Pharmacogenetics

Presentation by:
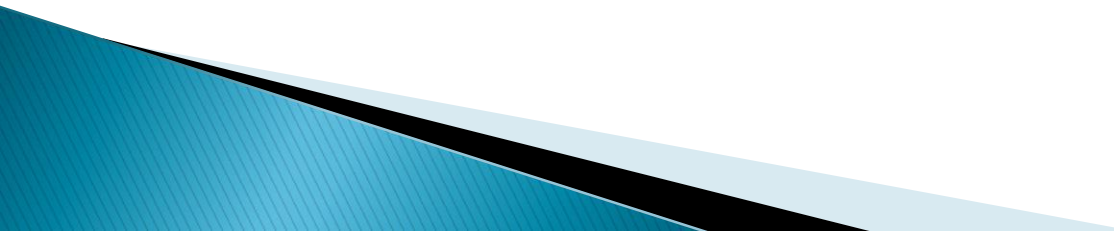
Moosareza Memari

Clinical pharmacologist

2022 JUNE

Topics

- **Introduction**
- **Pharamcogenetics Variation Mechanisms**
- **Pharmacogenetics & Pharmacotherapy**
- **Pharmcogenetics & ADR**
- **Personalized Medicine**

Introduction

▶ ## History:

- ▶ **Pythagoras experience (510 BCI)**
- ▶ **Paralysis by Succinylcholine (1950)**
- ▶ **Primaquine Sensitivity (1950)**
- ▶ **Pharmacogenetics term (1959)**
- ▶ **Neuropathy caused by Isoniazide**

History

Father of Pharmacogenetics Dies

Arno Motulsky, a former refugee from Nazi Germany and a pioneering medical geneticist at the University of Washington, has died at age 94.

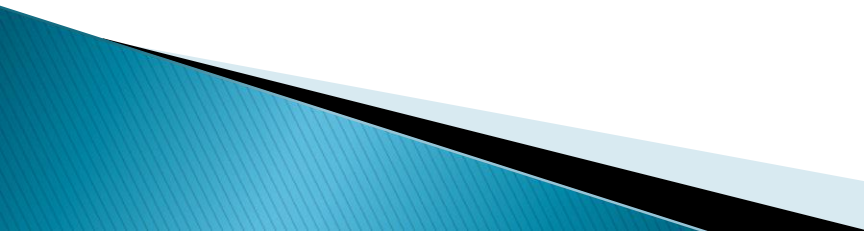By Catherine Offord | January 31, 2018

History

The term 'Pharmacogenetics' deffination.

Freidrich Vogel, Germany – <u>1959</u>

History

- **1970's-1990s:** many drug-gene interactions have been studied and investigated

- **The development of pharmacogenetics over the years**

- **'Pharmacogenomics' & the emergence of the Human Genome Project**

History

- **<u>2005</u>→ First FDA approval of a pharmacogenetic test**

- **<u>2006</u>→ First direct-to-consumer whole-genome test**

- **<u>2007</u>→ the FDA started to recognize the importance of pharmacogenomics, issued <u>black box warnings</u>, incorporated <u>genotype-guided dosing algorithms</u>, and included <u>pharmacogenomic information</u> in drug labeling**
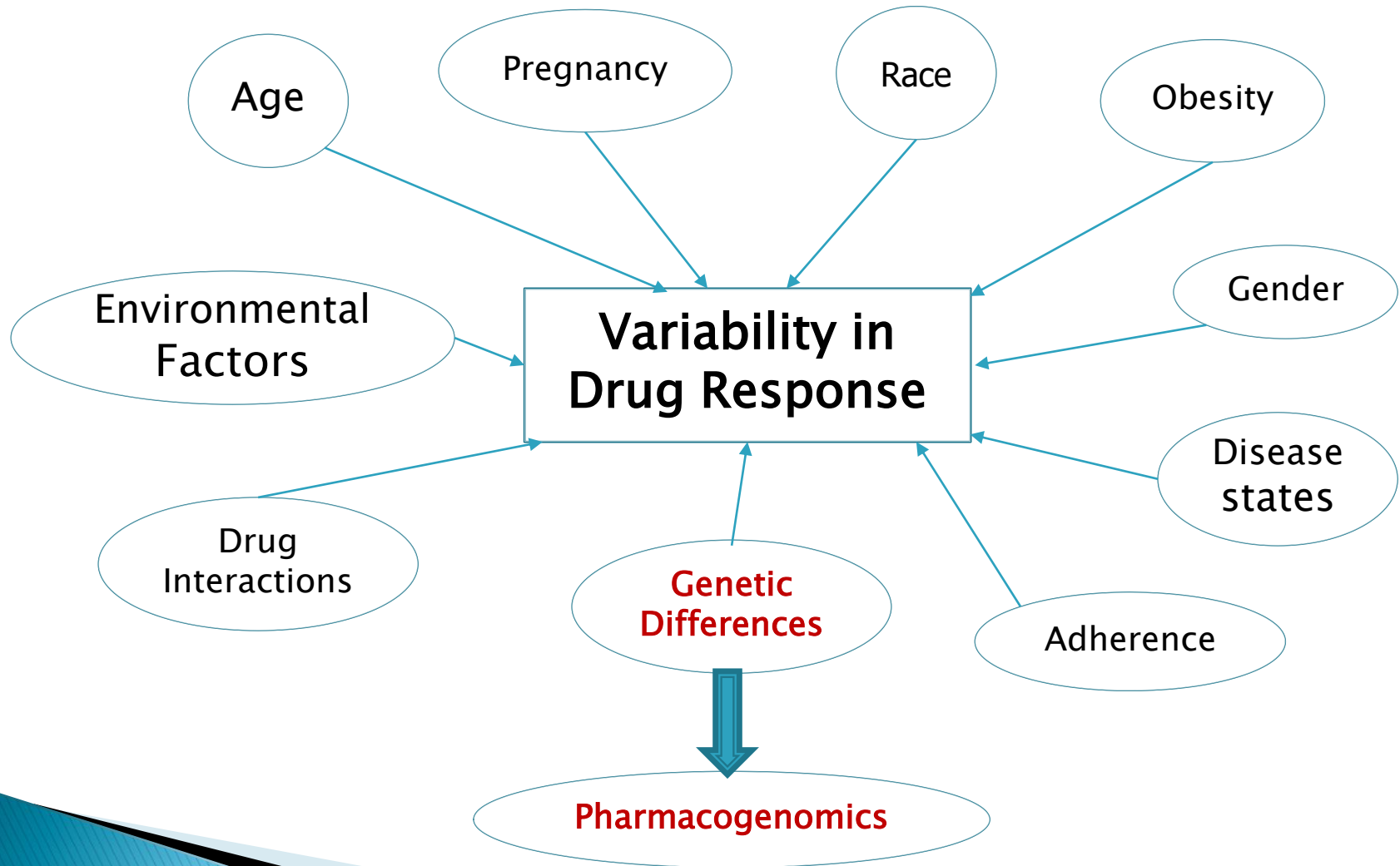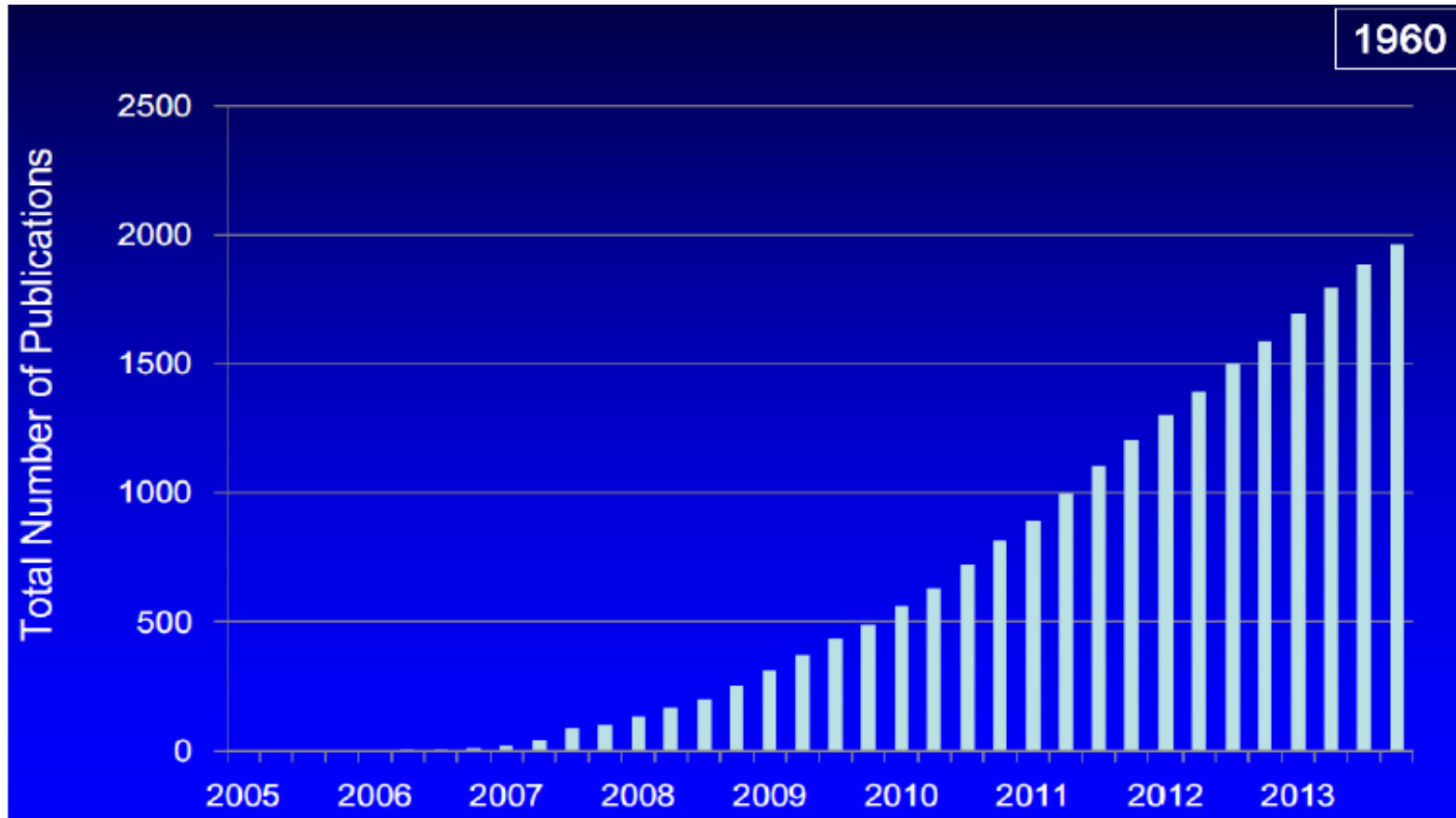
Human Genome Project (1990-2003)

- **The world's largest collaborative biological project, costed about $3-billion**

- **20 universities and research centers around the world**

- **Goals→ determining the sequence of the human DNA and identifying all of the genes (structure, function)**

Published Genome-Wide Association Reports, 2005-2013

History
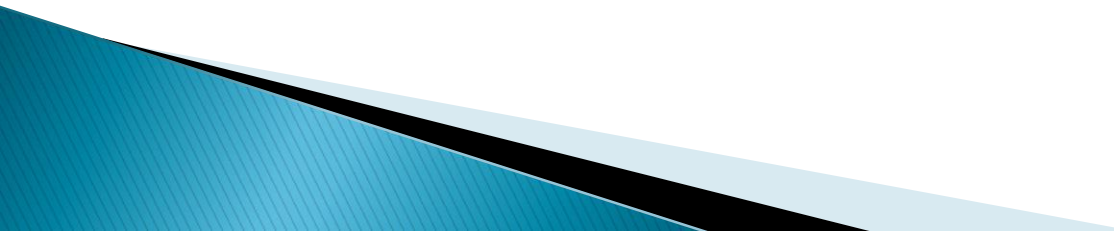
▸ **In 2014, eight of 41 of the new drugs approved had some type of genetic or biomarker data in the submission relative to efficacy, safety, or pharmacokinetics**

FDA approved pharmacogenetic tests

Gene	Drug	Consequence
TPMT	6MP	Toxicity
CYP2D6	Tamoxifen	Decreased efficacy
UGT1A1	Irinotecan	Toxicity
CYP2D6	Codeine	Ineffective analgesia

These genes all modulate Pharmokinetics

Pharmacogenetics

- **influence of genetic variation on an individual's response to pharmacologic agents**
- **Pharmacogenetics testing is not routinely used in clinical practice**

Pharmacogenetics

▸ **Pharmacokinetic**
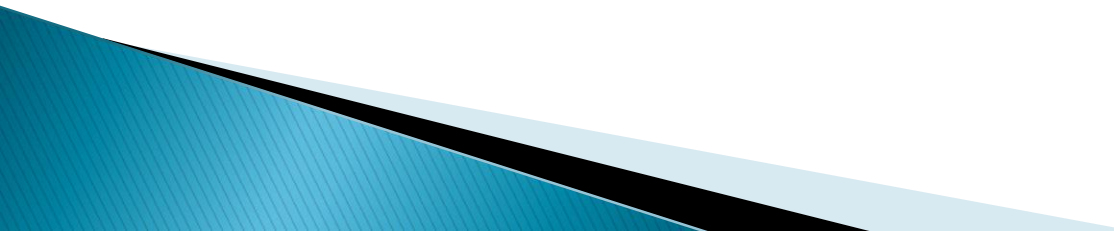
"The process by which a drug is absorbed, distributed, metabolized, and eliminated by the body"

▸ **Pharmacodynamic**

"the biochemical and physiological effects of drugs and the mechanisms of their actions"

Pharmacogenetics

Pharmacogenetics is the study of how genetic variations affect the disposition of drugs, including their metabolism and transport and their safety and efficacy

Pharmacogenetics

Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment

Pharamcogenetically Variations Mechanisms
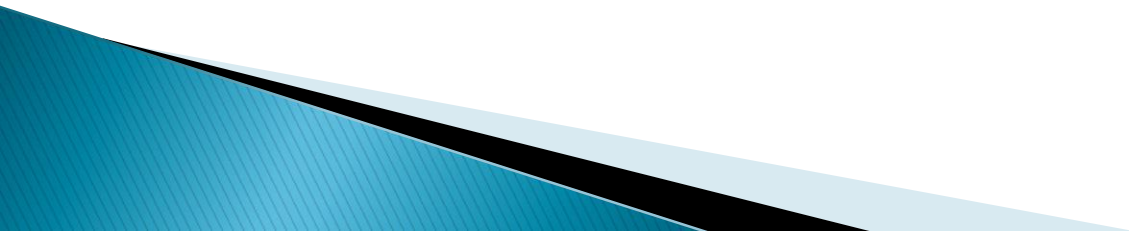
Single Nucleotide Polymorphisms (SNPs)

- **Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation in humans**
- **A single nucleotide is replaced in the genetic sequence**
- **Different SNP expressions may modify a drug's therapeutic response or adverse effect incidence**
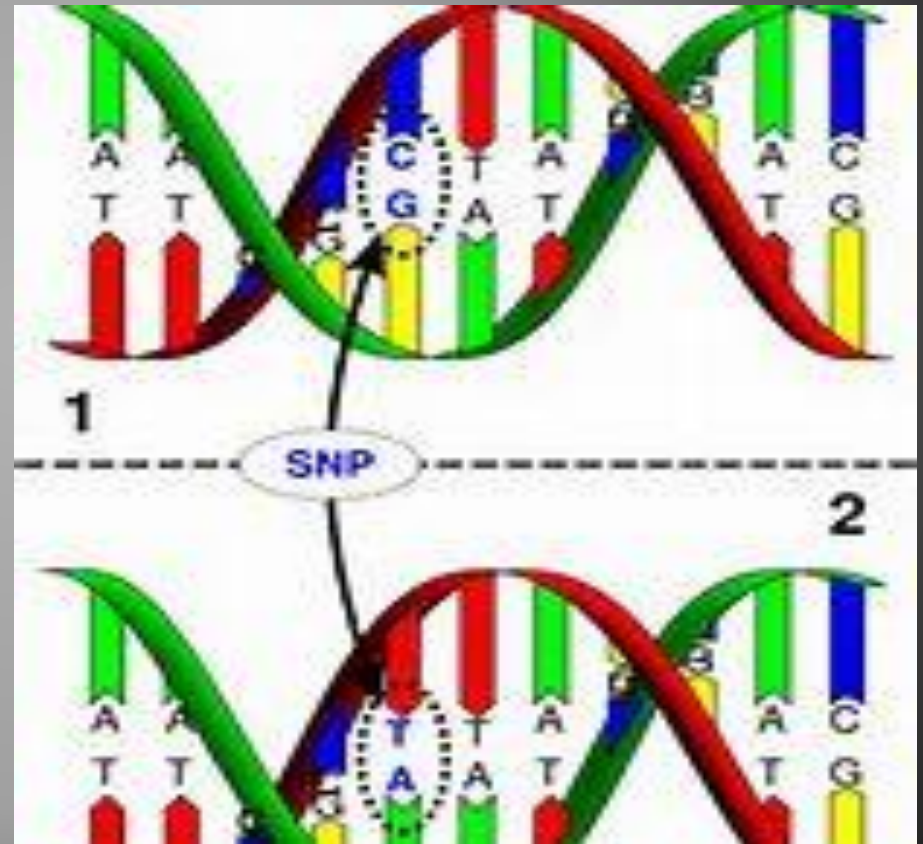
ADME VARIATION
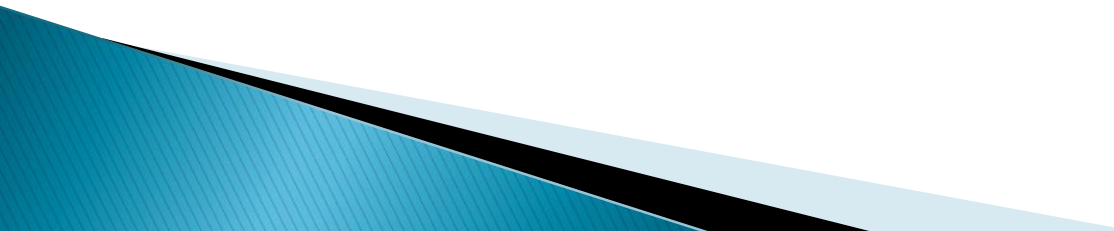
- **Absorption**

- **Distribution**

- **Metabolism**

- **Excretion**

ABCB1	CYP2C9	NAT1	SULT1A1
ABCC2	CYP2D6	NAT2	TPMT
ABCG2	CYP2E1	SLC15A2	UGT1A1
CYP1A1	CYP3A4	SLC22A1	UGT2B15
CYP1A2	CYP3A5	SLC22A2	UGT2B17
CYP2A6	DPYD	SLC22A6	UGT2B7
CYP2B6	GSTM1	SLCO1B1	VKORC1
CYP2C19	GSTP1	SLCO1B3	
CYP2C8	GSTT1	SLCO2B1	

HLA Polymorphism

Variant of *HLA* Gene	Drug and Adverse Effect
HLA-B*57:01	Abacavir-induced skin toxicity
HLA-B*58:01	Allopurinol-induced skin toxicity
HLA-DRB1 *15:01, DRB5 *01:01, DQB1 *06:02 haplotype	Amoxicillin-clavulanate-induced liver injury
HLA-B*15:02	Carbamazepine-induced skin toxicity
HLA-B *57:01	Flucloxacillin-induced liver injury
HLA-DQB1 *06, *02, HLA-DRB1 *15, *07	Various drugs, subgroup analysis for cholestatic or other types of liver injury
HLA-DRB1 *07, HLA-DQA1 *02	Ximelagatran, increased ALT

GENETIC VARIATION

- ENZYMES
- TRANSPORTS
- HLA
- IMMUNE SYSTEM FUNCTION
- POLYGENIC EFFECTS
- EPIGENOMICS

About the CYPs

- **Membrane bound enzymatic proteins**
  - ◦ **Involved in oxidation, peroxidation and reductive metabolism**
  - ◦ **Responsible for >90% of drug transformation**
- **Greater than 50 different *CYP* genes encoding 50 different proteins**
- **CYP2D6 present mainly in liver and a major player in drug metabolism from antidepressants to antihypertensive to chemotherapy**

Drug Metabolizing Enzymes
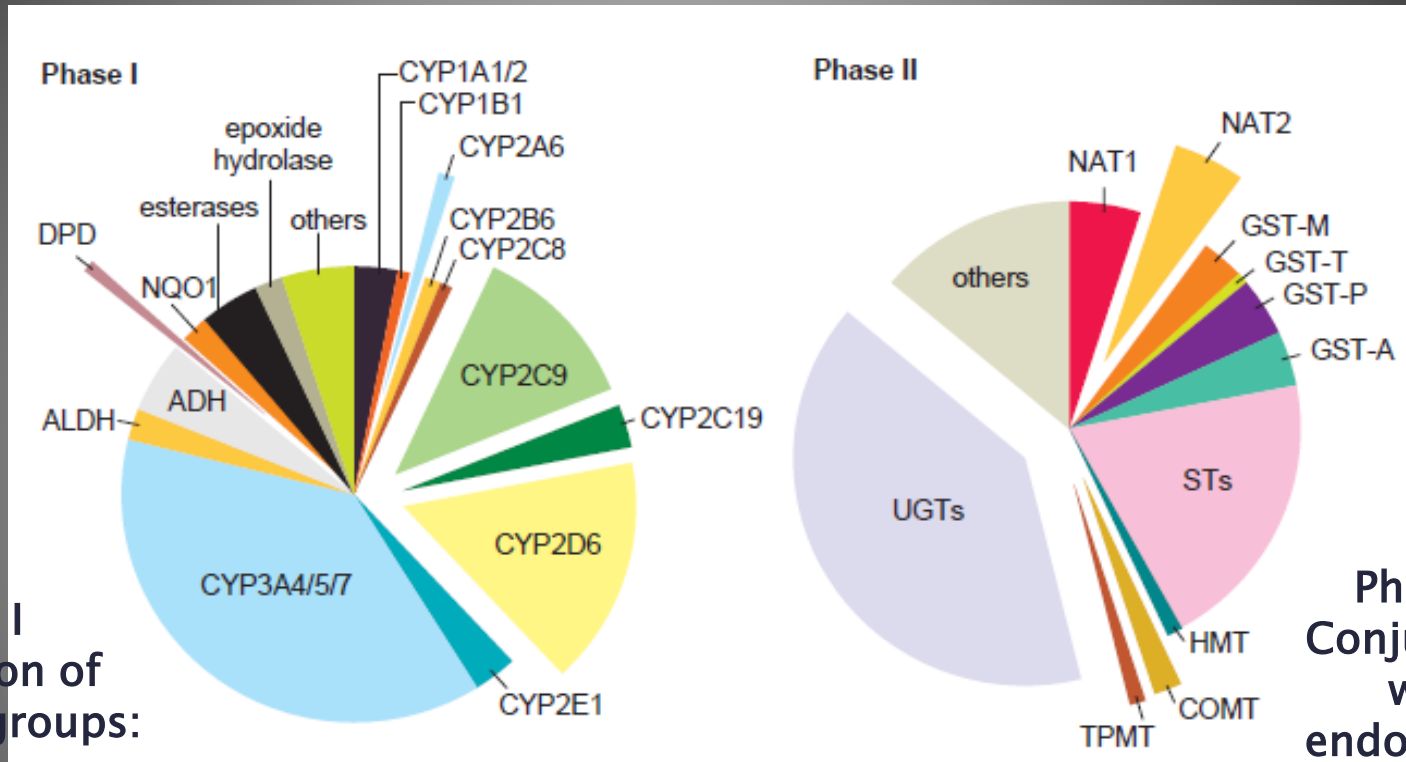
Phase I
Phase II

Phase I — Modification of functional groups:

Hydrolysis
Oxidation
Dealkylation
Dehydrogenation
Reduction
Deamination
Desulfuration

Evans and Relling, *Science* 1999

Phase II — Conjugation with endogenous substituents to form:

Glucuronide
Acetate
Glutathione
Sulfate
Methionine

Metabolism

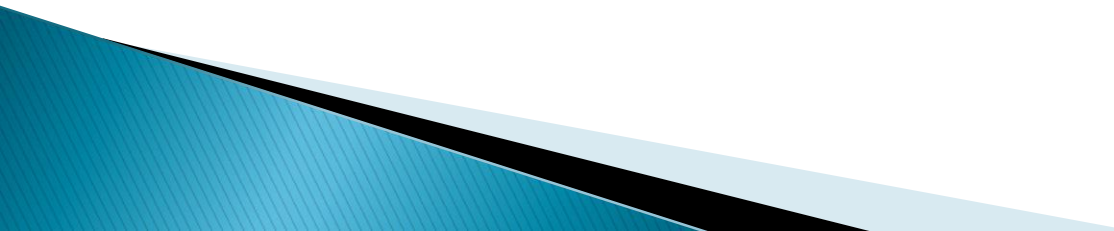| Enzyme Involved	Defect	Genotype	Drug and Therapeutic Use	Clinical Consequences[1]
CYP1A2	N-Demethylation	EM	Caffeine (CNS stimulant)	Reduced CNS stimulation due to increased gene inducibility and thus increased metabolism/clearance in cigarette smokers and frequent ingesters of omeprazole.
	N-Demethylation	PM	Caffeine (CNS stimulant)	Enhanced CNS stimulation.
CYP2A6	Oxidation	PM	Nicotine (cholinoceptorstimulant)	Nicotine toxicity. Lesser craving for frequent cigarette smoking.
	Oxidation	EM	Nicotine (cholinoceptorstimulant)	Increased nicotine metabolism. Greater craving for frequent cigarette smoking.
	Oxidation	PM	Coumarin (anticoagulant)	Increased risk of bleeding.
	Oxidation	EM	Coumarin (anticoagulant)	Increased clearance. Greater risk of thrombosis.
CYP2B6	Oxidation, N-Dechloroethylation	PM	Cyclophosphamide, ifosfamide (anti-cancer)	Reduced clearance. Increased risk of ADRs.
	Oxidation	PM	Efavirenz, nevirapine (anti-HIV)	Reduced clearance. Increased risk of ADRs.
CYP2C8	Hydroxylation	PM	Repaglinide, rosiglitazone, pioglitazone (antidiabetic)	Reduced clearance. Increased risk of ADRs.
	Hydroxylation	PM	Paclitaxel (anti-cancer)	Reduced clearance. Increased risk of ADRs (myelosuppression).
	N-Deethylation/N-Dealkylation	PM	Amodiaquine, chloroquine (antimalarial)	Reduced clearance. Increased risk of ADRs.
	N-Deethylation	PM	Amiodarone (antiarrhythmic)	Reduced clearance. Increased risk of ADRs.
CYP2C9	Hydroxylation	PM	Celecoxib, diclofenac, flurbiprofen, S-ibuprofen (NSAIDs)	Reduced clearance. Increased risk of ADRs.
	Hydroxylation	PM	S-Warfarin, S-acenocoumarol (anticoagulants)	Enhanced bleeding risk. Clinically highly relevant. Dose adjustment required.
	Hydroxylation	PM	Tolbutamide (antidiabetic)	Cardiotoxicity.
	Hydroxylation	PM	Phenytoin (antiepileptic)	Nystagmus, diplopia, and ataxia.
CYP2C19	N-Demethylation	PM	Amitriptyline, clomipramine (antidepressants)	Reduced clearance. Increased risk of ADRs. Dose adjustment required.
	Oxidation	PM	Moclobemide (MAOI)	
	N-Demethylation	PM	Citalopram (SSRI)	Increased risk of gastrointestinal side effects.
	O-Demethylation	PM	Omeprazole (PPI)	Increased therapeutic efficacy.
	Hydroxylation	PM	Mephenytoin (antiepileptic)	Overdose toxicity.
	N-Demethylation	EM	Escitalopram (antidepressants)	Increased gene transcription resulting in increased activity and thus reduced therapeutic efficacy.
	O-Demethylation	EM	Omeprazole (PPI)	Reduced therapeutic efficacy.
	Hydroxylation	EM	Tamoxifen (anti-cancer)	Increased metabolic activation, increased therapeutic efficacy; reduced risk of relapse. Dose adjustment required.
	Oxidative cyclization	EM	Chlorproguanil (antimalarial)	Increased metabolic activation, increased therapeutic efficacy. Dose adjustment required.
	Oxidation	EM	Clopidogrel (antiplatelet)	Increased metabolic activation, increased therapeutic efficacy. Dose adjustment required.
CYP2D6	Oxidation	PM	Bufuralol (β-adrenoceptor blocker)	Exacerbation of β blockade, nausea.
	O-Demethylation	PM	Codeine (analgesic)	Reduced metabolic activation to morphine and thus reduced analgesia.
	Oxidation	PM	Debrisoquin (antihypertensive)	Orthostatic hypotension.

Metabolism

Enzyme Involved	Defect	Genotype	Drug and Therapeutic Use	Clinical Consequences[1]
	N-Demethylation	PM	Nortriptyline (antidepressant)	Reduced clearance. Increased risk of ADRs.
	Oxidation	PM	Sparteine	Oxytocic symptoms.
	O-Demethylation	PM	Dextromethorphan (antitussive)	Reduced clearance. Increased risk of ADRs.
	O-Demethylation	PM	Tramadol (analgesic)	Increased risk of seizures.
	Hydroxylation	PM	Tamoxifen (anti-cancer)	Reduced metabolic activation to the therapeutically active endoxifen and thus reduced therapeutic efficacy.
	O-Demethylation	UM	Codeine (analgesic)	Increased metabolic activation to morphine and thus increased risk of respiratory depression.
	N-Demethylation	UM	Nortriptyline (antidepressant)	Reduced therapeutic efficacy due to increased clearance.
	O-Demethylation	UM	Tramadol (analgesic)	Reduced therapeutic efficacy due to increased clearance.
CYP3A4		PM?	All drugs metabolized by this enzyme would be potentially affected	Reduced clearance. Dose adjustment may be required to avoid drug-drug interactions.
CYP3A5		PM?	Saquinavir, and other CYP3A substrates	Usually less catalytically active than CYP3A4. A higher frequency of a functional CYP3A5*1 allele is seen in Africans than in Caucasians; the latter most often carry the defective CYP3A5*3 allele. This may significantly affect therapeutics of CYP3A substrates in CYP3A5*1 or CYP3A5*3 homozygous individuals.
ALDH	Aldehyde dehydrogenation	PM	Ethanol (recreational drug)	Facial flushing, hypotension, tachycardia, nausea, vomiting.
BCHE	Ester hydrolysis	PM	Succinylcholine (muscle relaxant)	Prolonged apnea.
			Mivacurium (neuromuscular blocker)	Prolonged muscle paralysis.
			Cocaine (CNS stimulant)	Increased blood pressure, tachycardia, ventricular arrhythmias.
GST	GSH-conjugation	PM	Acetaminophen (analgesic), Busulfan (anti-cancer)	Impaired GSH conjugation due to gene deletion.
NAT2	N-Acetylation	PM	Hydralazine (antihypertensive)	Lupus erythematosus-like syndrome.
	N-Acetylation	PM	Isoniazid (antitubercular)	Peripheral neuropathy.
TPMT	S-Methylation	PM	6-Thiopurines (anti-cancer)	Myelotoxicity.
UGT1A1	Glucuronidation	PM	Bilirubin (heme metabolite)	Hyperbilirubinemia.
			Irinotecan (anti-cancer)	Reduced clearance. Dose adjustment may be required to avoid toxicity (GI dysfunction, immunosuppression).

Gene	Drug	Diplotype[1]	Likely Phenotype (Activity Score)	Dosing Recommendation	Source of Recommendation
CYP2D6					
	Codeine	*1/*1xN, *1/*2xN	UM (> 2.0)	Alternative analgesic, eg, morphine or nonopioid; increased formation of morphine following codeine administration leads to higher risk of toxicity.	CPIC[2]
		*1/*1, *1/*2, *2/*2, *1/*41, *2/*5	EM (1.0–2.0)	• Standard starting dose.	
		*4/*10, *5/*41	IM (0.5)	• Standard starting dose; monitor closely for lack of analgesic response due to reduced morphine formation. Consider alternate analgesic, eg, morphine or nonopioid.	
		*3/*4, *4/*4, *4/*5, *5/*5, *4/*6	PM (0.0)	• Alternative analgesic, eg, morphine or nonopioid analgesic; greatly reduced morphine formation following codeine administration, leading to insufficient pain relief. Avoid higher doses, as central side effects do not differ in PMs.	
CYP2C19					
	Clopidogrel	*1/*17, *17/*17 (UM), and *1/*1 (EM)	UM, EM	• Standard dose.	CPIC
		*1/*2, *1/*3, *2/*17	IM	• Alternative antiplatelet agent, eg, prasugrel or ticagrelor.	
		*2/*2, *2/*3, *3/*3	PM	• Alternative antiplatelet agent, eg, prasugrel or ticagrelor.	
DPYD					
	Fluoropy-rimidines	*1/*1	Normal	• Standard dose.	CPIC
		*1/*2A, *1/*13, *1/rs67376798A	Reduced activity	• Reduce initial dose 50% and titrate based on toxicity or on pharmacokinetic test results (if available).	
		*2A/*2A, *2A/*13, *13/*13, rs67376798A/ rs67376798A	Complete deficiency	• Different non-fluoropyrimidine anticancer agent.	
UGT1A1					
	Irinotecan	*1/*1, *1/*28	Normal	• Standard starting dose.	
		*28/*28	Reduced	• Reduce starting dose by at least one dose level. Or,	Drug label
				• Dose > 250 mg/m²: Reduce starting dose 30% and increase in response to neutrophil count. Dose = 250 mg/m²: No dose adjustment.	DPWG[3]
	Atazanavir	*1/*1, *1/*36, *36/*36, rs887829 C/C	Normal	No reason to avoid prescribing atazanavir. Inform patient of risks. Based on this genotype, there is a less than 1 in 20 chance of stopping atazanavir for jaundice.	CPIC
		*1/*28, *1/*37, *36/*28, *36/*37, rs887829 C/T, *1/*6	Intermediate	No reason to avoid prescribing atazanavir. Inform patient of risks. Based on this genotype, there is a less than 1 in 20 chance of stopping atazanavir for jaundice.	
		*28/*28, *28/*37, *37/*37, rs887829 T/T (*80/*80), *6/*6	Reduced	Consider alternative agent. Based on this genotype, there is a high (20–60%) likelihood of developing jaundice that will result in discontinua-tion of atazanavir.	
TPMT					
	Thiopurines	*1/*1	Normal, high activity	• Standard starting dose.	CPIC
		*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4	Intermediate activity	• Start at 30–70% of target dose and titrate every 2–4 weeks with close clinical monitoring of tolerability, eg, white blood cell counts and liver function tests.	

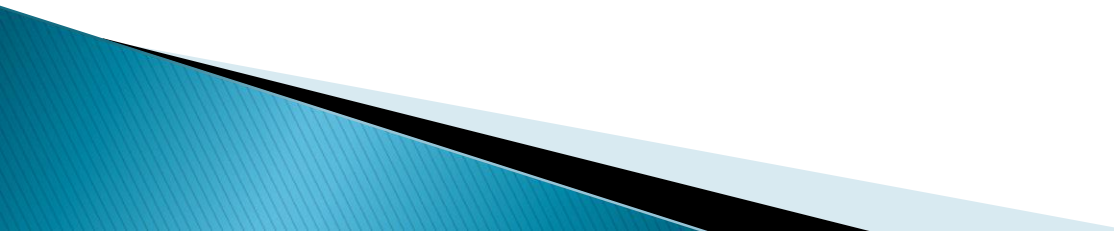| Gene	Drug	Diplotype[1]	Likely Phenotype (Activity Score)	Dosing Recommendation	Source of Recommendation
		3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4	Low activity	• Malignant disease: Drastic reduction of thiopurine doses, eg, tenfold given thrice weekly instead of daily. • Nonmalignant conditions: Alternative nonthiopurine immunosuppressive agent.	
G6PDX-linked trait		Genotype-to-phenotype predictions limited to males and homozygous females.			
	Rasburicase	B, A	Normal	• Standard dose.	Drug label/CPIC
		A-, Mediterranean, Canton	Deficient	• Alternative agent, eg, allopurinol: Rasburicase is contraindicated in patients with G6PD deficiency.	
		Variable	Unknown risk of hemolytic anemia	• Enzyme activity must be measured to determine G6PD status. An alternative is allopurinol.	
SLCO1B1					
	Simvastatin 40 mg	*1a/*1a, *1a/*1b, *1b/*1b	Normal activity	• Standard dose.	CPIC
		*1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17	Intermediate activity	• Prescribe a lower dose or consider an alternative statin, eg, pravastatin or rosuvastatin; consider routine CK monitoring.	
		*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17	Low activity	• Prescribe a lower dose or consider an alternative statin, eg, pravastatin or rosuvastatin; consider routine CK monitoring.	
HLA					
	Abacavir	*Other/*Other	Negative	• Standard dose.	CPIC
		*Other/*57:01, *57:01/*57:01	Positive	• Alternative agent: abacavir is contraindicated in HLA-B*57:01-positive patients.	
IFNL3					
	PEG-IFN-α/RBV	rs12979860/ rs12979860	Favorable	• PEG-IFN-α/RBV: Consider cure rates before initiating regimen; ~70% chance for SVR[4] after 48 weeks of therapy. • PEG-IFN-α/RBV + protease inhibitor combinations: Regimen recommended; ~90% chance for SVR after 24-48 weeks of therapy, with 80-90% chance for shortened duration of therapy.	CPIC
		Reference/reference or reference/rs12979860	Unfavorable	• PEG-IFN-α/RBV: Consider cure rates before initiating regimen; ~30% chance for SVR after 48 weeks of therapy. • PEG-IFN-α/RBV + protease inhibitor combinations: Consider cure rates before initiating regimen; ~60% chance for SVR after 24-48 weeks of therapy, with 50% chance for shortened duration of therapy.	
CYP2C9, VKORC1					
	Warfarin	*1/*1, *1/*2, *2/*2, *2/*3, *1/*3, *3/*3, 1639GG, 1639GA, 1639AA	Various	• Apply validated dosing algorithm, eg, www.warfarindosing.org (or IWPC*) for international normalized ratio target 2-3) or FDA-approved dosing table per manufacturer's labeling.	CPIC

TPMT
Thiopurine S-Methyltransferase

- **Main metabolizer of chemotherapeutic agents 6MP and azothiopurine (used mainly in blood based malignancies)**
- **TPMT deficiency leads to severe toxicity associated with treatment (potential mortality)**

Uridine 5'-Diphosphoglucuronosyl Transferase 1 (UGT1A1)

- **Gilbert's syndrome**

- **Irinotecan a topoisomerase I inhibitor prodrug**

GENETIC VARIATIONS IN IMMUNE SYSTEM FUNCTION

- **DRUG-INDUCED HYPERSENSITIVITY**

- **Primary Immunodeficiency**

G6PD

- **G6PD deficiency**
- **400 million people worldwide**
- **prevalence in persons of African, Asian, and Mediterranean descent**
- **X-linked recessive disorder**
- **24 to 72 hours after exposure to oxidant stress**

GENETIC VARIATIONS IN TRANSPORTERS

▸ **ORGANIC ANION TRANSPORTER (OATP1B1)**
▸ SLCO1B1
▸ **Statins**

HLA VARIATION

Variant of *HLA* Gene	Drug and Adverse Effect
*HLA-B*57:01*	Abacavir-induced skin toxicity
*HLA-B*58:01*	Allopurinol-induced skin toxicity
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*HLA-B*15:02*	Carbamazepine-induced skin toxicity
*HLA-B *57:01*	Flucloxacillin-induced liver injury
*HLA-DQB1 *06, *02, HLA-DRB1 *15, *07*	Various drugs, subgroup analysis for cholestatic or other types of liver injury
*HLA-DRB1 *07, HLA-DQA1 *02*	Ximelagatran, increased ALT

Pharmacogenetics & Pharmacotherapy
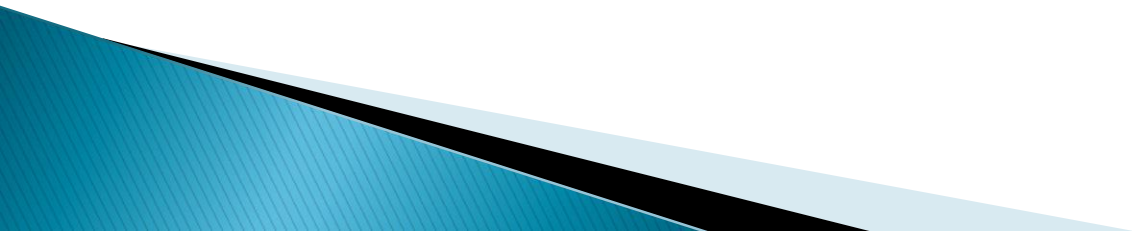
Pharmacogenetics & Pharmacotherapy

◦ **Provide real-time decision support thereby facilitating individualized drug therapy to maximize efficacy, minimize adverse drug reactions, and reduce health care costs**

Assemble multidisciplinary, multidepartment team

Pathology, Informatics, Pharmacy, Clinicians, Ethics, Legal, Regulatory
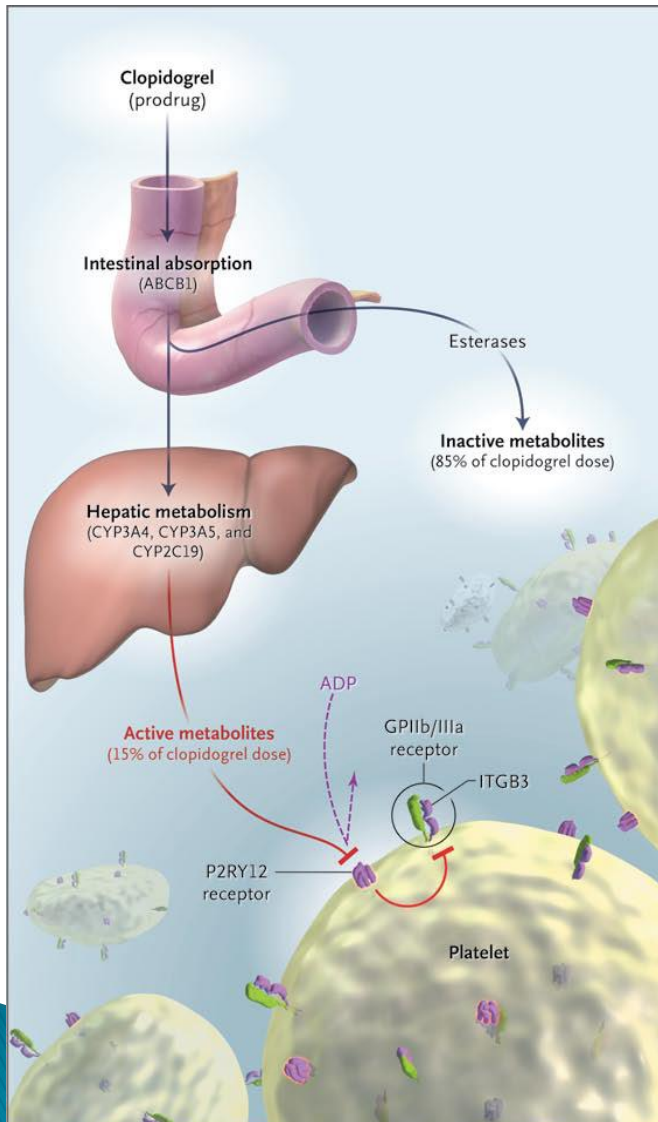
Clopidogrel (PLAVIX) – *CYP2C19*

- **FDA issued a "black box" warning regarding the clinical relevance of genotype analysis**
- **Widely prescribed to patients at our medical facility**
- **Could provide decision support and measure the change in prescribing behavior of the provider based on the given decision support**
- **Targeted patient population to launch model – the cardiac catheterization lab**
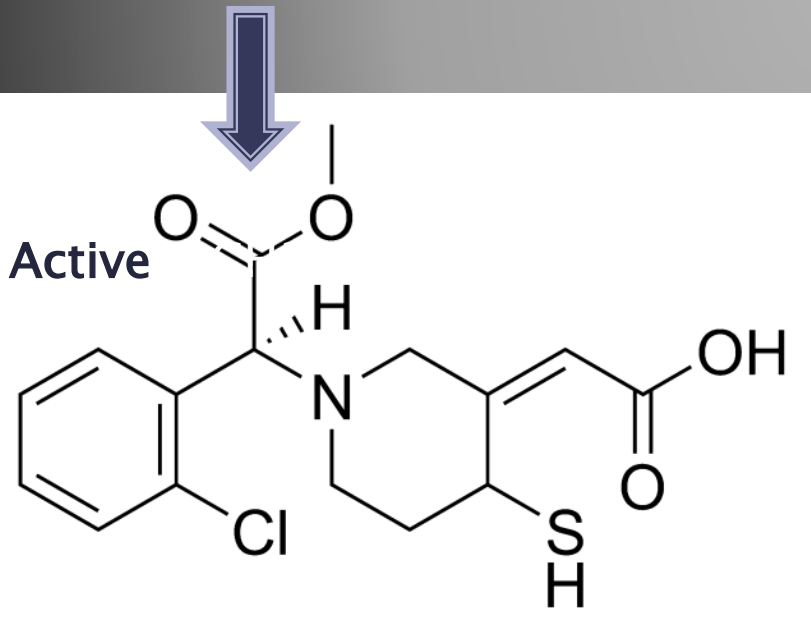
FDA – Black Box Warning Issued March 12, 2010
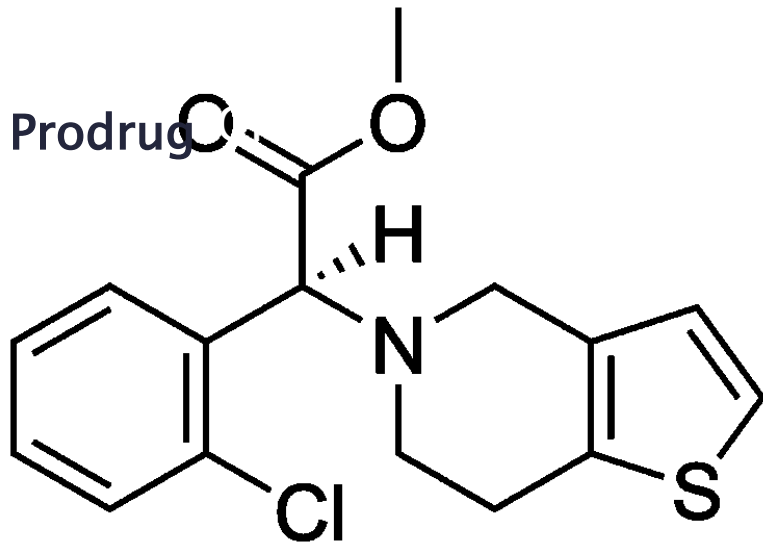
- **WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

- **activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.**
- **Poor metabolizers acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI)**
- **Tests patient's CYP2C19 genotype determining therapeutic strategy.**
- **Consider alternative treatment or treatment strategies**

Clopidogrel - PLAVIX

Clopidogrel (prodrug)

Intestinal absorption (ABCB1)

Esterases

Inactive metabolites (85% of clopidogrel dose)

Hepatic metabolism (CYP3A4, CYP3A5, and CYP2C19)

Active metabolites (15% of clopidogrel dose)

ADP

GPIIb/IIIa receptor

ITGB3

P2RY12 receptor

Platelet

- **Requires gastro-intestinal absorption and hepatic biotransformation**
- **Is an inhibitor to the P2RY12 receptor thereby preventing binding of ADP**
- **Increases risk of bleeding; especially GI bleeding when combined with warfarin and nonsteroidal anti-inflammatory drugs**
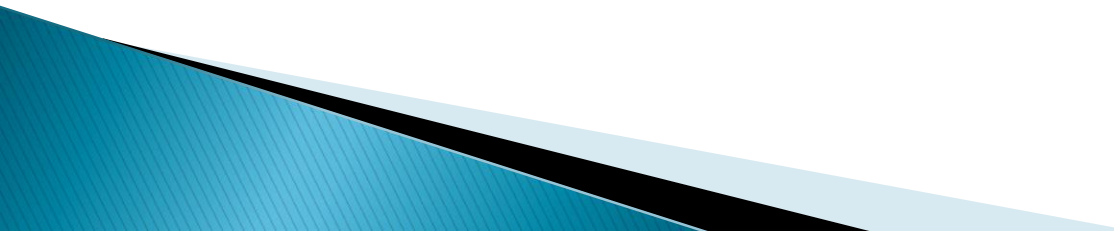
Prodrug

Active

- **Antiplatelet therapy, often prescribed in combination with aspirin**
- **Initial dose 300 mg followed by 75 mg daily**
- **Indications for use: acute coronary syndrome; recent myocardial infarction or stroke; peripheral arterial disease; or patients managed following angioplasty, bypass surgery or stent placement**

Plavix

‣ **WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

• **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.**

• **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.**

Plavix

- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.**

Tamoxifen

- **Needs to be converted to endoxifen to be active**
  - **catalysed by the polymorphic enzyme cytochrome P450 2D6 (CYP2D6)**
  - **6-10% European population deficient in this enzyme**
    - **Efficacy of tamoxifen likely low in this population**
    - **Suggests consider alterative treatments**

Pharmcogenetics
&
ADR
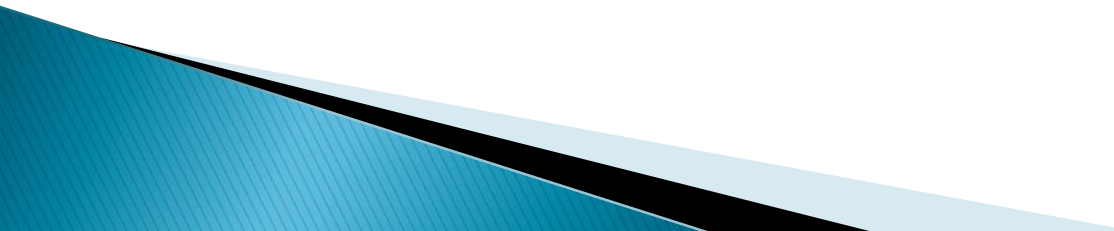
Favism

- **G6PD deficiency**
- **400 million people worldwide**
- **prevalence in persons of African, Asian, and Mediterranean descent**
- **X-linked recessive disorder**
- **24 to 72 hours after exposure to oxidant stress**

Favism contraindication

Name	Molecular Formula	Risk Level (note)	For Whom	Notes
2-Naphthol	$C_{10}H_8O$	High	All	
Acetanilide (acetanilid)	$C_8 H_9 N O$	High	Medit., Asian	
Acetazolamide	$C_4H_6N_4O_3S_2$	Medium	All	
Acetylphenylhydrazine (2-Phynylacetohydrazide)	$C_8 H_{10} N_2 O$	High	All	Note
Aldesulfone sodium (sulfoxone)	$C_{14} H_{14} N_2 Na_2 O_6 S_3$	High	All	
Aminophenazone (aminopyrine)	$C_{13} H_{17} N_3 O$	Medium	All	
Antazoline (antistine)	$C_{17} H_{19} N_3$	Medium	All	
Arginine (2-Amino-5-guanidinopentanoic acid)	$C_6H_{14}N_4O_2$	Medium	All	
Arsine	$As-H_3$	High	All	Note
Ascorbic Acid	$C_6H_8O_6$	High	All	
Bean of St.Ignatius (Strychnos ignatii)		Medium	All	
Benorilate	$C_{17}H_{15}NO_5$	Medium	All	
Beta-Naphthol (2-Naphthol)	$C_{10} H_8 O$	High	All	
Brinzolamide		High	All	Note
Bupivacaine	$C_{18}H_{28}N_2O$	High	All	

|◀ ◀ **1** 2 3 4 5 6 7 8 9 ▶ ▶| Page size: 15 ▾ 131 items in 9 pages

Favism contraindication

Name	Molecular Formula	Risk Level (note)	For Whom	Notes
Enoxacin	$C_{15}H_{17}F_4N_4O_3$	High	All	
Epirubicin	$C_{27}H_{29}NO_{11}$	Medium	All	
Flumequine	$C_{14}H_{12}FNO_3$	Medium	All	
Furazolidone	$C_8 H_7 N_3 O_5$	High	All	
Glibenclamide	$C_{32} H_{28} Cl N_3 O_5 S$	High	Medit., Asian	Note
Glibornuride	$C_{18}H_{26}N_2O_4S$	Medium	All	
Gliclazide	$C_{15}H_{21}N_3O_3S$	High	All	
Glimepiride	$C_{24}H_{34}N_4O_5S$	High	All	
Glipizide	$C_{21}H_{27}N_5O_4S$	High	All	
Glucosulfone (glucosulfone sodium)	$C_{24} H_{34} N_2 Na_2 O_{18} S_3$	High	All	
Hydroxychloroquine	$C_{18}H_{26}ClN_3O$	High	All	
Indigofera Tinctoria		Medium	All	
Isobutyl Nitrite	$C_4 H_9 N O_2$	High	Medit., Asian	
Isoniazid	$C_6 H_7 N_3 O$	Medium	All	
Lawsone Inermis		Medium	All	

|◁ ◁ 1 2 **3** 4 5 6 7 8 9 ▷ ▷| Page size: 15 ▾   131 items in 9 pages

Favism contraindication

Name	Molecular Formula	Risk Level (note)	For Whom	Notes
Sulfasalazine, Salazosulfapyridine (salazopyrin)	$C_{18}H_{14}N_4O_5S$	High	All	Note
Sulfoxone	$C_{14}H_{16}N_2O_6S_3$	Medium	All	
Thiamphenicol	$C_{12}H_{15}Cl_2NO_5S$	High	All	
Thiazosulfone (thiazolesulfone)	$C_9H_9N_3O_2S_2$	High	Medit., Asian	
Tiaprofenic Acid	$C_{14}H_{12}O_3S$	Medium	All	
Tolonium Chloride, Tolonium Chloride (toluidine blue)	$C_{15}H_{16}ClN_3S$	High	All	
Trihexyphynidyl (benzhexol)	$C_{20}H_{31}NO$	Medium	All	
Trimethoprim	$C_{14}H_{18}N_4O_3$	Medium	All	Note
Trimethoprim + Sulfamethoxazole		High	All	
Trinitrotoluene (2,4,6-Trinitrotoluene)	$C_7H_5N_3O_6$	High	Medit., Asian	
Tripelennamine	$C_{16}H_{21}N_3$	Medium	Medit., Asian	

|◀ ◀ 1 2 3 4 5 6 7 8 9 ▶ ▶| Page size: 15 ▼   131 items in 9

Favism contraindication

Name	Molecular Formula	Risk Level (note)	For Whom	Notes
Niridazole	$C_6 H_6 N_4 O_3 S$	High	All	
Nitric Oxide	NO	High	All	
Nitrofural (nitrofurazone)	$C_6 H_6 N_4 O_4$	High	All	
Nitrofurantoin	$C_8 H_6 N_4 O_5$	High	All	
Nitroglycerin	$C_3 H_5 N_3 O_9$	High	All	
Noramidopyrine	$C_{13} H_{16} N_3 NaO_4 S$	High	All	
Norfloxacin	$C_{16} H_{18} F N_3 O_3$	Medium	All	
O-Acetylsalicylic Acid (acetylsalicylic acid)	$C_9 H_8 O_4$	High	Medit., Asian	Note
O-Acetylsalicylic Acid + Acetanilide		High	Medit., Asian	
O-Acetylsalicylic Acid + Ascorbic Acid		High	All	
O-Acetylsalicylic Acid + Paracetamol		High	All	
Ofloxacin		High	Medit., Asian	
Oxidase, Urate (urate oxidase)		High	Medit., Asian	
Pamaquine	$C_{42} H_{45} N_3 O_7$	High	All	
Para-Aminobenzoic Acid (4-Aminobenzoic Acid)	$C_7 H_7 N O_2$	Medium	All	

Favism contraindication

Calcium Carboxylate		Medium	All	
Carbutamide	$C_{11}H_{17}N_3O_3S$	Medium	All	
Chloramphenicol	$C_{11} H_{12} C_{12} N_2 O_5$	High	Medit., Asian	
Chloroquine	$C_{18} H_{26} Cl N_3$	High	Medit., Asian	Note
Chloroquine + Proguanil		High	Medit., Asian	
Ciprofloxacin		High	All	
Colchicine	$C_{22} H_{25} N O_6$	Medium	All	
Dapsone (diaphenylsulfone)	$C_{12} H_{12} N_2 O_2 S$	High	All	Note
Diethylamine	$C_4H_{11}N$	High	All	
Dimenidrinato	$C_{24}H_{28}ClN_5O_3$	High	All	
Dimercaprol	$C_3 H_8 O S_2$	High	All	
Diphenhydramine (difenilhydramine)	$C_{17} H_{21} N O$	Medium	All	
Dopamine	$C_8 H_{11} N O_2$	Medium	All	
Dorzolamide		High	All	Note
Doxorubicin	$C_{27} H_{29} N O_{11}$	High	Medit., Asian	

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131 items in 9 pages

Carbamazepine (Tegretol)

- Genetic variants have been associated with two forms of life-threatening skin conditions (Stevens-Johnson syndrome and toxic epidermal necrolysis) experienced by carbamazepine patients.
- In particular, two HLA-related variants (HLAB*1502 in Asian populations and HLA-A* 3101 in Caucasians populations) are more likely than other patients to have dangerous skin reactions
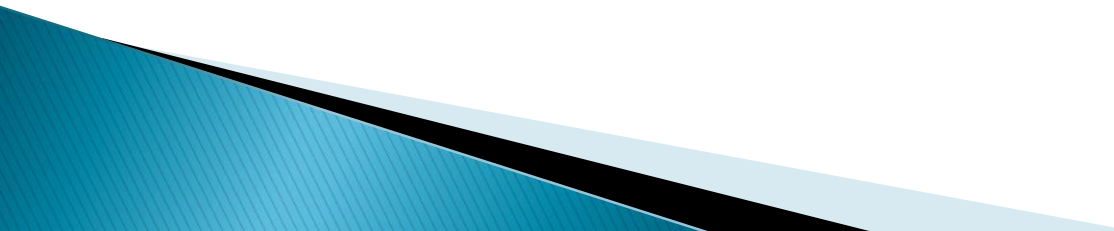- Testing of this allele can reduce the frequency of these reactions

Abacavir (Ziagen)

- **Nucleoside analog reverse transcriptase inhibitor (NRTI) used to treat HIV and AIDS first approved in 1998**
- **Subsequent studies showed that patients who carry the HLA-B*5701 allele were at high risk for hypersensitivity to abacavir due to this allele being strongly associated with a single-nucleotide polymorphism at the HLA-B*5701 locus**
- **The label was changed to recommended pre-therapy screening for the HLA-B*5701 allele and the use of alternative therapy in subjects with this allele.**
- **Clinicians can now safely prescribe Abacavir for the right patient and the incidence of these reactions has diminished worldwide.**
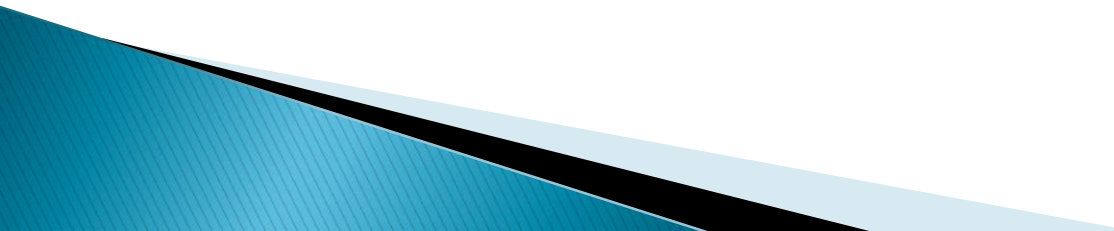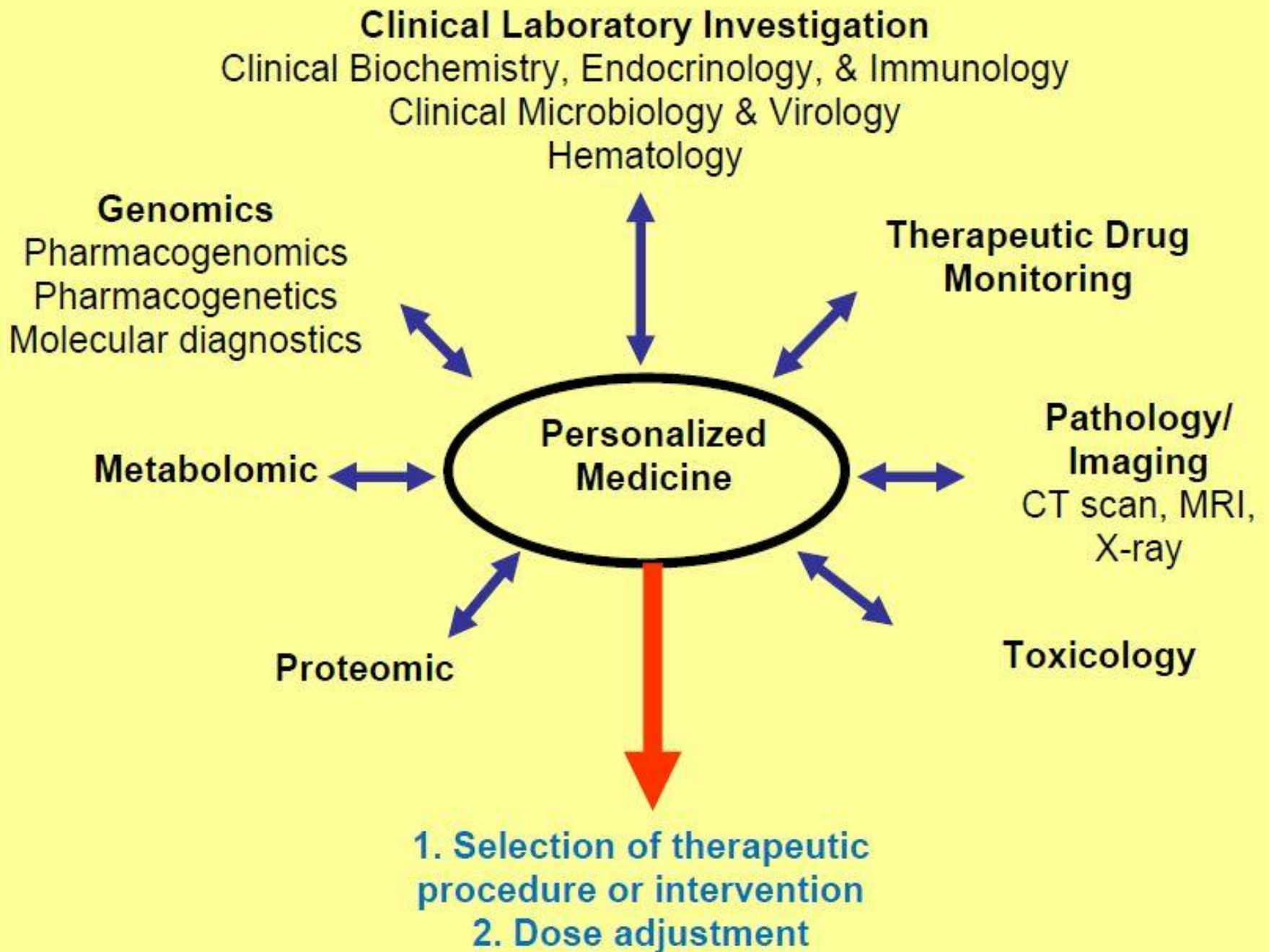
Perdonalized Medicine

- **Aim**→ **understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease**

- **Goals:**
- **Short-term**→ **expanding precision medicine in the area of cancer research**
- **Long-term**→ **bringing precision medicine to all areas of healthcare on a large scale**

Personalized Medicine

- **Male & Female difference: ethanol, propranolol, some benzodiazepines, estrogens, and salicylates**
- **Diet & Environmental Factors**
- **Diseases Affecting Drug Metabolism**
- **Drug-Drug Interactions during Metabolism**

Duloxetin

- Side Effects

- Metabolism

- Polymorphism

Clinical Laboratory Investigation
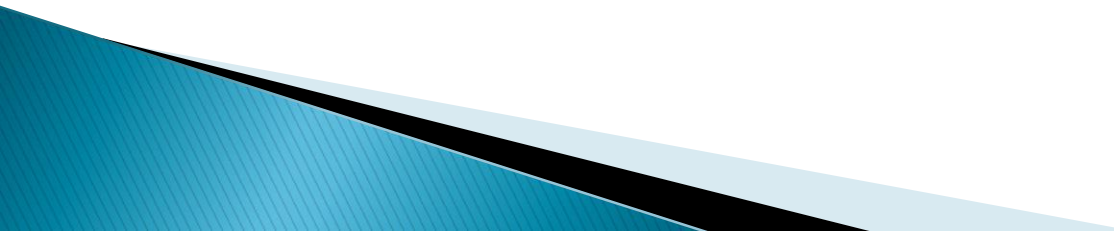Clinical Biochemistry, Endocrinology, & Immunology
Clinical Microbiology & Virology
Hematology

Genomics
Pharmacogenomics
Pharmacogenetics
Molecular diagnostics

Therapeutic Drug Monitoring

Personalized Medicine

Metabolomic

Pathology/ Imaging
CT scan, MRI, X-ray

Proteomic

Toxicology

1. Selection of therapeutic procedure or intervention
2. Dose adjustment

Personalized Medicine

◦ **Provide real-time decision support thereby facilitating individualized drug therapy to maximize efficacy, minimize adverse drug reactions, and reduce health care costs**
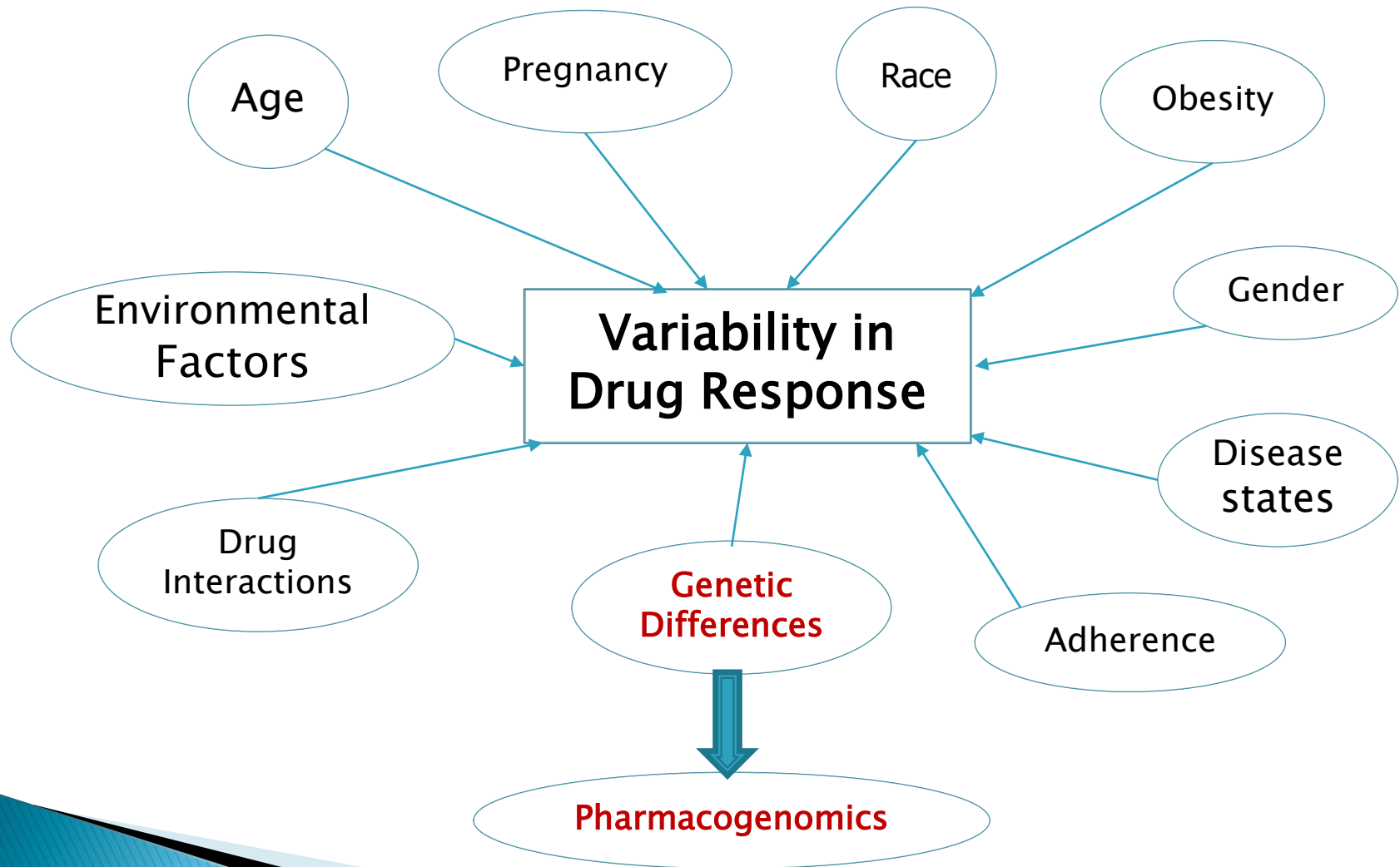
Personalized Medicine

- **Raw data converted to drug genome interaction fact for computerized decision support in electronic health record (EHR)**
- **Provider accesses EHR; alerted to results**
- **Provider receives decision support regarding dosing or alternative medications**
- **Provider optimizes patient management utilizing information provided by genotyping**

Personalized Medicine

- **Consent process**
  - **Adult Admitting & ED Registration**
  - **"CONSENT FOR ROUTINE TESTS, MEDICAL TREATMENT, AND GENETIC TESTS TO GUIDE DRUG THERAPY…"**
- **Provider discusses genotyping studies**
  - **Blood drawn**
- **Sample arrives in laboratory**
  - **DNA extracted (day 1)**
  - **Assay performed (day 2)**
  - **Results reviewed and released (day 3)**

Potential Benefits of Personalized Medicine

Improve drug's efficacy

Decrease drug's adverse events

Savings: time, money, illness

Personalized Medicine

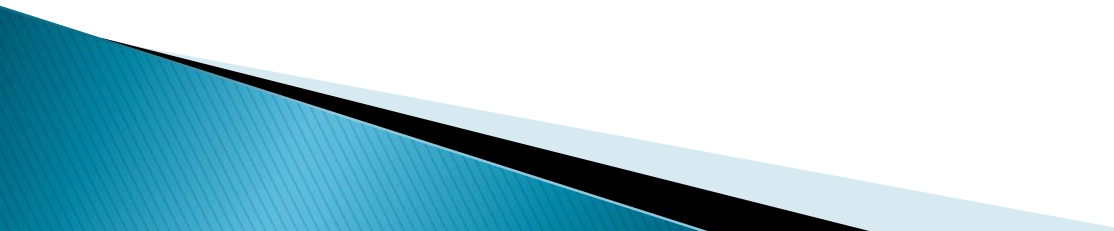Genetic variation inter-individual differences in drug response phenotype at every pharmacologic step

Through individualized treatments, pharmacogenetics and pharmacogenomics are <u>expected</u> to lead to:

- Better, safer drugs the first time
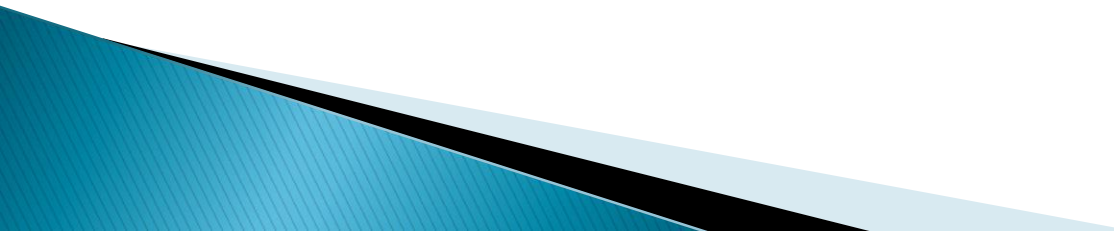- More accurate methods of determining appropriate drug dosages

Pharmacogenomics offers unprecedented opportunities to understand the genetic architecture of drug response
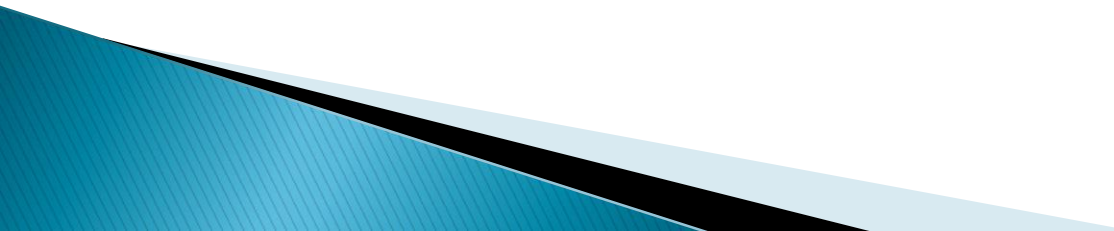
Potential Benefits of Personalized Medicine

- **Shift the emphasis in medicine from reaction to prevention**
- **Predict susceptibility to disease, improve disease detection, preempt disease progression**
- **Customize disease-prevention strategies**
- **Prescribe more effective drugs and avoid prescribing drugs with predictable side effects**

Potential Benefits of Personalized Medicine

- Increase patient adherence to treatment by targeting the right patient with the right drug
- Improve quality of life
- Reduce the time, cost, and failure rate of pharmaceutical clinical trials
- Revive drugs that failed in clinical trials or were withdrawn from the market
- Control health care cost by avoiding unnecessary costs where drug is proven ineffective.

The Societal Impact of Personalized Medicine

▶ **Potential legal and ethical questions that we must answer as a society**
  ◦ **Who should have access to a person's genetic profile?**
  ◦ **How will we protect genetic privacy and prevent genetic discrimination in the workplace and in our health care?**
  ◦ **How will we as consumers use genetic information o our benefit?**

Pharmacogenomic Biomarkers in Drug Labeling

▸ **Drug labeling 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**

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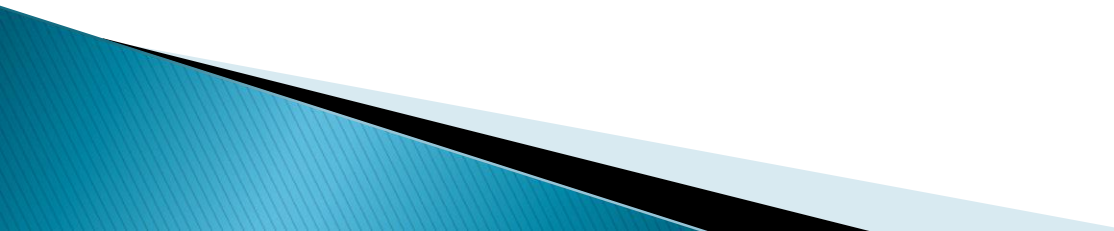
Trastuzumab (Herceptin)

- **Human Epidermal Growth Factor 2 (HER-2) positive tumors comprise 20-25% of all breast cancers and are associated with worse clinical outcomes [1]**
- **Trastuzumab is a humanized monoclonal antibody designed to target the HER2 receptor domain[2]**
- **Today, HER2 testing is a routine part of clinical diagnosis for breast cancer patients**
- **Likewise, due to specific biomarker data, trastuzumab is a foundation therapy for many patients with HER-2 positive breast cancer[2]**

Warfarin (Coumadin)

- **Warfarin has a narrow therapeutic window and a wide range of inter-individual variability in response, requiring careful clinical dose adjustment for each patient.**
- **In 2007, FDA approved label changes to Warfarin noting precautions for patients with variations in two genes, CYP2C9 and Vitamin K Epoxide Reductase Complex-1 (VKORC1) which may require a lower initial dose.**
- **Testing for these variants can assist in dosing**
- **Individualized dosing can possibly increase effectiveness of therapy while decreasing the risk of adverse events**

Carbamazepine (Tegretol)

- Genetic variants have been associated with two forms of life-threatening skin conditions (Stevens-Johnson syndrome and toxic epidermal necrolysis) experienced by carbamazepine patients.

- In particular, two HLA-related variants (HLAB*1502 in Asian populations and HLA-A* 3101 in Caucasians populations) are more likely than other patients to have dangerous skin reactions

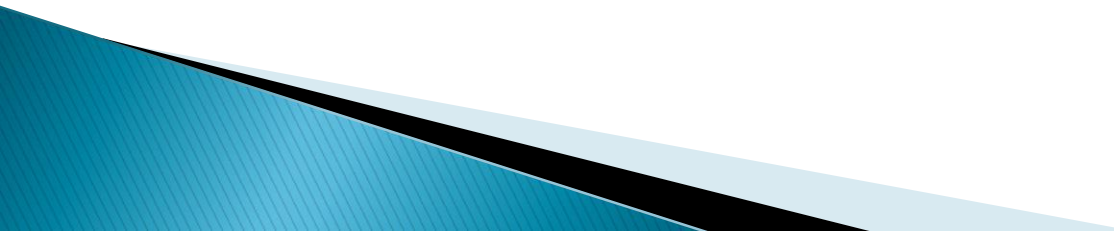- Testing of this allele can reduce the frequency of these reactions

New Approved Drugs%
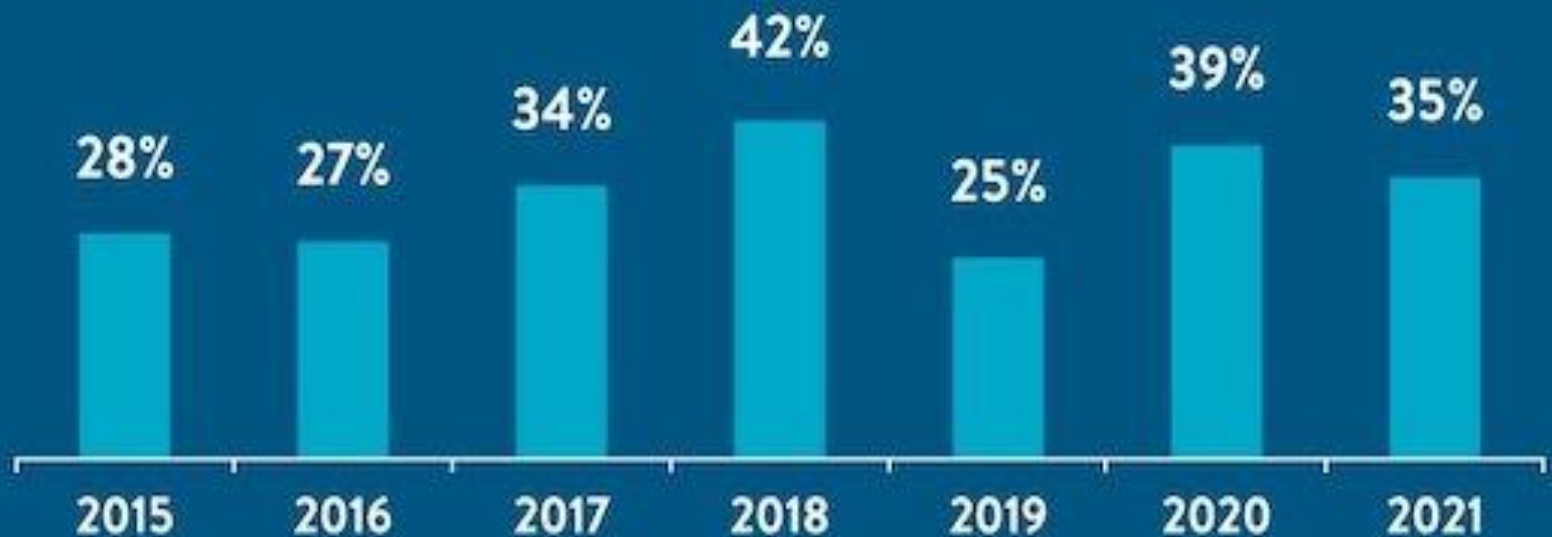
Limitations of Personalized Medicine

- Reimbursement pathway of testing not established
- Ethical issues with genetic testing and data sharing
- Integration of pharmacogenomics, personalized medicine, and the payer and regulatory environment is still ongoing
- Clinician are generally not educated concerning available tests, associate drugs, and outcomes
- The response to a medication may be a result of the interactions of multiple genes

Resources for More Information

- Personalized Medicine Coalition. http://www.personalizedmedicinecoalition.org/
- National Human Genome Research Institute. http://www.genome.gov/
- U.S. Food and Drug Administration. http://www.fda.gov/ScienceResearch/SpecialTopics/PersonalizedMedicine/ucm20041021.htm
- NIH: Pharmacogenomics Knowledge Base http://www.pharmgkb.org/
- FDA Table of approved valid genomic biomarkers http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
- AMCP Format for Formulary Submission Version 3.1 (Companion Diagnostics Addendum, pages 21-26) http://amcp.org/practice-resources/amcp-format-formulary-submisions.pdf