



U.S. Food and Drug Administration
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Progress in PGx and its promise for Medicine



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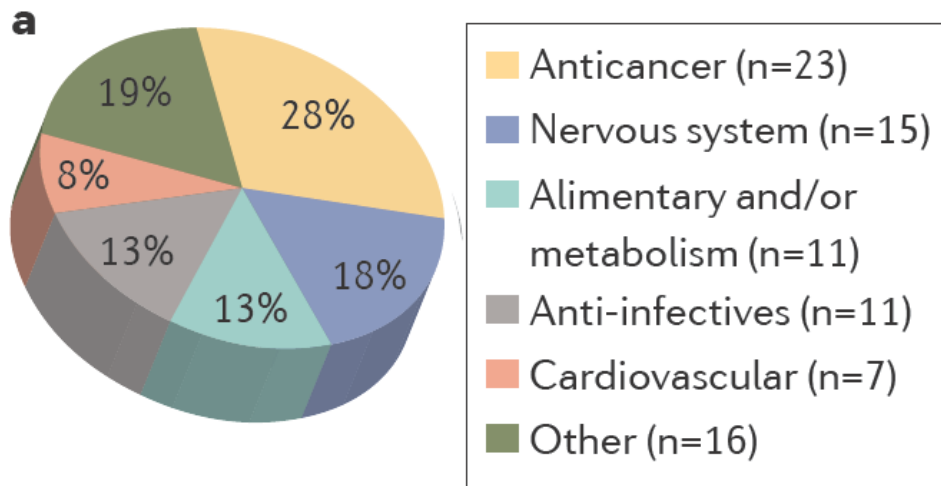
Overview

- **What is PGx and Why Do We Care?**
- **PGx in Drug Development and Regulatory Consideration**
- **PGx Progress in New Drug Application (NDA)**
- **PGx Lessons and Future**

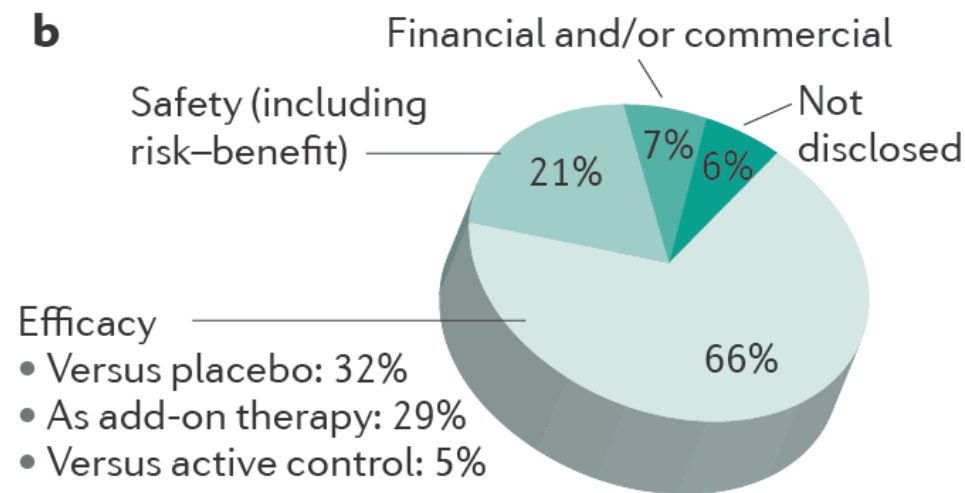
Pharmacogenomics/genetics

- Pharmacogenomics (PGx): The study of variations of DNA and RNA characteristics as related to drug response.
- Pharmacogenetics (PGt): A subset of PGx; the study of variations in DNA sequence as related to drug response.

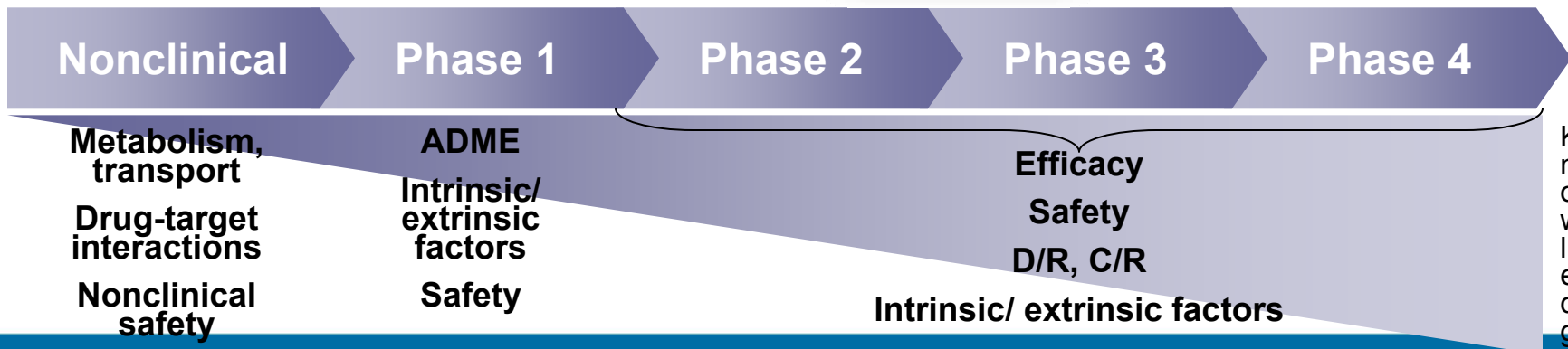
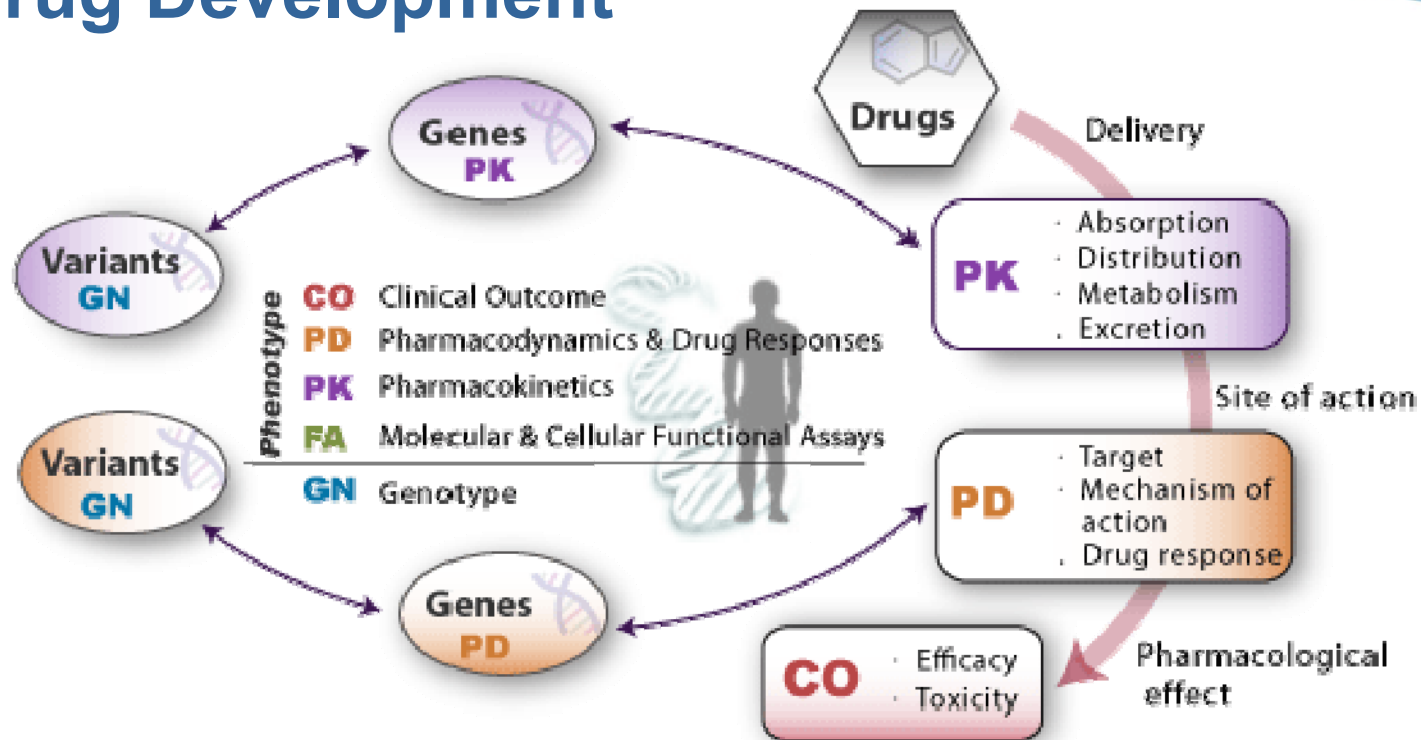
Why Do We Care?



High-quality scientific evidence
Well-defined end points
Right patient population



Pharmacogenomic Strategy in Drug Development



* Can also be retrospectively derived



PGx Regulatory Guidance

2005	Guidance on PG Data Submissions
	Concept Paper on Drug-Diagnostic Co-Development
2007	Companion Guidance on PG Data Submissions
	Guidance on PG Tests and Genetic Tests for Heritable Markers
2010	ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards
	Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment
	Guidance on Qualification Process for Drug Development Tools
2011	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
Preparation	Guidance on Clinical Trial Designs Employing Enrichment Designs to Support Approval of Human Drugs and Biological Products

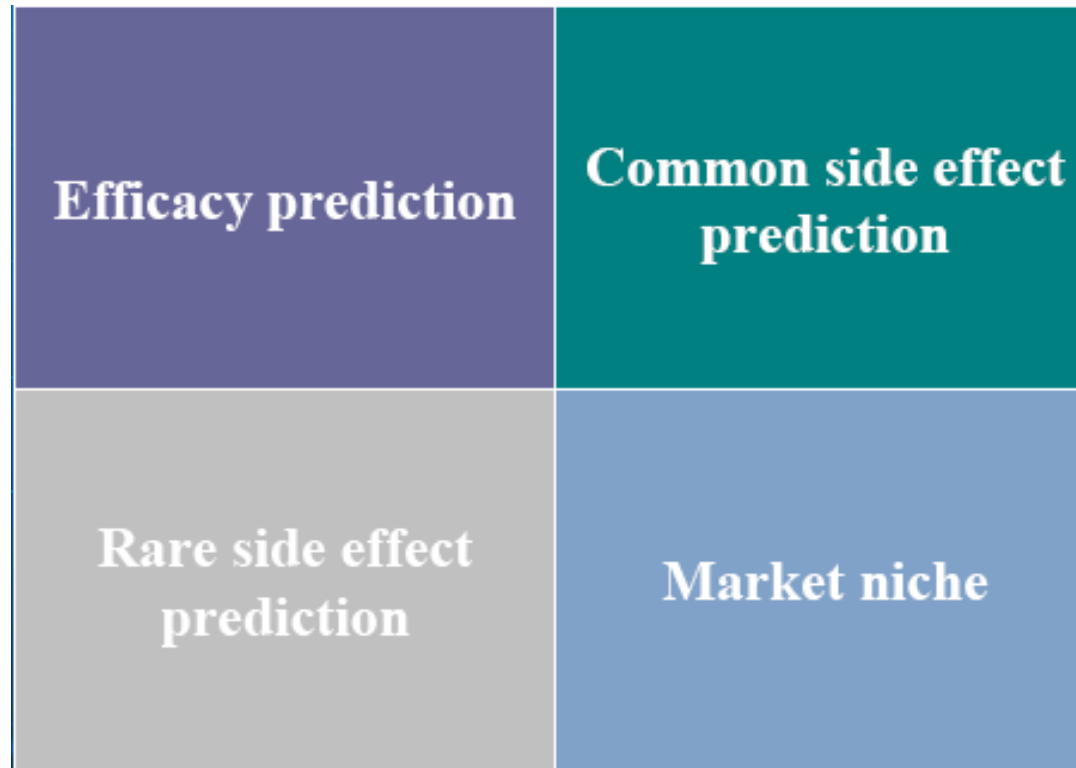
Clinical Evaluation of PGx – General Considerations

- Identifying the basis for PK outliers and inter-subject variability in clinical response
- Ruling out the role of polymorphic pathways as clinically significant contributors to variable PK/PD, efficacy/safety
- Estimating the magnitude of potential DDI
- Designing clinical trials to test for greater effects in specific subgroups, possibly for use in study enrichment strategies

Principles of Including PGx Info in Labeling

- Test available, “to be considered”, “recommended”, or “necessary”
- PGx information related to proper patient selection (e.g., the need for PGx testing) — **INDICATIONS AND USAGE**
- Different dosing recommendations for subgroups of patients based on genetic makeup — **DOSAGE AND ADMINISTRATION**
- PGx information affecting drug safety — **BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and/or ADVERSE REACTIONS**
- Relevant information concerning the role of genetic variations in drug-drug interactions and the clinical consequences of the combination of genetic polymorphisms in protein(s) in the context of the drug’s metabolism, transport and action — **DRUG INTERACTIONS**
- PGx impact on PK or PD (if not included in another section) — **CLINICAL PHARMACOLOGY**
- Efficacy differences related to PGx — **CLINICAL STUDIES** (if studied and the evidence is substantial)
- Genotype(s) that are known to be associated with an adverse reaction in a specific population — **USE IN SPECIFIC POPULATIONS**

PGx in New Drug Application (NDA)





Efficacy Prediction



Anti-Hepatitis C Virus (HCV) Example

Background for HCV

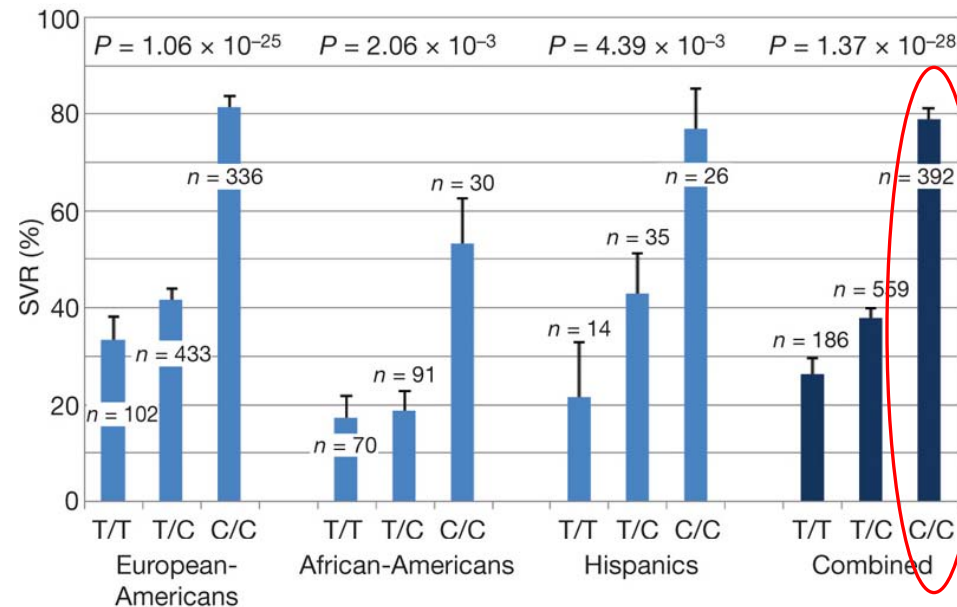
- Discovered in late 1980's
- World wide ~170 million infected, 10~20K death in the US/year
- Leading cause of cirrhosis, a common cause of hepatocellular carcinoma, and as a result of these conditions it is the leading reason for liver transplantation in the U.S.
- 11 major genotypes; genotype 1 accounts for ~80% of HCV patients in the U.S. and ~60% worldwide.

Sustained Viral Response (SVR) Rate by rs12979860 (IL28B) Genotype

- SOC: Injected *peginterferon alpha* + Oral form *Ribavirin*
- PegIntron¹

Population	CC	CT	TT
Caucasian	69% (301/436)	33% (196/596)	27% (38/139)
African-American	48% (20/42)	15% (22/146)	13% (15/112)
Hispanic	56% (19/34)	38% (21/56)	27% (7/26)

- Ribavirin²



Boceprevir (Merck) & Teleprevir (Vertex), 2011

- Chronic hepatitis C genotype 1 infection in combination with peginterferon alfa and ribavirin
- Inhibitor of the HCV non-structural protein 3 (NS3) serine protease
- Genetic biomarker IL28B genotype information in drug labels. SVR rates tended to be lower in subjects with the rs12979860 C/T and T/T genotypes compared to those with the C/C genotype
- [A new standard of care](#) is emerging



Anti-Metastatic Melanoma (MM) Example

Background for MM

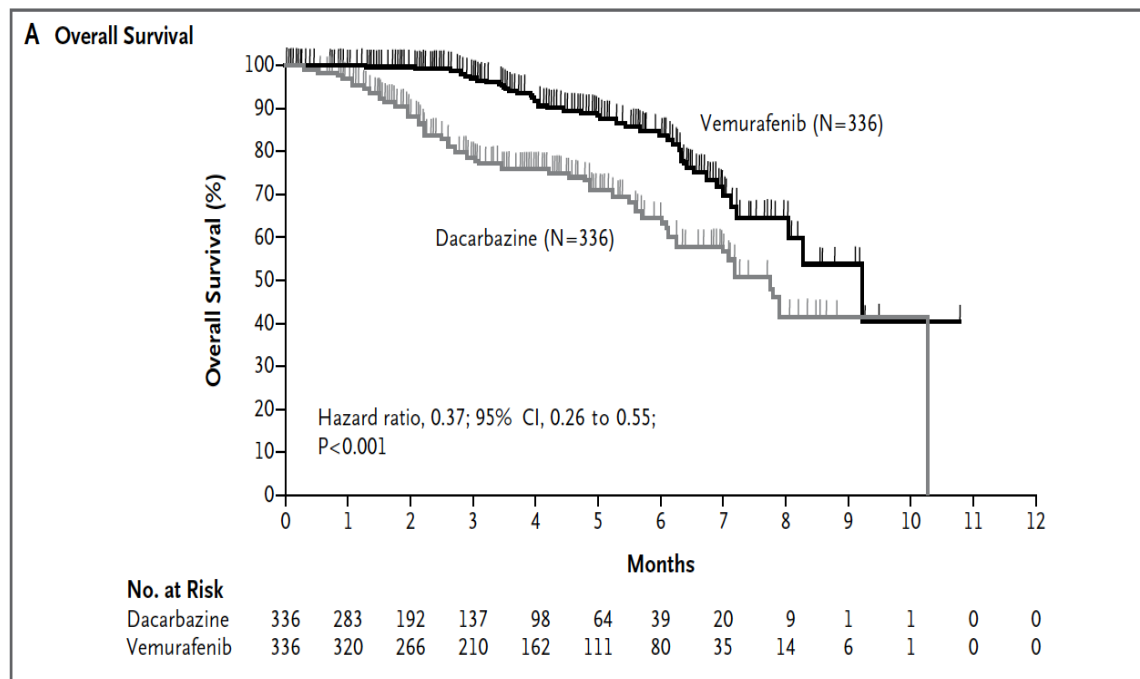
- A malignant tumor of melanocytes, predominantly occurring in skin.
- Worldwide ~160K diagnosis/yearly,
- Median survival 6-9 month, 8700 death@U.S. (2010)
- Some genes have been identified as increasing the risk of developing melanoma. Genetic testing can be used to determine whether a person has one of the currently known mutations.

SOC for MM

- Dacarbazine (chemotherapy, 1975)
 - Class of alkylating agents
 - Average response rate ~ 15.3% with no significant improvement in overall survival¹
- Interleukin-2 (immunotherapy, 2008)
 - Type of cytokine immune system signaling molecule
 - Higher response rates when IL-2 + peptide vaccine (22%) compared to IL-2 alone (13%)²
- Ipilimumab (2011)
 - Human monoclonal antibody binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), sustaining an active immune response
 - Response rates range from 13% with ipilimumab + vaccine (stage IV disease) to 17% and 22% with ipilimumab + dacarbazine or interleukin-2³

Vemurafenib (2011)

- B-Raf enzyme inhibitor– BRAFV600E in~ 60% melanomas
- Melanoma without BRAFV600E not inhibited by vemurafenib; the drug paradoxically promote tumor growth
- [Cobas 4800 BRAF V600 Mutation Test](#): determine a patient’s eligibility using DNA isolated from tissue sample
- Enrichment Design showed OS: 9.2mo (vemurafenib) vs. 7.8 mo (dacarbazine); ORR (CR+PR): 48% (vemurafenib) vs. 5% (dacarbazine)



Influence of Host Genetic Variation on Efficacy-- Selected Examples

Drug	Efficacy endpoint	Genetic Factor		
	Endpoint	Efficacy Allele	Frequency	Effect
Warfarin	Hospitalization due to clotting events (Medco)	<i>CYP2C9</i> *2/*3 <i>VKORC1</i> G>A	<i>CYP2C9</i> : 0.11 (*2); 0.07 (*3); <i>VKORC1</i> : 0.39	1.4 HR for PGx guided dosing
Pazopanib	Progression-free survival (renal cell carcinoma)	<i>IL8</i> 2767 (TT vs AA genotypes)	0.18 for TT genotype	1.8 HR
Peginterferon plus ribavirin	Sustained virologic response (SVR) in hepatitis C infection	<i>IL28B</i> rs12979860 (CC vs. CT and TT)	0.2-1.0 among racial groups	6-7
Lucentis (ranibizumab), Avastin (bevacizumab)	Visual acuity – age-related macular degeneration	<i>CFH</i> Y402H (CT and TT vs. CC)	0.22 for CC genotype	10
AFQ056	Aberrant Behavior Checklist-Community Edition score – Fragile X	Methylation status of <i>FMR1</i> promoter	0.28 full methylators	37



Common Side Effect Prediction



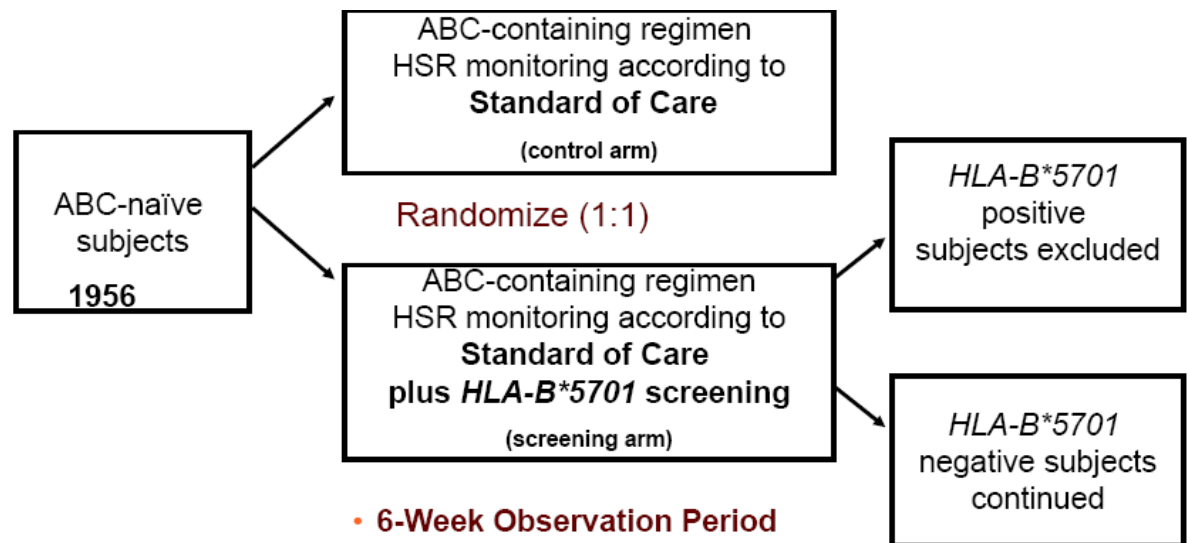
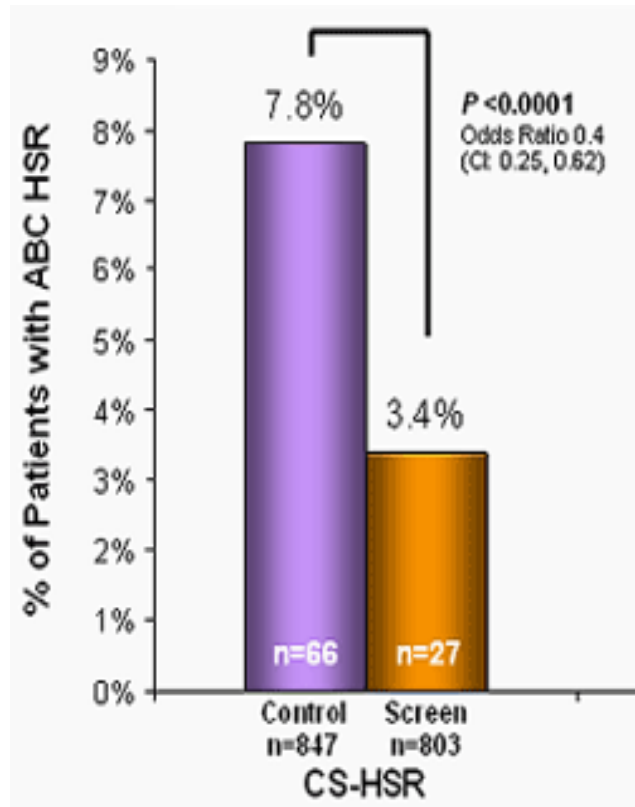
Anti-Human Immunodeficiency Virus (HIV) Example

Abacavir Hypersensitivity and HLA

- Abacavir belongs to the nucleoside reverse transcriptase inhibitor (NRTI) class with potent antiviral activity against HIV
- Hypersensitivity reactions (HSR) to Abacavir occur in 5-8% of patients
- Consists of fever, rash, GI symptoms, respiratory symptoms, generally resolves upon discontinuation
- Rechallenging patients can produce a severe and potentially fatal reaction
- HLA-B*5701 allele associated with HSR in multiple studies

HLA Screening Decreases Incidence of Abacavir HSR

PREDICT-1 Trial (83% Ca+12%AA)



Independent Cohorts:

Australia Cohort: 8% -> 2%

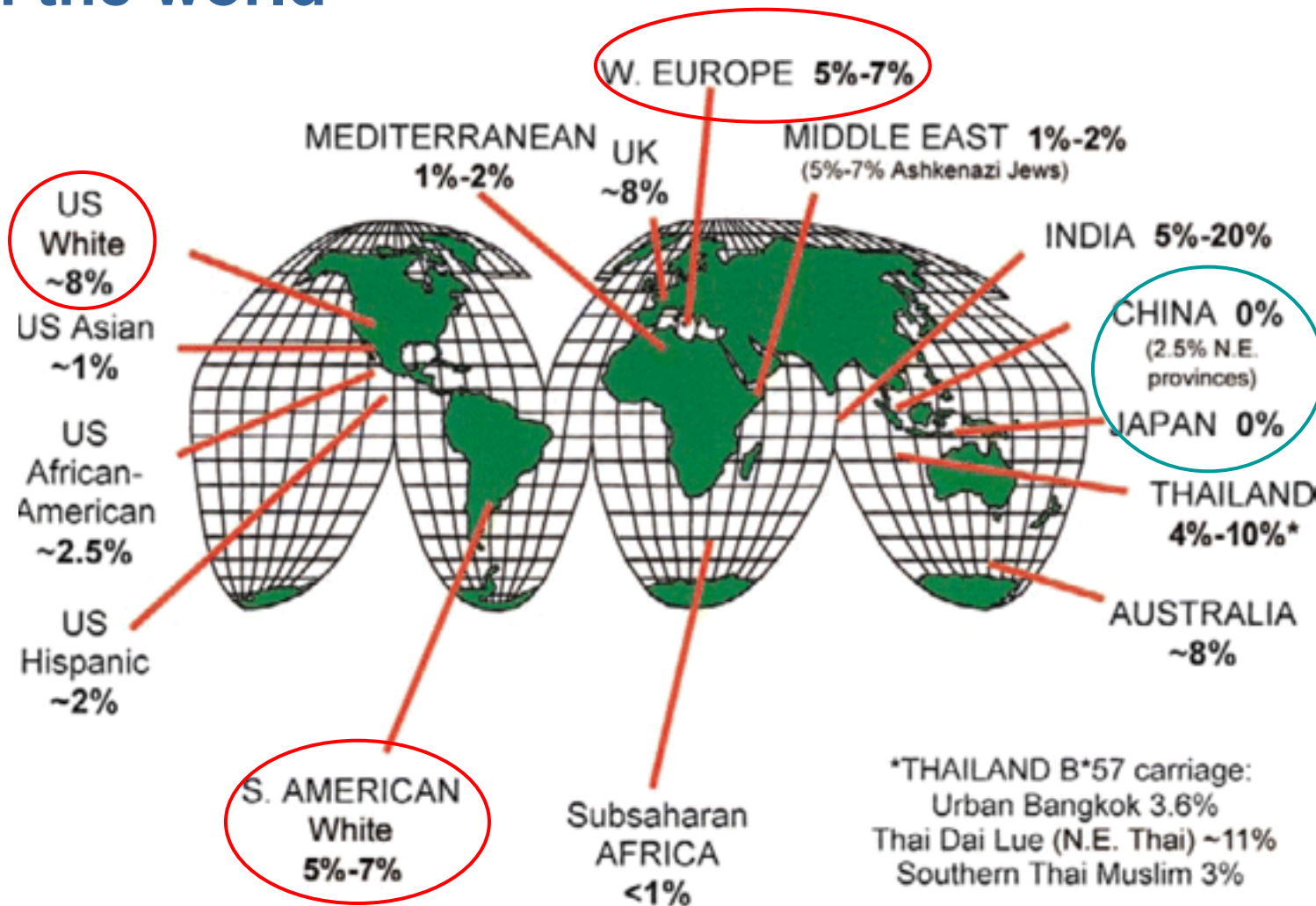
UK Cohort: 7.5% -> 3%

France Cohort : 12%->0%

FDA Black Box Warning

- **Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir.**
- **Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended.**
- **HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive**

Prevalence of HLA-B*5701 in the world





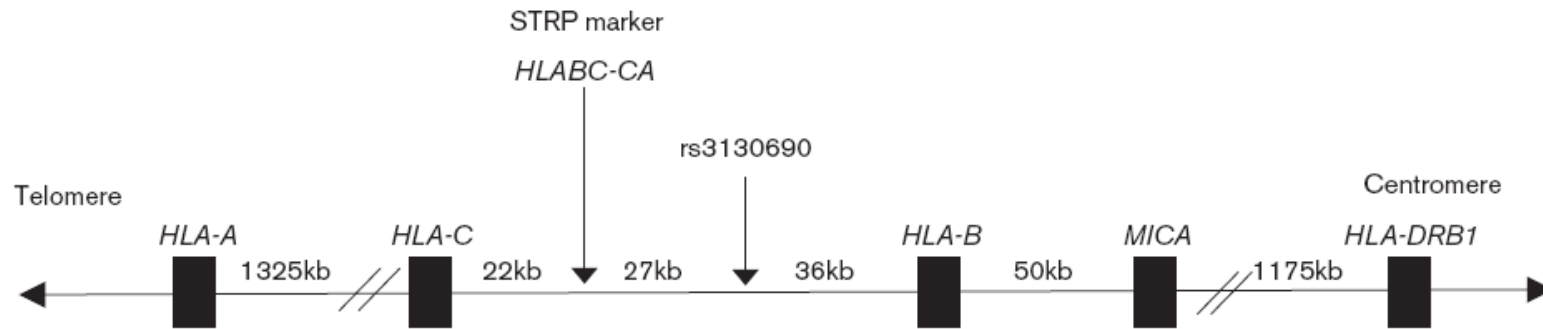
Anti-Epilepsy Example

Carbamazepine-induced Cutaneous Reactions and HLA-B*1502

- Proposed mechanism: Antigen-presenting cells present CBZ via MHC II to CD4+ T-cell receptor
- Infiltrating inflammatory cells found in skin lesions
- [SJS/TEN](#) – high mortality rates
- More common in Chinese patients

Carbamazepine-induced Cutaneous Reactions and HLA-B*1502

- Cutaneous skin reaction cases (n=91, SJS/TEN n=60) collected from 1997-2004; 144 tolerant controls



	A*1101	Cw*0801	HLABC-CA*119	rs3130690 T allele	B*1502	MICA*019	DRB1*1202
SJS/TEN	70%	93.3%	90%	95%	98.3%	95%	68.3%
Tolerant	46.5%	13.9%	4.2%	6.9%	4.2%	13.2%	16%
<i>P</i> value	0.003	4×10^{-28}	2×10^{-35}	4×10^{-36}	4×10^{-43}	5×10^{-30}	7×10^{-13}
<i>P_c</i> value	N.S	8×10^{-27}	4×10^{-34}	1×10^{-35}	2×10^{-41}	1×10^{-28}	2×10^{-11}
Odds ratio	2.7	86.8	207.0	254.6	1357	125	11.4
(95% C.I.)	(1.4–5.1)	(29.3–254.6)	(65.0–659.1)	(70.4–901.9)	(193.4–8838.3)	(37.3–412.4)	(5.64–22.9)



Susceptible region

FDA Black Box Warning

- HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia.
- Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Carbamazepine.
- The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.



Rare Side Effect Prediction

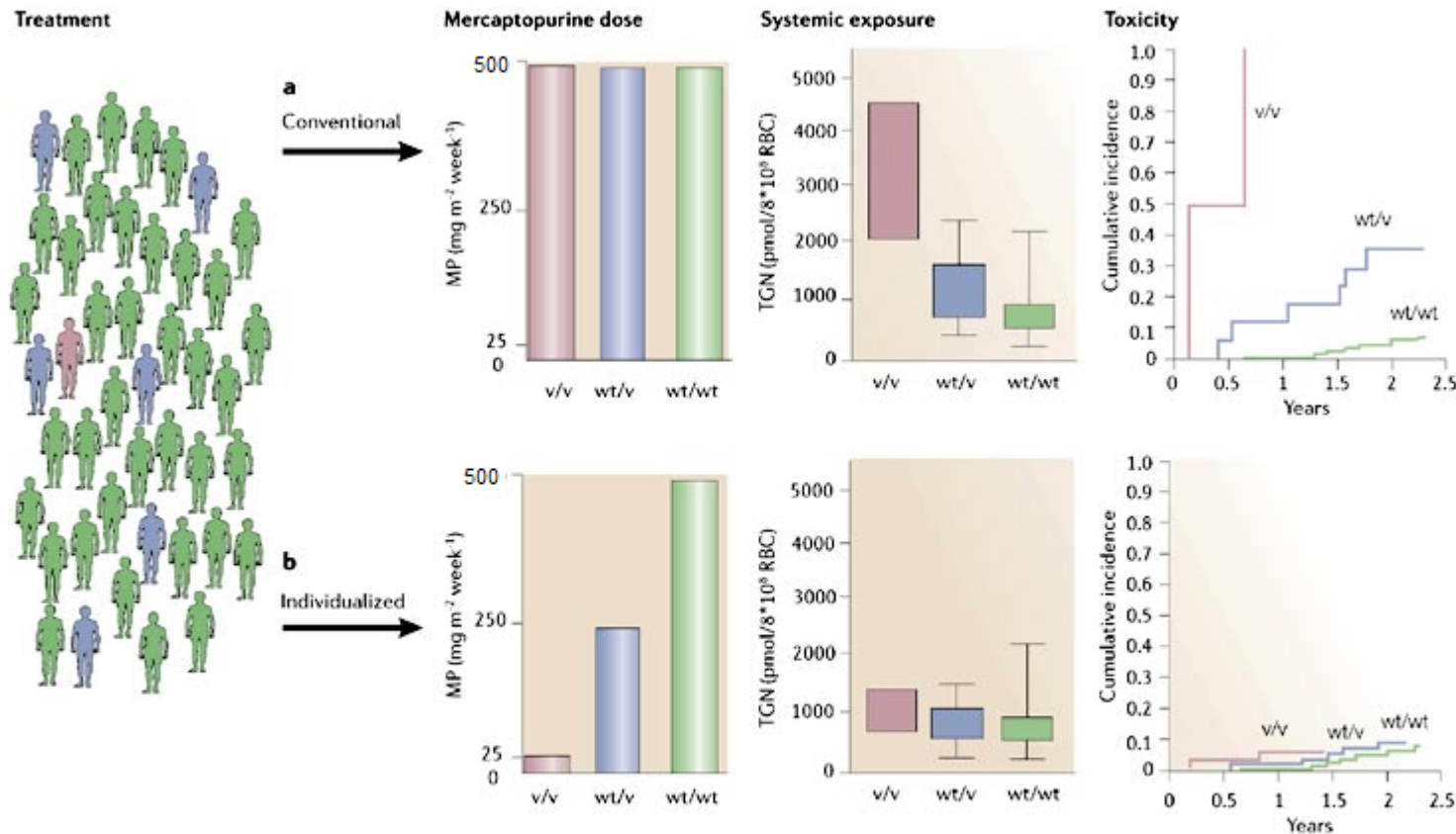


Anti-Acute Lymphatic Leukemia (ALL) Example

6-Mercaptopurine (6MP) and Thiopurine Methyltransferase (TPMT)

- ALL is a life-threatening disease and 6MP can cause life-threatening toxicities
- 6MP metabolized to pharmacologically active thiopurine nucleotides (6-TGN) by TPMT
- TPMT- deficient metabolizers can have increased level of 6-TGN and are at higher risk for severe, sometimes fatal, myelosuppression.
- Myelosuppression, bone marrow suppression, decreases the number of cells responsible for providing immunity, carrying oxygen, and normal blood clotting

Avoid ADRs by Dose adjustment



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- Predominantly genotyping (TPMT*2, TPMT*3A and TPMT*3C) or phenotyping for TPMT variant alleles is recommended before 6MP therapy.

FDA Black Box Warning

- Laboratory tests are available, both genotypic and phenotypic, to determine the TPMT status. Substantial dose reductions are generally required for homozygous-TPMT deficiency patients to avoid the development of life threatening bone marrow suppression.
- Although heterozygous patients with intermediate TPMT activity may have increased mercaptopurine toxicity. If a patient has clinical or laboratory evidence of severe toxicity, particularly myelosuppression, TPMT testing should be considered.

Influence of Host Genetic Variation on Adverse Event Risk -- Selected Examples

Drug	Adverse Drug Reaction		Genetic Risk Factor		
	Reaction	Prevalence	Risk Allele	Freq. ¹	Effect ²
Clopidogrel*	Stent thrombosis	0.13	<i>CYP2C19*2/3/4/5</i>	0.03	3
Gefitinib	Diarrhea	0.28	<i>ABCG2 Q141K</i>	0.07	5
Isoniazid	Hepatotoxicity	0.15	<i>CYP2E1*1 & NAT2</i>	0.13 ³	7
Augmentin	Hepatotoxicity	<0.001	<i>HLA-DRB1*15:01</i>	0.20	10
Pazopanib	Hyperbilirubinemia	0.17	<i>UGT1A1*28</i>	0.40	13
Irinotecan	Neutropenia	0.20	<i>UGT1A1*28</i>	0.32	28
Ticlopidine	Hepatotoxicity (cholestatic)	<0.001	<i>HLA-A*33:03</i>	0.14	36
Flucloxacillin	Hepatotoxicity	<0.001	<i>HLA-B*57:01</i>	0.04	81
Allopurinol	Severe cutaneous reaction	<0.001	<i>HLA-B*58:01</i>	0.15	678
Abacavir	Hypersensitivity reaction	0.08	<i>HLA-B*57:01</i>	0.04	>1000
Carbamazepine	Stevens-Johnson syndrome	<0.001	<i>HLA-B*15:02</i>	0.04	>1000

¹Allele frequency of the AE susceptibility variant in population under study

²Genotype relative risk for susceptible homozygous compared to low risk homozygotes

³Frequency of the *CYP2E1*1* and *NAT2* slow acetylator homozygous genotype in Europeans



Market Niche

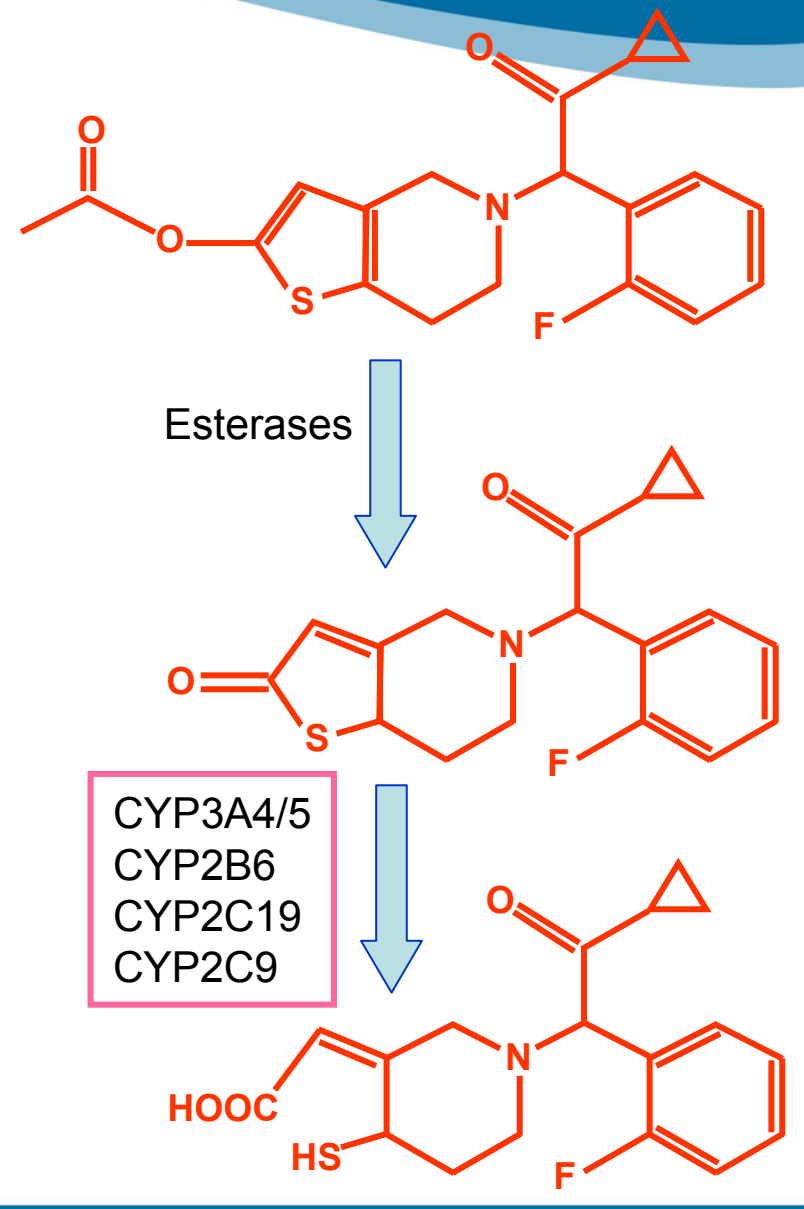
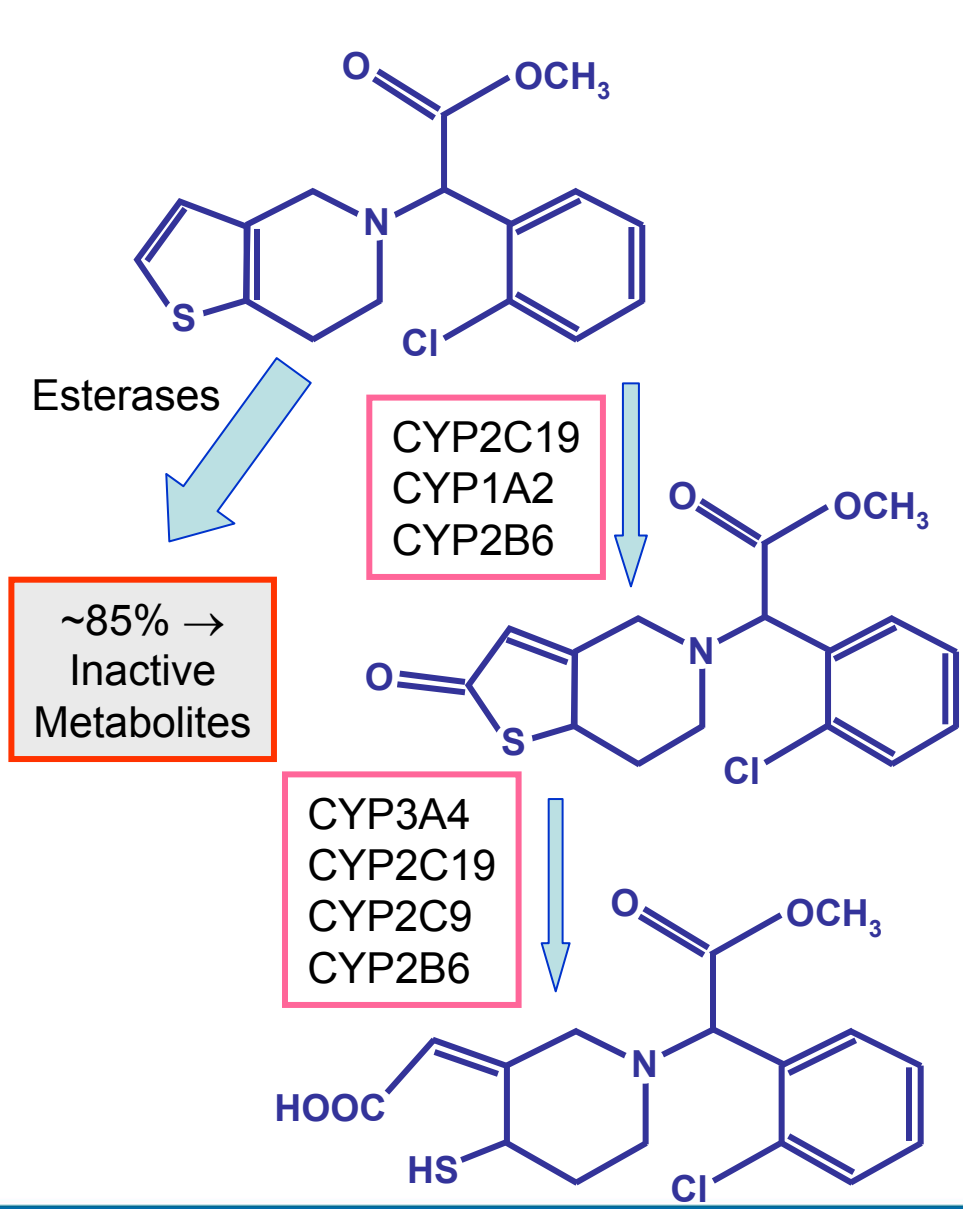


Acute Coronary Syndrome Example

Thienopyridines

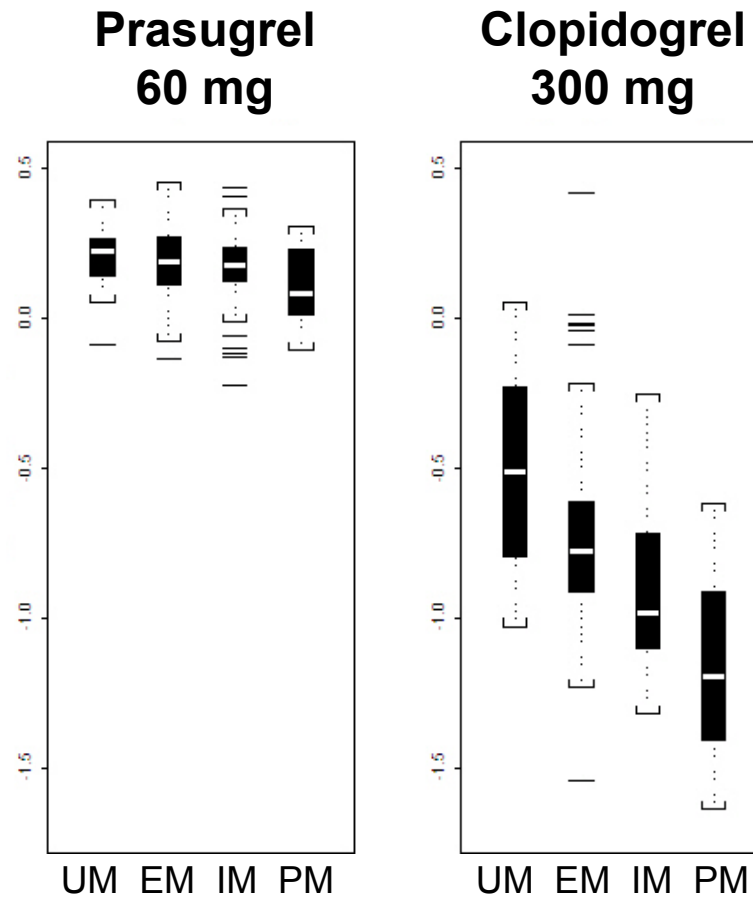
- Prodrugs that are metabolized in vivo to generate an active metabolite that inhibits the platelet P2Y₁₂ receptor
- Thienopyridines:
 - Clopidogrel – second generation thienopyridine
 - Prasugrel – third generation thienopyridine

Clopidogrel



Integrated Genomic Analysis: CYP450 Genotypes Do Not Influence Prasugrel Active Metabolite Pharmacokinetics

Log AUC_(0-tlast)

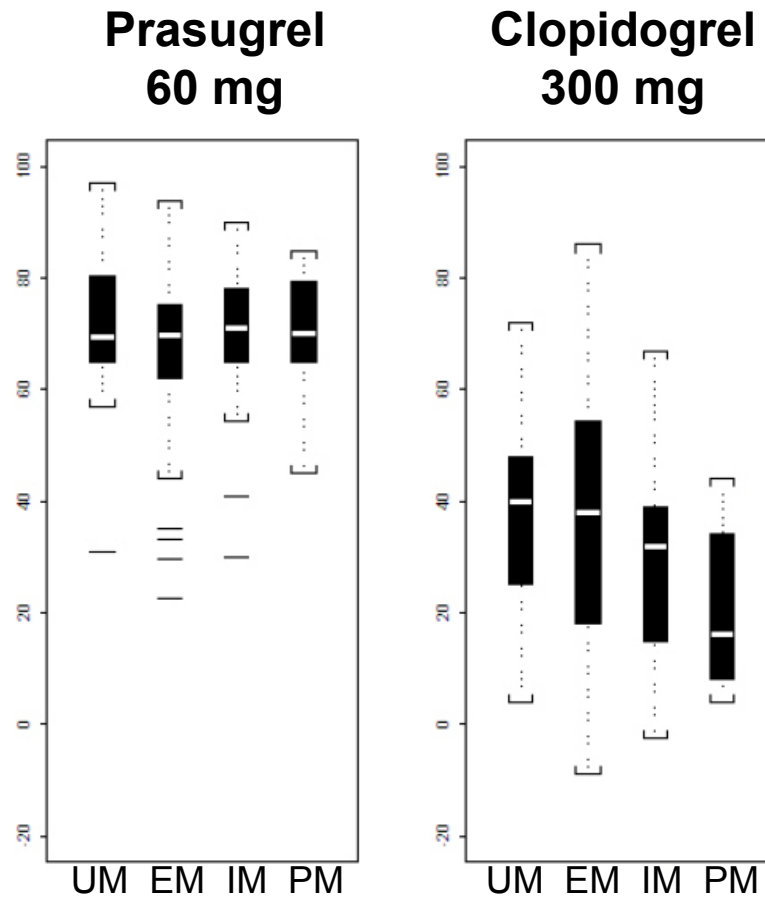


N=307

CYP2C19

Integrated Genomic Analysis: CYP450 Genotypes Do Not Influence Prasugrel Antiplatelet Responses

Δ MPA at
4 hours



N=277

CYP2C19

TRITON TIMI 38

CYP2C19, 2C9 May Affect Prasugrel vs. Clopidogrel

		Event Rate (%)		HR (95%CI)	P-Value
		Pra	Clo	P vs. C	
<i>All ACS</i>	EM	9.06	7.88	1.15 (0.83-1.59)	0.45
	PM	8.43	11.39	0.74 (0.45-1.14)	0.19
<i>UA/NSTEMI</i>	EM	9.73	7.54	1.30 (0.88-1.91)	0.21
	PM	6.34	12.37	0.50 (0.28-0.88)	0.018

Marketing Label

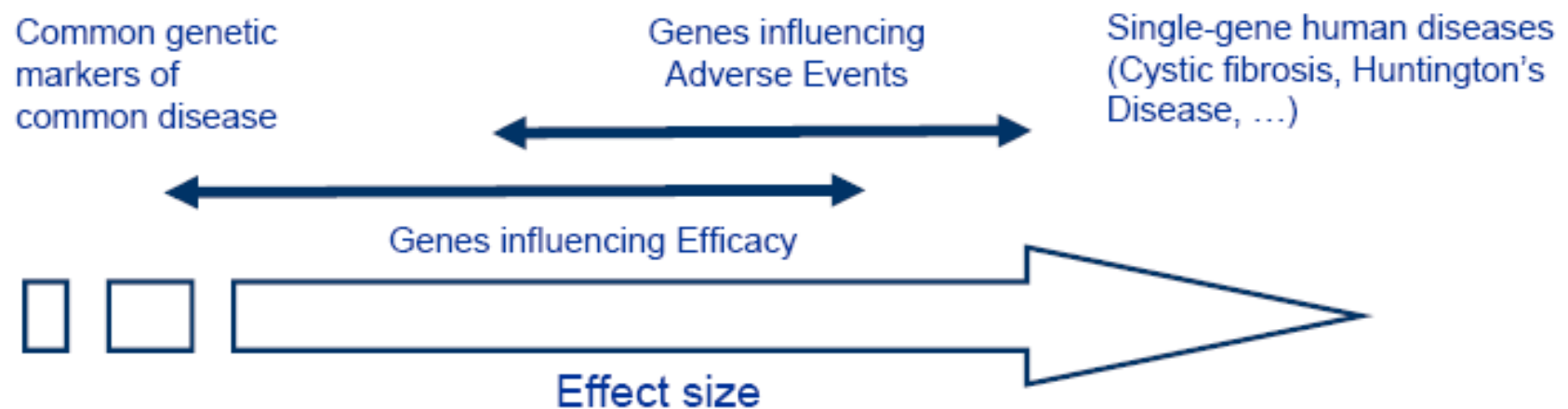
- Prasugrel
 - There is **no relevant effect of genetic variation** in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.
- Clopidogrel
 - Clopidogrel **active metabolite pharmacokinetics and antiplatelet effects, differ** according to CYP2C19 genotype. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite.

Barriers to Translation

- Test factors : assay validity, time to results, cost
- Scientific factors : the evidence conundrum
- Decisional factors : uncertainty/interpretation
- Practice factors : limited incorporation into clinical guidelines

Lessons Learned from PGx Research

- Genetic architecture is not the same for all traits, drug responses or diseases
- Genes for drug-associated adverse events with high sensitivity/specificity offer promising classifiers for personalized medicine. But not all genetic effects offer such specificity
- Need to plan for genes of intermediate effect (safety & efficacy)



Personalized Medicine = New Paradigm for Optimizing Drug Therapy

