1. Strongly Disagree
2. Disagree
3. Neutral
4. Agree
5. Strongly Agree



Healthcare Provider Perceived Knowledge of Pharmacogenomics

Anticoagulation:

Pharmacists: 48.4% felt they were adequately informed about pharmacogenetic testing.

- 66% of healthcare providers (N = 286 Pharmacists, 102 Nurses, 52 Physicians, 8 Other) expressed a general lack of knowledge related to PGx.[b]

76% of nursing students (N = 275) expressed minimal or no knowledge related to PGx.[a]

Physicians (psychiatric residents and faculty) knowledge of pharmacogenetic testing: 56% minimal, 21% moderate, 5% extensive, 5% none.[c]

[a] Dodson Ch, Lewallen LP. Nurse Educ. Today 31(4), 333-339, 2011.

[b] Kadafour M, et al. Pharmacogenomics 10(11), 1853-1860,2009.

[c] Hoop JG, et al. Psychiatrist 71(6), 745-753, 2010.

Pharmacogenetics/Genomics Education in the Academic Setting

2001 – NCHPEG disseminates "Core Competencies in Genetics Essential for All Health-Care Professionals."

- Stressed the need for all educators to incorporate genetic information into all levels of professional education.

2002 – AACP Academic Affairs Committee presents the potential impact of pharmacogenomics and pharmacogenetics on the future roles of pharmacists.

- Pharmaceutical education driving curricular outcomes, instructional strategies, faculty development, and resource implications.

2011 – ACPE Guidance on the science foundation for the Doctor of Pharmacy curriculum. (ACCREDITATION STANDARDS AND GUIDELINES… January 23, 2011; Effective February 14, 2011).

Pharmacogenetics/Genomics Education

How are we doing in the academic setting?

Question	2005[a] (N = 41) %	2010[b] (N = 75) %
Is pharmacogenetics/pharmacogenomics taught at your school?	78	92
Where does the subject reside in the PharmD curriculum?		
-Stand alone required didactic course.	9.8	21.7
-Included as part of a required didactic course(s).	46.3	72.5
-Elective didactic course.	2.4	34.8

[a] Latif DA and McKay AB. Am J Pharm Educ 2005; 69(2) article 23.
[b] Murphy JA, Green JS, Adams LA, et al. Am J Pharm Educ 2010; 74(1) article 7.

How are we doing in the academic setting? (cont).

Question	2005[a] (N = 41) %	2010[b] (N = 75) %
What is the present state of pharmacogenomics instruction at most schools of pharmacy?		
-Very Good	2.4	0
-Good	9.8	2.7
-Adequate	36.6	26.7
-Poor	31.7	53.3
-Not at all adequate	7.6	8
-No response	11.9?	9.3

How are we doing in the academic setting? (cont).

Question	2010 (N = 75) %
Does your school plan to: -Develop a center of excellence in the next 5 years. -Develop a research focus in this subject over the next 5 years. -Work with industry or other schools to provide external instructors. -Other -No response	 12 13.3 10.7 10.7 53.3
Is your school interested in accessing shared curriculum? (UCSD – PharmGenEd program) Yes No Maybe No response	 70.7 4 17.3 8

Murphy JA, Green JS, Adams LA, et al. Am J Pharm Educ 2010; 74(1) article 7.

Pharmacogenetics/Genomics Education in the Academic Setting

Current Deficit:

- Crowded curricula.
- Misconception that this is related only to inherited diseases.
- Lack of faculty trained to teach the subject.
- Little or no representation of pharmacogenomics on licensure exams.
- Provided in basic sciences, but left out of clinical education. (i.e. personalized medicine)

Education for Pharmacists

- UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences Pharmacogenomics Education Program: (http://pharmacogenomics.ucsd.edu/home.aspx)
  - Module I: Pharmacogenomic Principles and Concepts
  - Module 2: Clinical Applications of Pharmacogenomics
  - Shared curriculum for colleges of pharmacy and individuals.
- Pharmacogenomics: Bridging the gap between science and practice:

  http://www.pharmacytoday.org/pdf/2009/Dec_CE_exam.pdf
- Personalized Medicine and the Future of Pharmacy Practice:

  https://secure.pharmacytimes.com/lessons/201004-01.asp
  - ACPE 0.2 CEU; Expires April 1, 2012
- Potential roles for pharmacists in pharmacogenomics:

  http://www.pharmacytoday.org/pdf/2008/Feb_CE_exam.pdf

Pharmacogenomics and Health IT

Personalized Medicine will not succeed until we have an information management system that can:

- Handle a large volume of information generated from tens of thousands of human genes and proteins.
- Relate genetic data to clinical results to define correlations.
- Support healthcare providers in making decisions at a time when the practical knowledge can no longer be contained within the training, experience, or memory of a single practitioner.

Government Support for Health IT

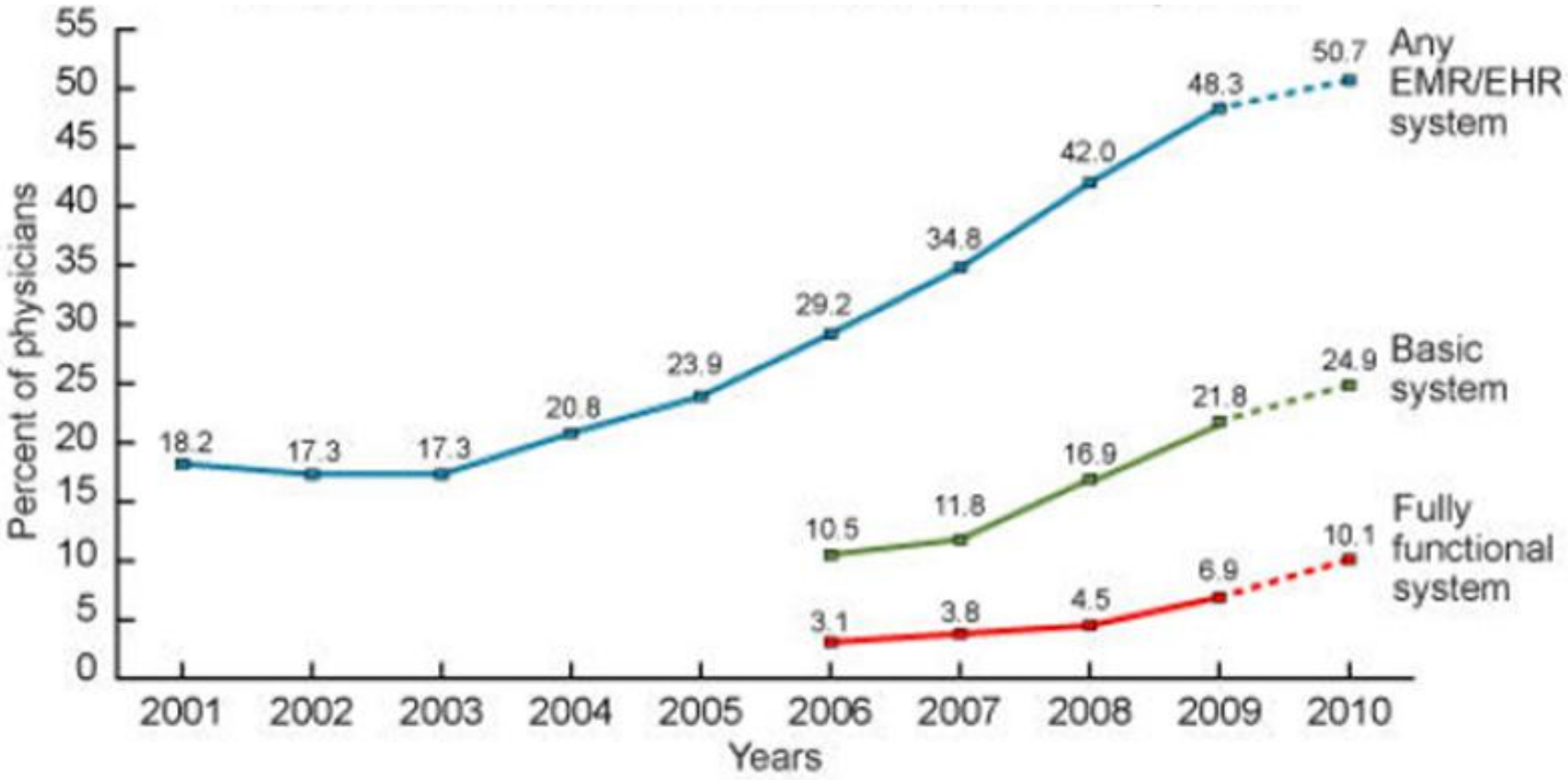
- $44 billion included in the Health Information Technology for Economic and Clinical Health act (HITECH; February 2009).
  - Electronic health records
    - After 2015, penalties will be incurred by hospitals not using HER in a “meaningful way”.

EHR Progression

- Hospitals with fully implemented EHRs:
  - 4% in 2008
  - 22% in 2009
- ~50% of the US population had medical information recorded in EHRs in 2010.
- 95% of people in Holland have EHRs.

HIMSS 2011 Leadership survey. http://www.himss.org/2011Survey/healthcareCIO_final01.asp; Accessed 15 September 2011.
Hsiao CJ, Hing E, Socey TC, et.al. CDC. http://www.cdc.gov/nchs/data/hestat/emr_ehr_09.pdf; Accessed 15 September 2011.
Hiller L, McMullen M, Chumney W, Baumer D. J Sci Tech Law 2011.
Conn J. Modern Healthcare 2011.

Office-based EHRs



Personalized Medicine Coalition. The case for personalized medicine 2011. http://pmc.org; Accessed 3 September 2011.

Regulation

Genetic Tests

- Genetic-based susceptibility testing:
  - Disease
  - Drug Sensitivity
  - Disease carrier status

vs.

- Genetic test to inform clinical decision making

Laboratory Developed Tests (LDTs) vs. In Vitro Diagnostics (IVDs)

LDTs

- Often require more extensive sample and reagent preparation.
- Specialized laboratory equipment.
- Skilled technicians
- FDA has jurisdiction via the Clinical

Laboratory Improvement Amendment (CLIA).

- Most genetic tests are considered LDTs.

Laboratory Developed Tests vs. In Vitro Diagnostics

IVDs

- Examination of specimens derived from the human body.

- Solely or principally for the purpose of giving information about a physiological or pathological state.

Test Safety

- Proliferation of genetic tests and services linked to major health decisions and targeted directly to consumers.
- May 2010 FDA informed test manufacturers that the FDA was taking a more active approach to oversee tests labeled as “Personalized”.
  - Misinterpretation

Examples – Direct to Consumer

Personal genome service PGS™

- **get to know your DNA, all it takes is a little bit of spit!**

Here's what you do:

1. Order a kit from our online store.
2. Register your kit, spit into the tube, and send it to the lab.
3. Our CLIA-certified lab analyzes your DNA in 6-8 weeks.
4. Log in and start exploring your genome.

The specificity and sensitivity of the analytical procedure goes hand-in-hand with education.

Companion Diagnostics

- A clear regulatory path is necessary for developing genetic tests that are directly related to a “companion drug”.
  - Example Herceptin®/Hercep Test™
  - 2005 The FDA released the “Drug-Diagnostic” Co-Development Concept Paper.
  - European Medicines Agency(EMEA) and FDA are now mandating or recommending “biomarker” testing be performed prior to prescribing certain drugs.
    - Table of genomic biomarkers

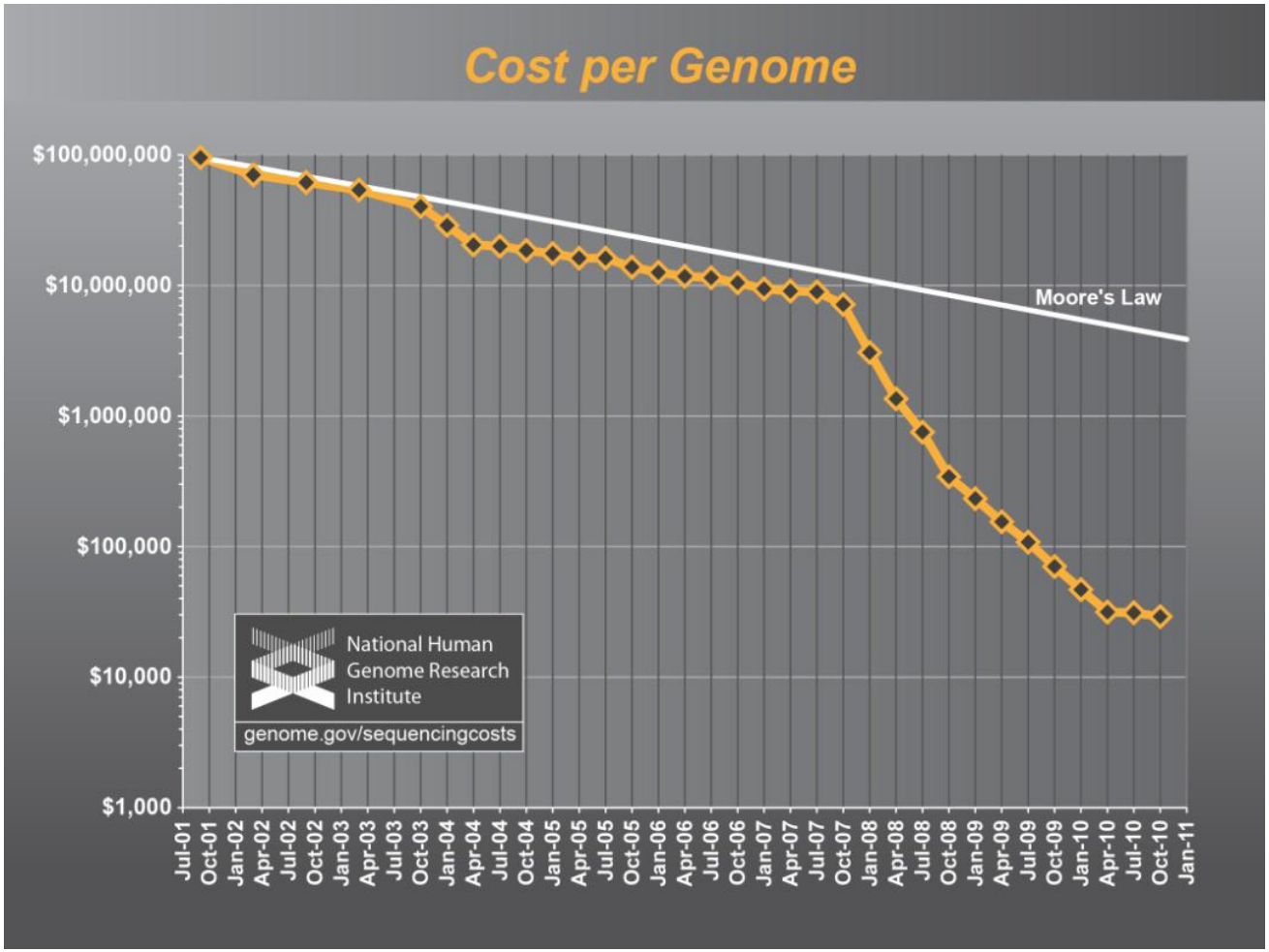
Carver KH. Companion Diagnostics: Evolving FDA Regulation and Issues for Resolution. Accessed 15 September 2011.

Voluntary Exploratory Data Submissions

- Voluntary Exploratory Data Submission program, which was launched in 2004.
  - Pharma is free to discuss genetic information without jeopardizing approval.
  - Encourages genetic testing which may be related to “adaptive” clinical trials. This can lead to genetically enriched clinical studies.
    - ~10% of product labels inform or recommend molecular or genetic tests for optimal treatment.
    - 8 labels currently require pharmacogenetic tests prior to a drug’s use.

Frueh FW. et. al. Pharmacogenomic biomarker information in drug labels. Pharmacotherapy 28:992-998, 2008.

Technology and the Cost of a Genome



Currently the cost is about $5000, and it is expected to drop to ~$1000 by 2013.

Technology and the Cost of a Genome

Genotyping: A genotype describes the DNA bases present at a specific location in the two copies. With genotyping, only a certain number (1 to 100,000s) of specific DNA changes (SNPs) are assessed.

- $207

Sequencing: Decodes the entire sequence of your two copies of DNA

- $5000

Insurance and Reimbursement

- Regulatory approval is necessary.
- Genetic testing is understood by public and private insurers on a conceptual basis. They are seeking evidence of the value.
  - Medicare rejected paying for genetic guided warfarin dosing even after the FDA recommended it!

Insurance and Reimbursement

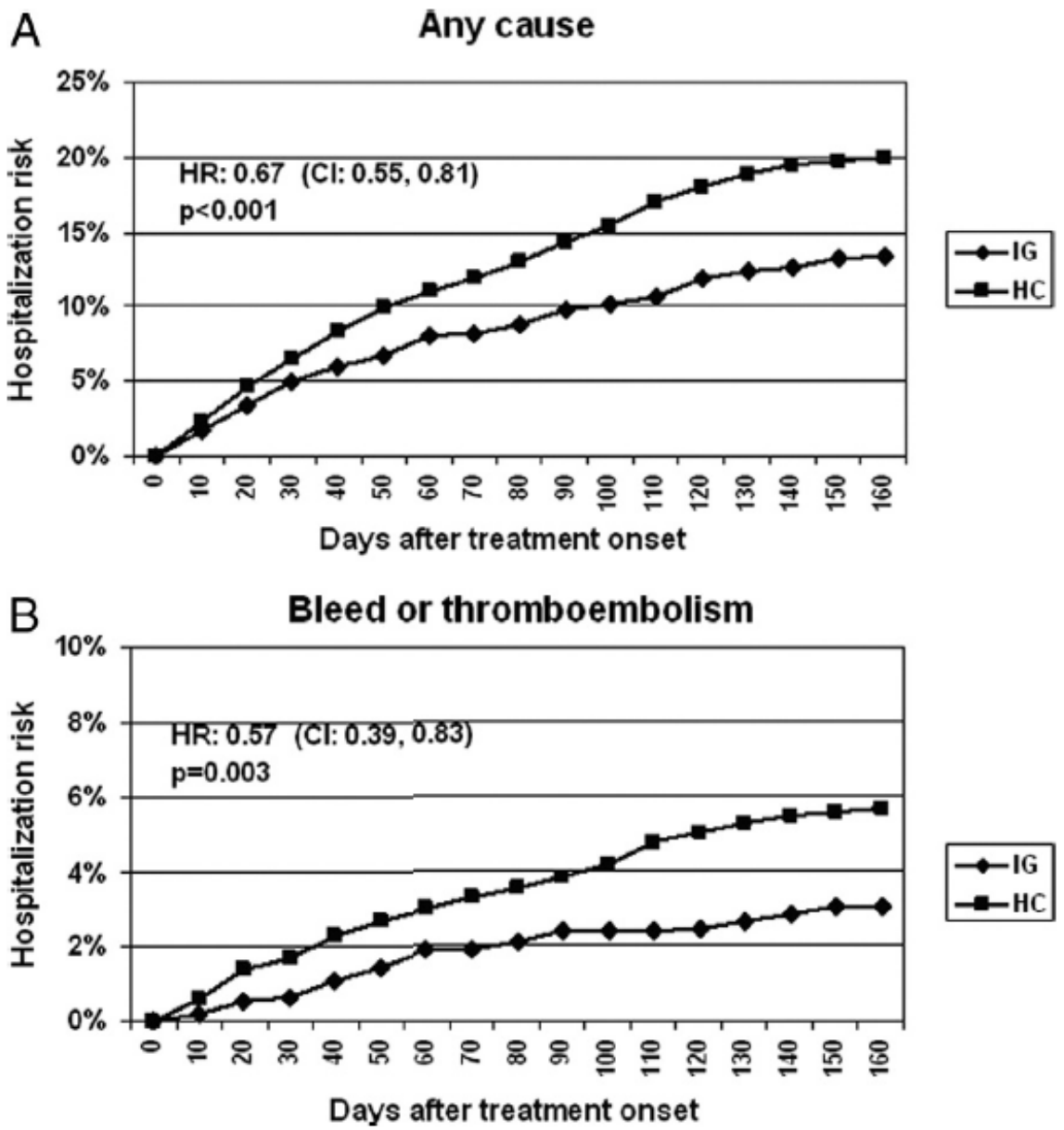
"Catch 22"

- Insurers want studies to prove the utility of genetic tests, but won't pay to have the large expensive randomized trials conducted to validate the tests.

-PBM's can offer clinically validated tests to patients and then gather data from the "real world".

-Medco: 900 patient study showed the utility of genetic dosing of warfarin.

Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates. J Am Coll Cardiol 2010; 55:2804-2812.



IG = intervention (genetic testing) group; HC = historical controls

Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates. J Am Coll Cardiol 2010; 55:2804-2812.

Genetic Privacy

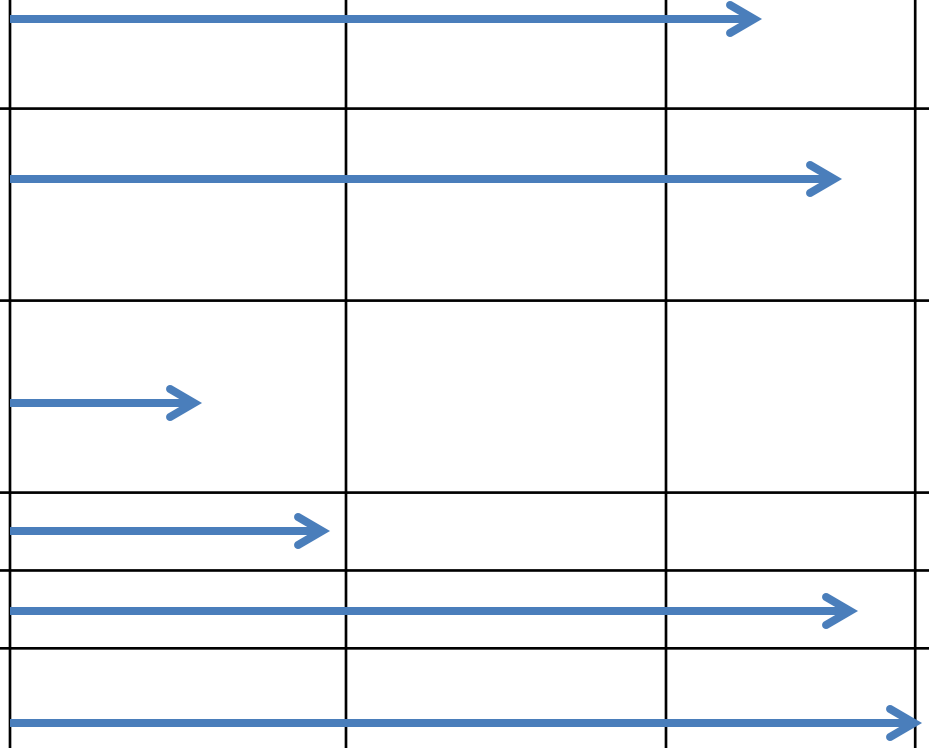
GINA – Genetic Information Nondiscrimination Act

Explicitly prohibits employers and health insurers from discriminating against individuals based on their genetically-based risk factors.

The patient has the right to present information to a healthcare provider and not allow it to be given to the insurer.

Pharmacogenetic testing does not distinguish disease risk. It does allow for specific therapy (i.e. right drug, right dose).

	Recognition of value	Enactment of policy and legislation	Pilot and precedent	Full implementation and standardization
Genetic privacy and legal protections				
Healthcare information technology				
Insurance coverage and reimbursement				
Medical education				
Regulation				
Technology and tools				



With respect to pharmacogenetics:

1. I have minimal knowledge.
2. I have moderate knowledge.
3. I have extensive knowledge.
4. I have no knowledge.