Personalized Medicine: Implementation into Clinical Practice

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The Problems with Prescription Medications:

Adverse Drug Reactions (ADRs) account for:

- 2 million serious health events and 100,000 deaths per year[1]
- 4th leading cause of death in the U.S.[2]
- 7% of all hospital admissions[3]
- 700,000 ED visits and 120,000 hospital visits[1]
- $3.5B in additional healthcare costs per year[1]

Other health concerns related to medications:

- 80% of adults in the U.S. are on at least one drug and over 30% take five or more
- 50-90% of patients quit taking their medication within the first year & do not comply with Rx
- Toxicology testing required when using opioids for pain management

Medications with FDA labeling:

- Over 100 drugs with FDA labeling for genetic biomarkers
- 10% of prescription drugs have FDA labeling related to pharmacogenetics (up to 80% of commonly prescribed medications)

[1] http://www.cdc.gov/medicationsafety/basics.html
[2] New England Journal of Medicine, July 22, 2010
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm114848.htm

The Solution

Precision Medicine:

"*An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.*"

– National Institutes of Health

- **Pharmacogenetics** – Testing for individual's ability to process medications based on their DNA
- **Genetics** – Testing for patients' genetic predispositions to various diseases
- **Toxicology** – Confirming the presence of drug metabolites in blood, urine or saliva. Detects illicit drug use or drug diversion

What is Pharmacogenetics?

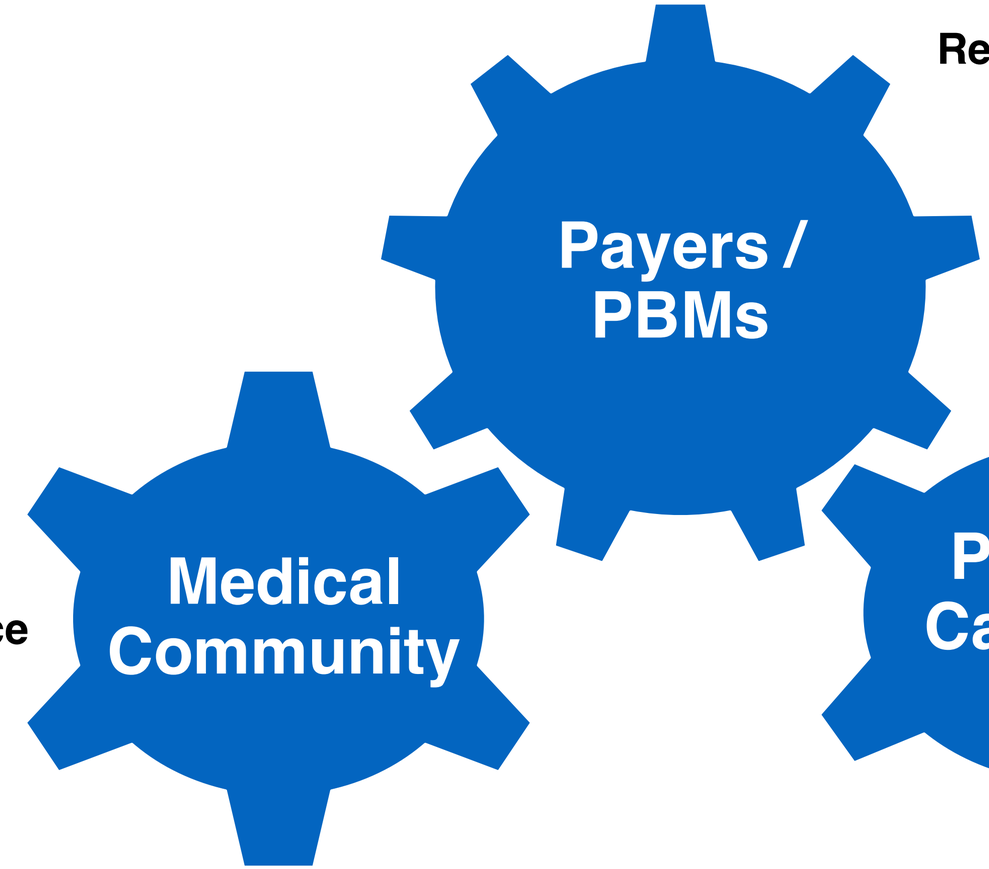
Testing *a person's* ***DNA*** *for genetic programming for specific proteins: the science of* ***genetic differences between individuals*** *which can affect* ***individual responses to drugs****, both in terms of therapeutic effect as well as adverse effects.*

Goals of PGx:

- **Optimize drug choice and effectiveness**
- **Understand Adverse Drug Reaction Risk**
- **Select the right drug for the right patient at the right dose**

The lack of evidence-based tools to guide therapeutic decisions contributes to poor treatment outcomes

Personalized Medicine creates value through alignment with stakeholder objectives



Reduced Costs

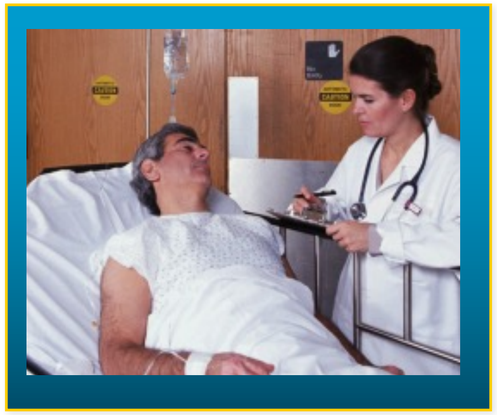
Better outcomes

Enhanced performance metrics

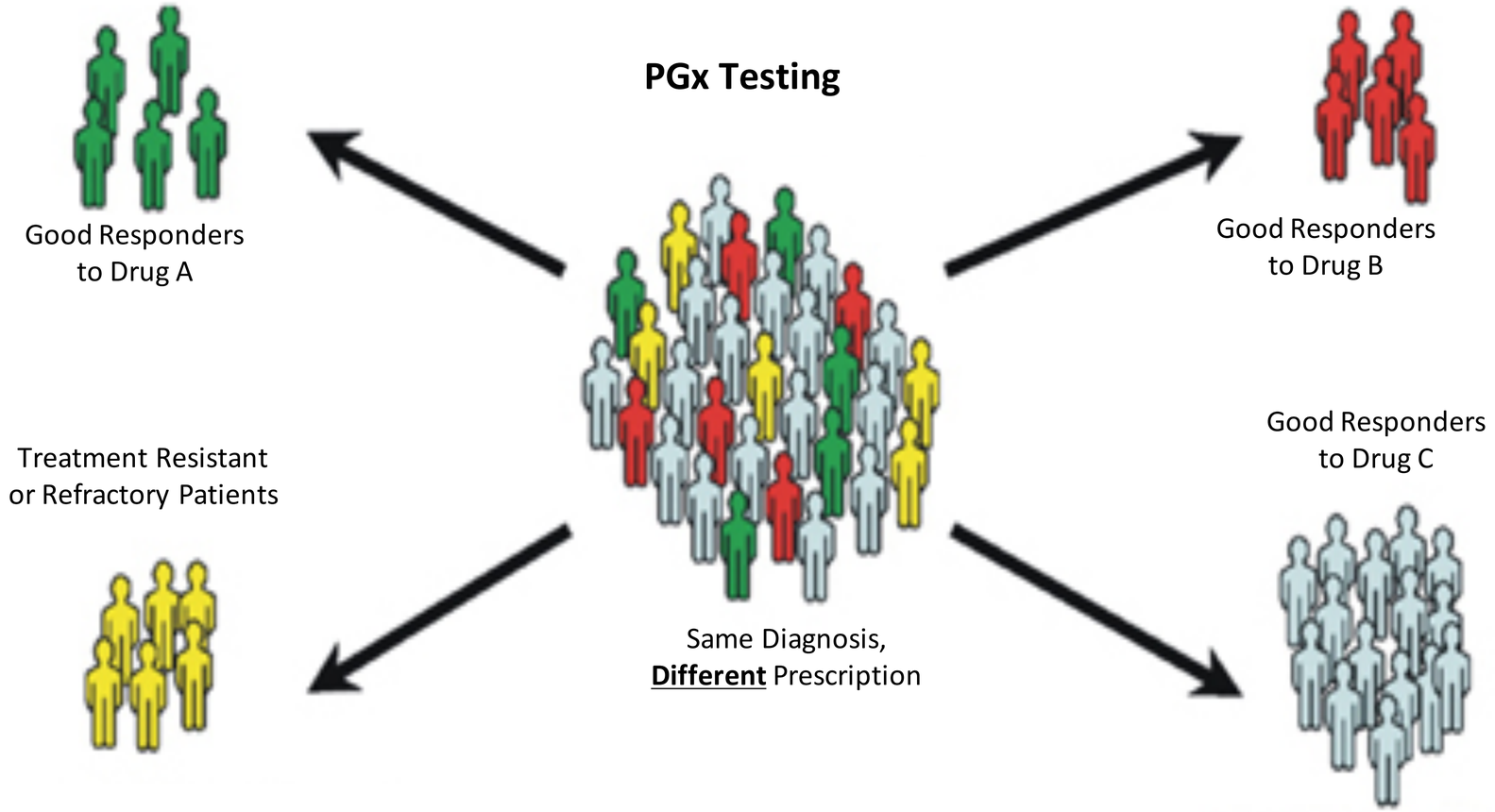
Reduced hospitalizations

Enhanced disease management

Higher quality of life

Patient	Treatment Choices	Outcome
	Drug A	+
	Drug B	--
	Drug C	-
	Drug A	-
	Drug B	+
	Drug C	++

Patients respond differently to medications, thus requiring personalized treatment



U.S. Department of Health & Human Services

Table of Pharmacogenomic Biomarkers in Drug Labels

The table below lists FDA-approved drugs with pharmacogenomic information in their labels. Some, but not all, of the labels include specific actions to be taken based on genetic information. Biomarkers may include gene variants, functional deficiencies, expression changes, chromosomal abnormalities, and others.

Drug	Therapeutic Area	Biomarker	Label Sections
Aripiprazole	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration
Atomoxetine	Psychiatry	CYP2D6	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Carisoprodol	Musculoskeletal	CYP2C19	Clinical Pharmacology, Special Populations
Carvedilol	Cardiovascular	CYP2D6	Drug Interactions, Clinical Pharmacology
Celecoxib	Analgesics	CYP2C9	Dosage and Administration, Drug Interactions, Use in Specific Populations, Clinical Pharmacology
Cevimeline	Dermatology and Dental	CYP2D6	Drug Interactions
Chlordiazepoxide and Amitriptyline	Psychiatry	CYP2D6	Precautions
Citalopram (1)	Psychiatry	CYP2C19	Drug Interactions, Warnings
Citalopram (2)	Psychiatry	CYP2D6	Drug Interactions
Clobazam	Neurology	CYP2C19	Clinical Pharmacology, Dosage and Administration, Use in Specific Populations
Clomipramine	Psychiatry	CYP2D6	Drug Interactions
Clopidogrel	Cardiovascular	CYP2C19	Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Clozapine	Psychiatry	CYP2D6	Drug Interactions, Clinical Pharmacology
Codeine	Analgesics	CYP2D6	Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology
Desipramine	Psychiatry	CYP2D6	Drug Interactions
Desloratadine and Pseudoephedrine	Allergy	CYP2D6	Clinical Pharmacology
Dexlansoprazole (1)	Gastroenterology	CYP2C19	Clinical Pharmacology, Drug Interactions
Dexlansoprazole (2)	Gastroenterology	CYP1A2	Clinical Pharmacology
Dextromethorphan and Quinidine	Neurology	CYP2D6	Clinical Pharmacology, Warnings and Precautions
Diazepam	Psychiatry	CYP2C19	Drug Interactions, Clinical Pharmacology
Doxepin	Psychiatry	CYP2D6	Precautions
Drospirenone and Ethinyl Estradiol	Reproductive	CYP2C19	Precautions, Drug Interactions
Esomeprazole	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology
Fluoxetine	Psychiatry	CYP2D6	Warnings, Precautions, Clinical Pharmacology
Fluoxetine and Olanzapine	Psychiatry	CYP2D6	Drug Interactions, Clinical Pharmacology
Flurbiprofen	Rheumatology	CYP2C9	Clinical Pharmacology, Special Populations
Fluvoxamine	Psychiatry	CYP2D6	Drug Interactions
Galantamine	Neurology	CYP2D6	Special Populations

U.S. Department of Health & Human Services

Iloperidone	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration, Drug Interactions, Specific Populations, Warnings and Precautions
Imipramine	Psychiatry	CYP2D6	Drug Interactions
Metoprolol	Cardiovascular	CYP2D6	Precautions, Clinical Pharmacology
Modafinil	Psychiatry	CYP2D6	Drug Interactions
Nefazodone	Psychiatry	CYP2D6	Drug Interactions
Nortriptyline	Psychiatry	CYP2D6	Drug Interactions
Omeprazole	Gastroenterology	CYP2C19	Dosage and Administration, Warnings and Precautions, Drug Interactions
Pantoprazole	Gastroenterology	CYP2C19	Clinical Pharmacology, Drug Interactions, Special Populations
Paroxetine	Psychiatry	CYP2D6	Clinical Pharmacology, Drug Interactions
Perphenazine	Psychiatry	CYP2D6	Clinical Pharmacology, Drug Interactions
Pimozide	Psychiatry	CYP2D6	Warnings, Precautions, Contraindications, Dosage and Administration
Prasugrel	Cardiovascular	CYP2C19	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Propafenone	Cardiovascular	CYP2D6	Clinical Pharmacology
Propranolol	Cardiovascular	CYP2D6	Precautions, Drug Interactions, Clinical Pharmacology
Protriptyline	Psychiatry	CYP2D6	Precautions
Quinidine	Antiarrhythmics	CYP2D6	Precautions
Rabeprazole	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology
Risperidone	Psychiatry	CYP2D6	Drug Interactions, Clinical Pharmacology
Terbinafine	Antifungals	CYP2D6	Drug Interactions
Tetrabenazine	Neurology	CYP2D6	Dosage and Administration, Warnings, Clinical Pharmacology
Thioridazine	Psychiatry	CYP2D6	Precautions, Warnings, Contraindications
Ticagrelor	Cardiovascular	CYP2C19	Clinical Studies
Tolterodine	Reproductive and Urologic	CYP2D6	Clinical Pharmacology, Drug Interactions, Warnings and Precautions
Tramadol and Acetaminophen	Analgesics	CYP2D6	Clinical Pharmacology
Trimipramine	Psychiatry	CYP2D6	Drug Interactions
Venlafaxine	Psychiatry	CYP2D6	Drug Interactions
Voriconazole	Antifungals	CYP2C19	Clinical Pharmacology, Drug Interactions
Warfarin (1)	Hematology	CYP2C9	Dosage and Administration, Precautions, Clinical Pharmacology
Warfarin (2)	Hematology	VKORC1	Dosage and Administration, Precautions, Clinical Pharmacology

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Pharmacogenomic information can appear in different sections of the label. For more information on the relevance of information in various parts of the drug label (e.g. Indications and Usage, Dosage and Administration, Boxed Warning, etc.), please go to the relevant labeling guidance [1]. For information on the FDA's initiative to improve prescription drug labels, visit the FDA/CDER Learn website [2].

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

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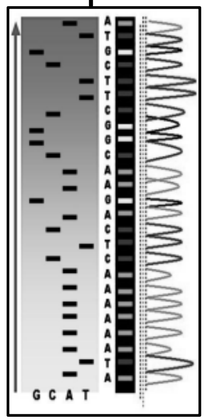
Watson & Crick describe the structure of DNA and its function as the basis for heredity

1956

1963

Sanger develops a primer method for DNA sequencing



DOE approves budget for the Human Genome Project

1987

1990

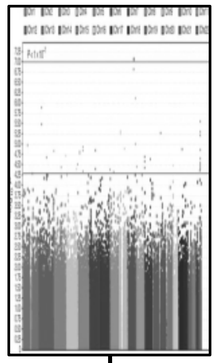
Human Genome Project is started

Venter & Collins announce the sequencing of the human genome

2000

2003

Publication of the map of DNA haplotypes



GWAS identify genes associated with human diseases

2007

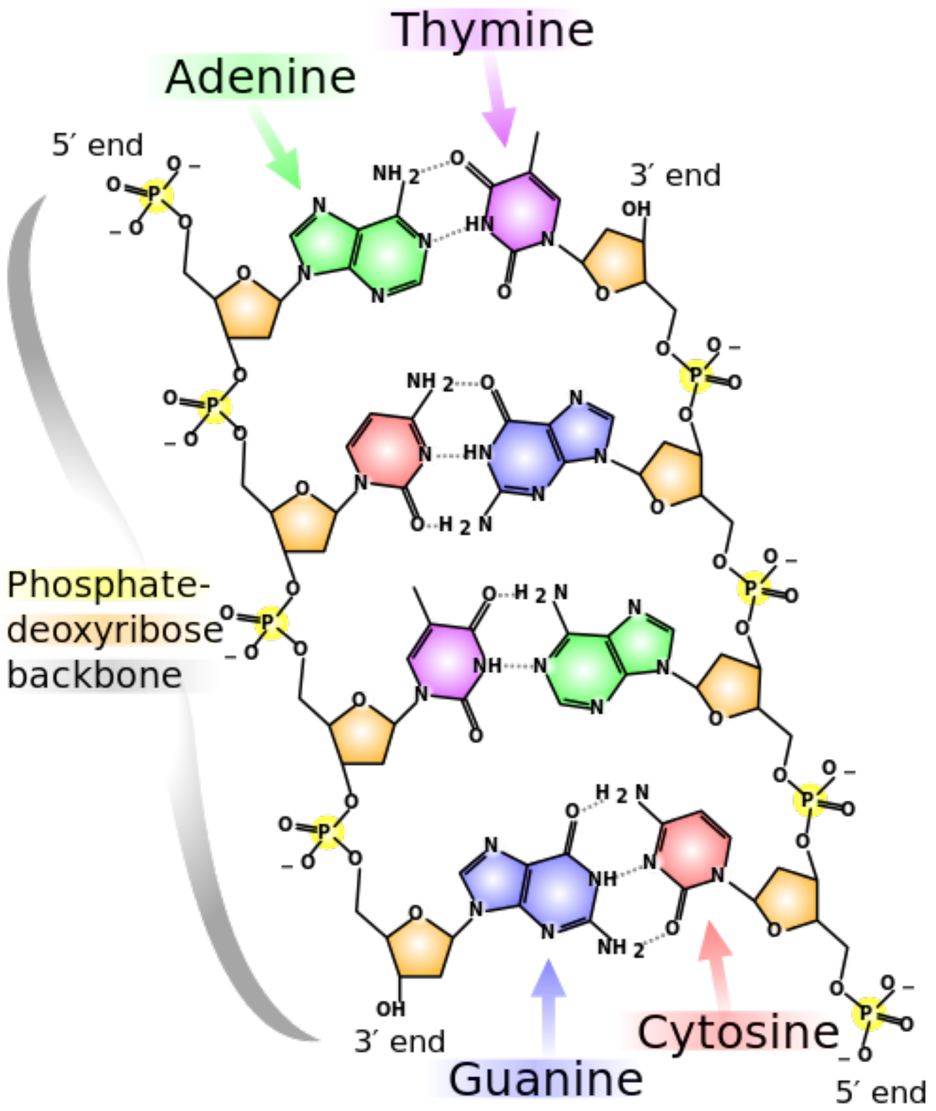
Genes and Proteins

- Genes are made of DNA and function as the molecular unit of heredity.
    - Each gene codes for a specific protein.
    - Four nucleotides make up the “alphabet” of the DNA “coding language”
        - Adenine, Thymine, Cytosine, and Guanine (A, T, C, and G)
- Proteins are large, complex “action” molecules that impact our physiology.
    - Proteins perform a vast array of biological functions including:
        - Catalyzing metabolic reactions
        - DNA replication
        - Response to stimuli
        - And transporting molecules from one location in the body to another.
- Some gene variants result in changes to the protein, for which it codes, that impact the protein’s function, how much of the protein you produce, or whether you produce the protein at all.
- These inherited changes in protein function can have a dramatic impact on biological function, and in the case of pharmacogenetics, how we respond to medicines.

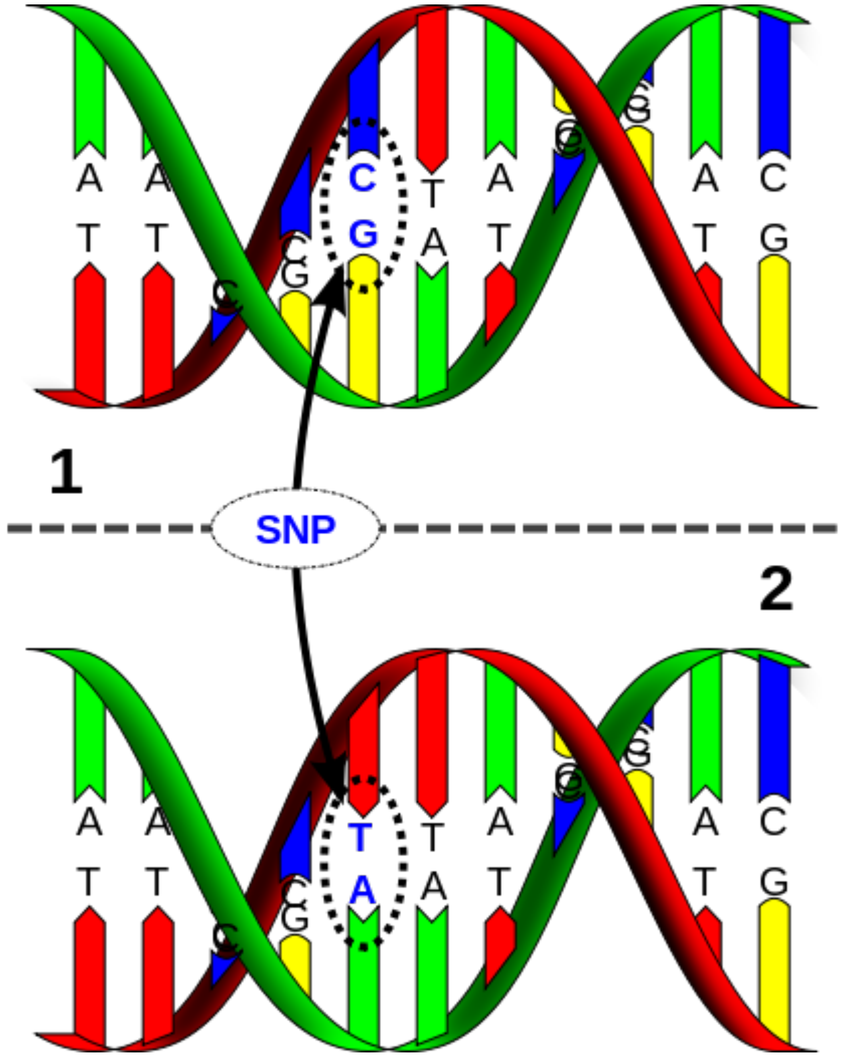
Basic Genetic Concepts

- **Alleles** - alternative forms of the same gene.
- **Genotype** - set of alleles that determines the expression of a particular characteristic or trait.
- **Phenotype** - composite of an organism's observable characteristics resulting from the expression of an organism's genes as well as the influence of environmental factors and the interactions between the two.
- **Single nucleotide polymorphism (SNP)** - a DNA sequence variation occurring when a single nucleotide — A, T, C or G — in a gene (or other shared sequence) differs between members of a biological species or paired chromosomes in a human.

Structure of DNA



Single Nucleotide Polymorphism (SNP)



What pharmacogenomic tools are currently available to healthcare professionals?

- Genetic tests predictive of drug response
  - Genetic markers that **indicate an innate propensity** to response related to the drug's mechanism of action or distribution (response markers)
  - Genetic markers that **indicate an alteration in the innate ability to metabolize** particular drugs via particular metabolic enzymes (metabolic markers) resulting in altered pharmacokinetics

Pharmacogenetic Response Markers

- OPRM1 – Determines effectiveness of opiate analgesics
- SLC6A4 – Differential antidepressant response
- SLCO1B1 – Affects the safety and efficacy of statins
- VKORC1 – Affects sensitivity to warfarin
- MTHFR – Affects the ability to convert dietary folate into its active form, methyl-folate

Genetic Markers of Addiction Risk

- BDNF – Affects neurodevelopment of the mesolimbic dopamine system involved in reward systems
- DRD2 – Affects dopamine type 2 receptors that are involved in brain reward systems

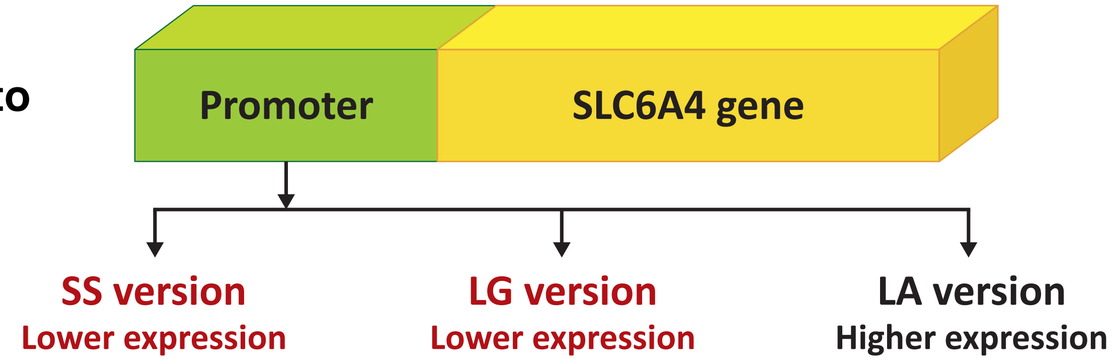
What is OPRM1?

- The *OPRM1* gene encodes for the μ opiate receptor through which opiate analgesics produce their effects.
    - Activation of the μ receptor by an agonist such as morphine causes analgesia, sedation, slightly reduced blood pressure, itching, nausea, euphoria, respiratory depression, miosis, and decreased bowel motility leading to constipation.
- The A355G polymorphism in the *OPRM1* gene results in a decrease in expression of μ opiate receptors which may decrease the analgesic response to opiates. Patients with this variant have shown a lower pain threshold and a higher drug consumption in order to achieve effective analgesia.
- Paradoxically, this same mutation results in an apparent gain of function with respect to response to endogenous opioids, like β-endorphins. individuals who carry at least 1 G allele have significantly better outcomes with naltrexone therapy for alcoholism and drug abuse.

Serotonin Transporter Response Marker

Genetic variation in the serotonin transporter gene (SLC6A4) that impacts response to SSRIs.

Promoter variants lead to altered transporter production



Response to SSRIs is influenced by number of LA versions of SLC6A4

2 copies of LA version – Normal responders
Expected response to SSRIs

1 copy of LA version – Intermediate responder
Possible increased risk of poor response and adverse events

0 copies of LA version – Poor responder
Increased risk of poor response and adverse events

What is SLCO1B1?

- The *SLCO1B1* gene encodes for a membrane-bound sodium-independent organic anion transporter protein OATP1B1.

- OATP1B1 is involved in active cellular influx of many endogenous and xenobiotic compounds.

- OATP1B1-dependent transport is an important step in mediating drug hepatic clearance, especially HMG-CoA reductase inhibitors (i.e.statins).

- OATP1B1 transport is particularly important for hepatic accessibility of pravastatin. Pravastatin is too hydrophilic to gain significant heptocellular entry through passive transport, and thus OATP1B1 active transport plays an important role in pravastatin getting to its site of action.

- *SLCO1B1* variants are strongly-associated with simvastatin-induced myopathies.

What is VKORC1?

- The *VKORC1* gene encodes the enzyme VKORC1 (Vitamin K epoxide reductase) protein, the key enzyme involved in Vitamin K recycling. Vitamin K must be in its reduced form to act as a cofactor in blood clotting.
    - Warfarin and other similar anti-clotting agents act via inhibition of VKORC1.
    - *VKORC1* genotype appears to be the single biggest predictor of warfarin dose, with *VKORC1* polymorphisms accounting for ~25% of the variance in stabilized warfarin dose.
    - In 2007, pharmacogenomic information for warfarin was approved by FDA to be included in the product label stating that VKORC1 and CYP2C9 genotypes may be useful in determining the optimal initial dose of warfarin.

What is MTHFR?

- The *MTHFR* gene codes for an enzyme called methylenetetrahydrofolate reductase. Methylenetetrahydrofolate reductase is converts the B-vitamin folate to 5-methyltetrahydrofolate, the active form that can get into the brain.
    - Methyl-folate is involved in the synthesis of serotonin.
- As many as 20% of the population has inherited a defective copy of MTHFR and thus do not get adequate amounts of folate across the blood-brain barrier to support optimal function.
    - These patients have an increased risk of depression, and also may predispose them to be resistant to medical treatment.
    - In these patients, methyl-folate supplementation may enhance response to antidepressant therapy (e.g. Deplin).

What is BDNF?

- The *BDNF* gene encodes brain-derived neurotrophic factor (BDNF).
- Brain-Derived-Neurotrophic-Factor (BDNF) is involved in the neurodevelopment of dopaminergic (DA)-related systems and interacts with the meso-limbic DA systems, involved in the therapeutic response to antipsychotic drugs and susceptibility for substance abuse.
    - Patients with psychosis have a 700% greater risk of drug abuse than the general population.
- The mesolimbic dopamine system contains dopaminergic circuits that regulate the "pleasure center" of the brain. Altered mesolimbic dopamine function can make one experience greater pleasure from abused drugs.
- Knowing *BDNF* function can allow for classification of addiction risk and relapse.

What is DRD2?

- The *DRD2* gene encodes the enzyme dopamine type 2 receptor. The dopamine 2 receptor plays an important role in the reward system of the brain.

- The dopamine 2 receptor influences how the brain responds to dopamine, a neurotransmitter that regulates rewards (i.e. “pleasure”) and behaviors that lead to rewarding events.

    - Certain variants of this gene may lead to increased consumptive behaviors such as over-eating and increased propensity for drug abuse.

Pharmacogenetic Metabolic Markers

- Cytochrome P450 Hepatic Isozymes
  - Modify drugs so that they are polar and can be eliminated by the kidneys (e.g. hydroxylation)
  - CYP isozymes that are important in the metabolism and elimination of commonly prescribed drugs include: CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP2B6, and CYP1A2

Metabolizer Phenotypes and Rates of Drug Metabolism

Variation in the metabolic genes CYP2D6, CYP2C9, CYP2C19, CYP3A4/5, CYP2B6, and CYP1A2 can lead to higher or lower concentrations of drugs. Since recommended dosing assumes normal metabolism, individuals with genetic variants that impact drug metabolism may require dose adjustments or, in some cases, should avoid drugs impacted by genetic variants.

General Principles of Pharmacology

ADME: Absorption, Distribution, Metabolism, and Elimination

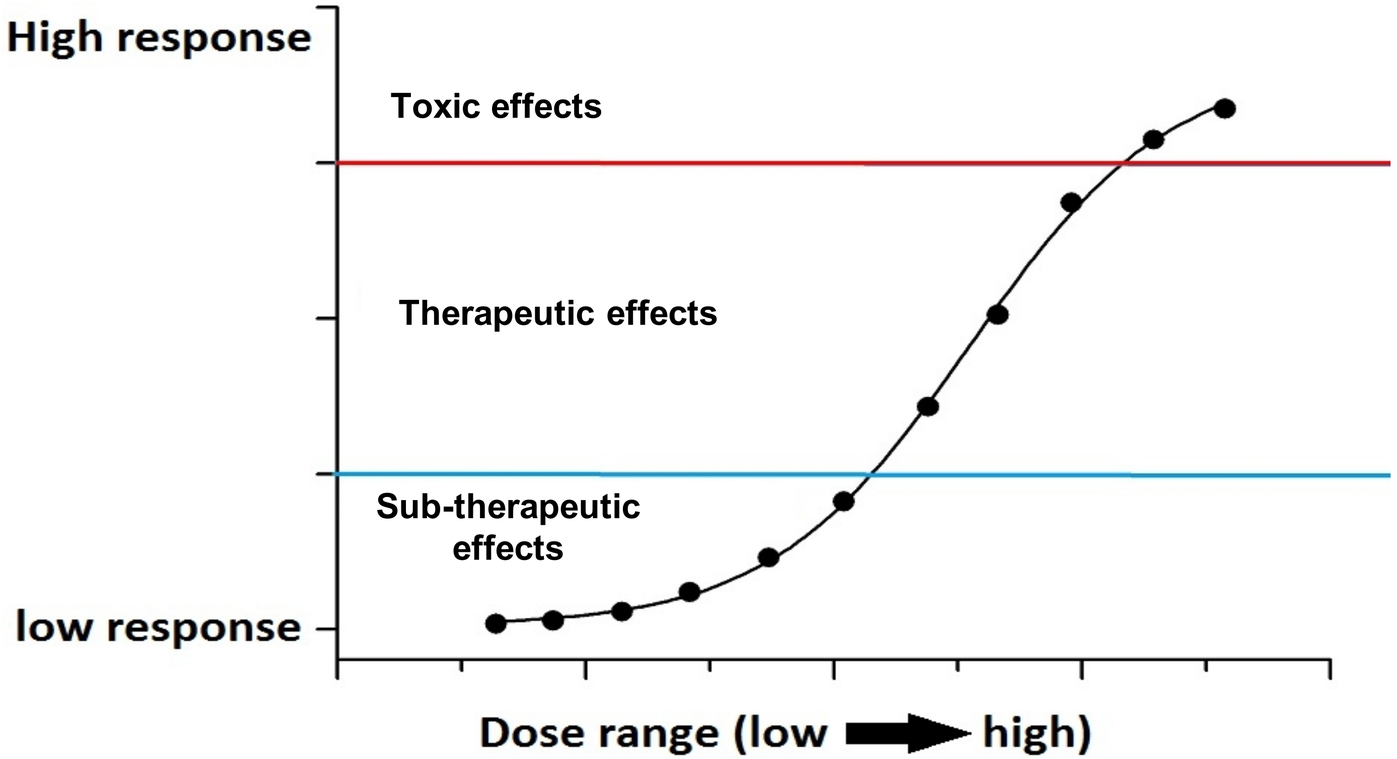
- Describes the disposition of a drug from the time of its introduction into the body until its elimination from the body
- These processes determine the extent and duration of the exposure of the body to the drug and its metabolites (both active and inactive
- Well-accepted and proven laws of therapeutics

General Principles of Pharmacology

The Dose – Response Relationship

- Drug exposure determines the response or impact of the drug (and its metabolites) for/on the person taking it
- The greater the exposure or dose, the greater the response
- Well-accepted and proven laws of therapeutics

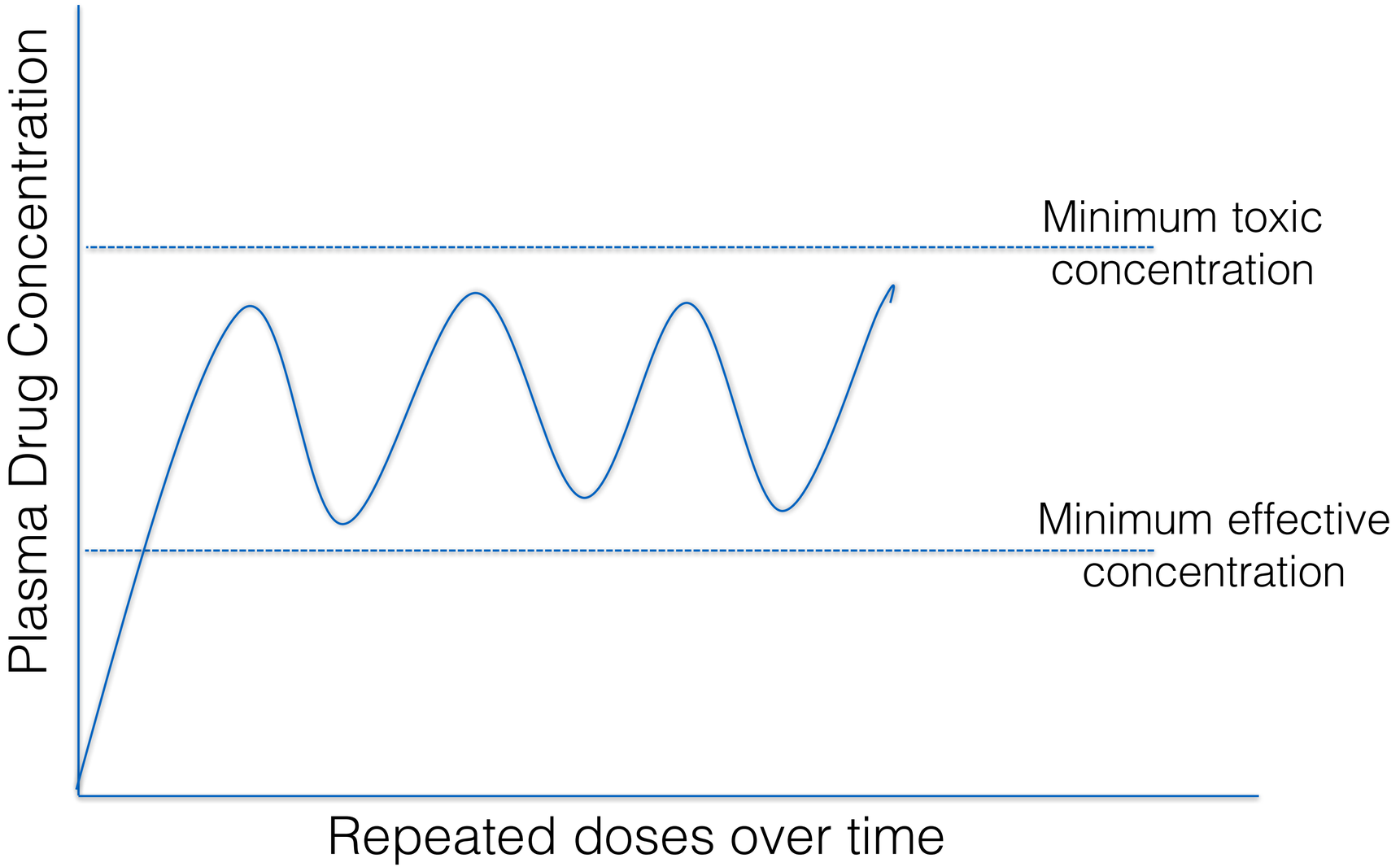
Dose relationship between blood concentrations of drug and efficacy and toxicity (single-dose)



Phenotype prevalence for commonly tested cytochrome P450 isozymes

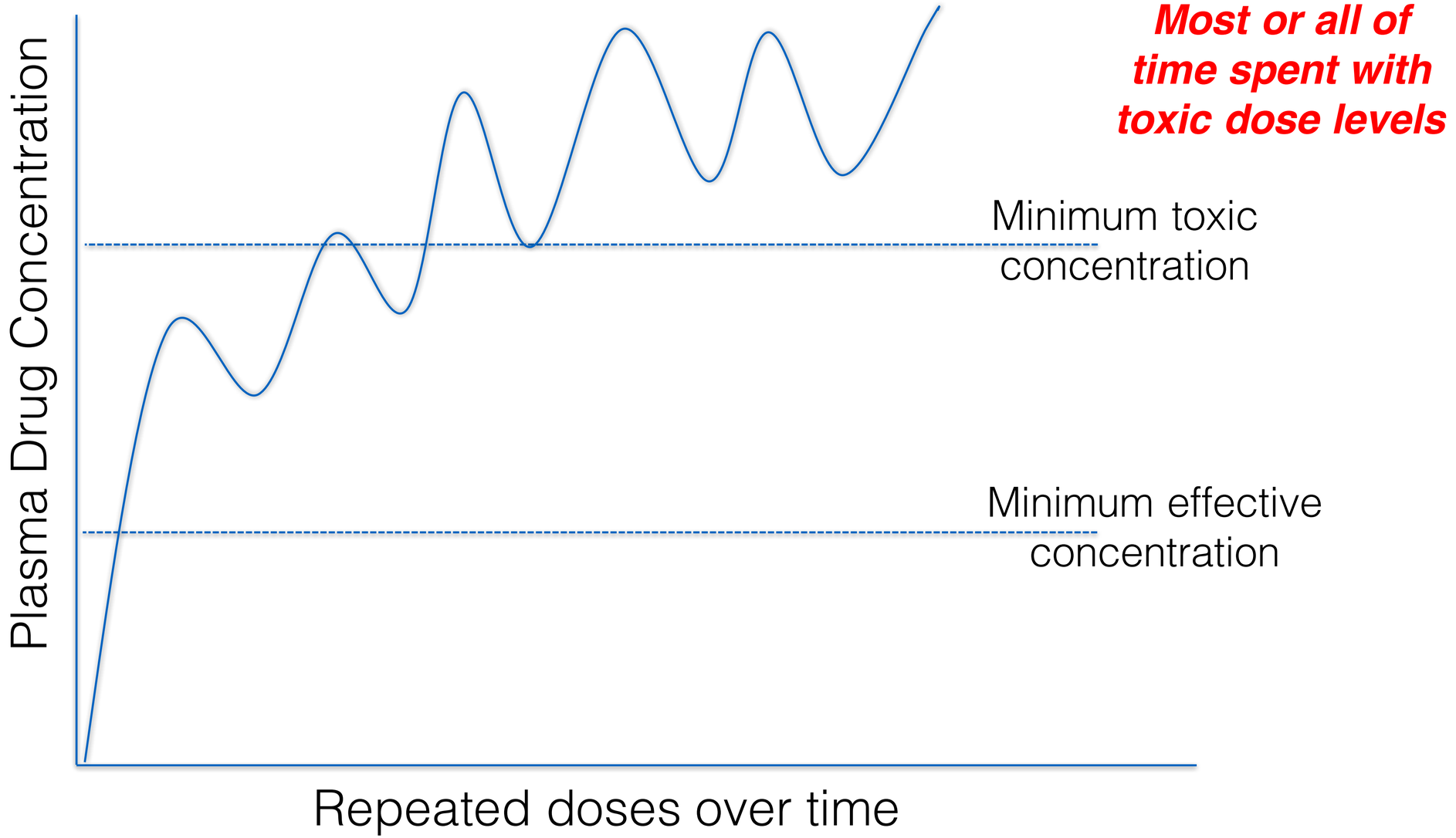
Gene	Extensive Metabolizer (NORMAL)	Intermediate Metabolizer (Impaired)	Poor Metabolizer (Elevated Risk)	Ultra-rapid Metabolizer (Elevated Risk)
2D6	53%	35%	10%	2%
2C19	36%	32%	4%	28%
2C9	57%	40%	3%	NA
3A4	87%	12%	1%	NA
3A5	1%	18%	81%	NA

Normal metabolism of drug

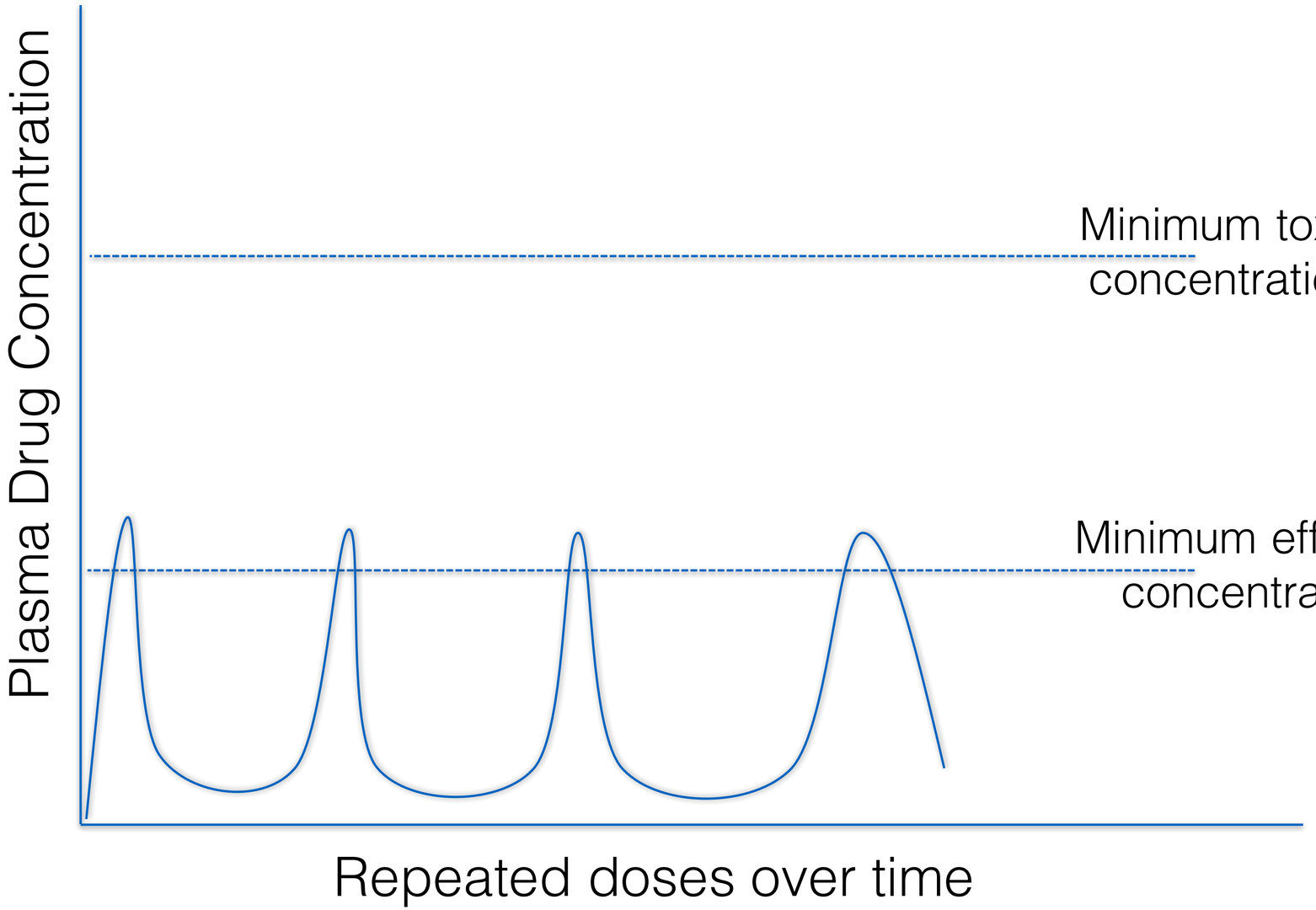


Most or all of time spent with safe and effective levels

Poor metabolism of drug



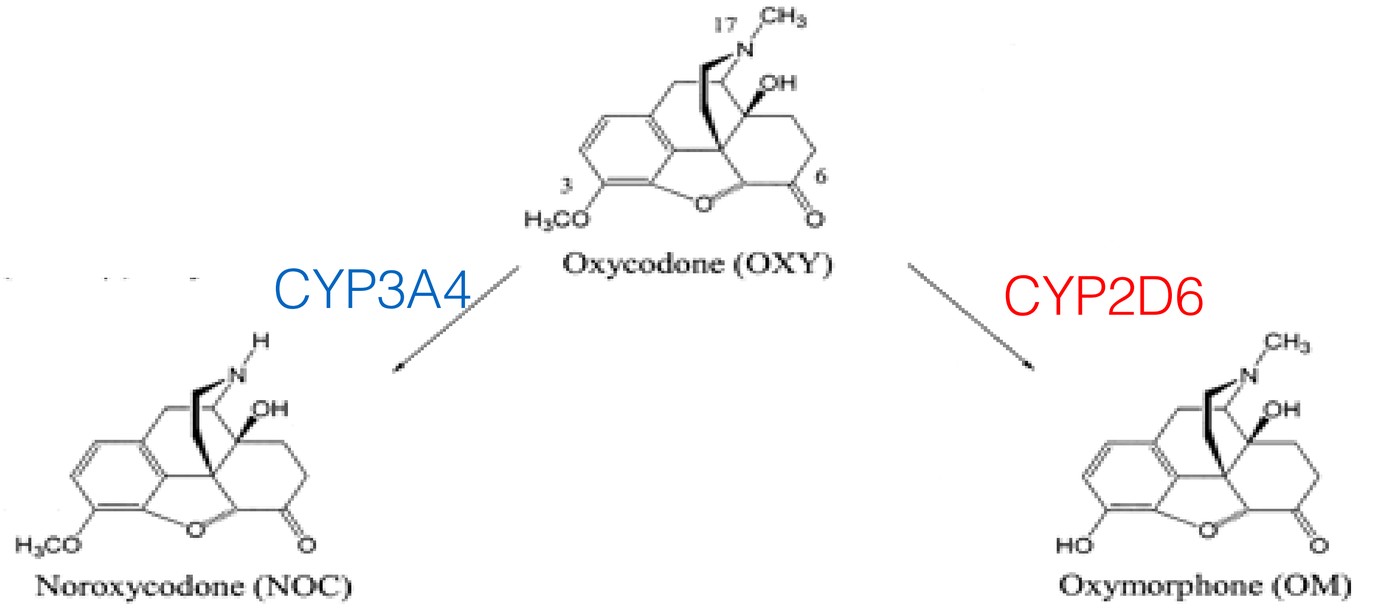
Ultra rapid metabolism of drug



Most or all of time spent with levels below efficacious dose

Oxycodone and Metabolites

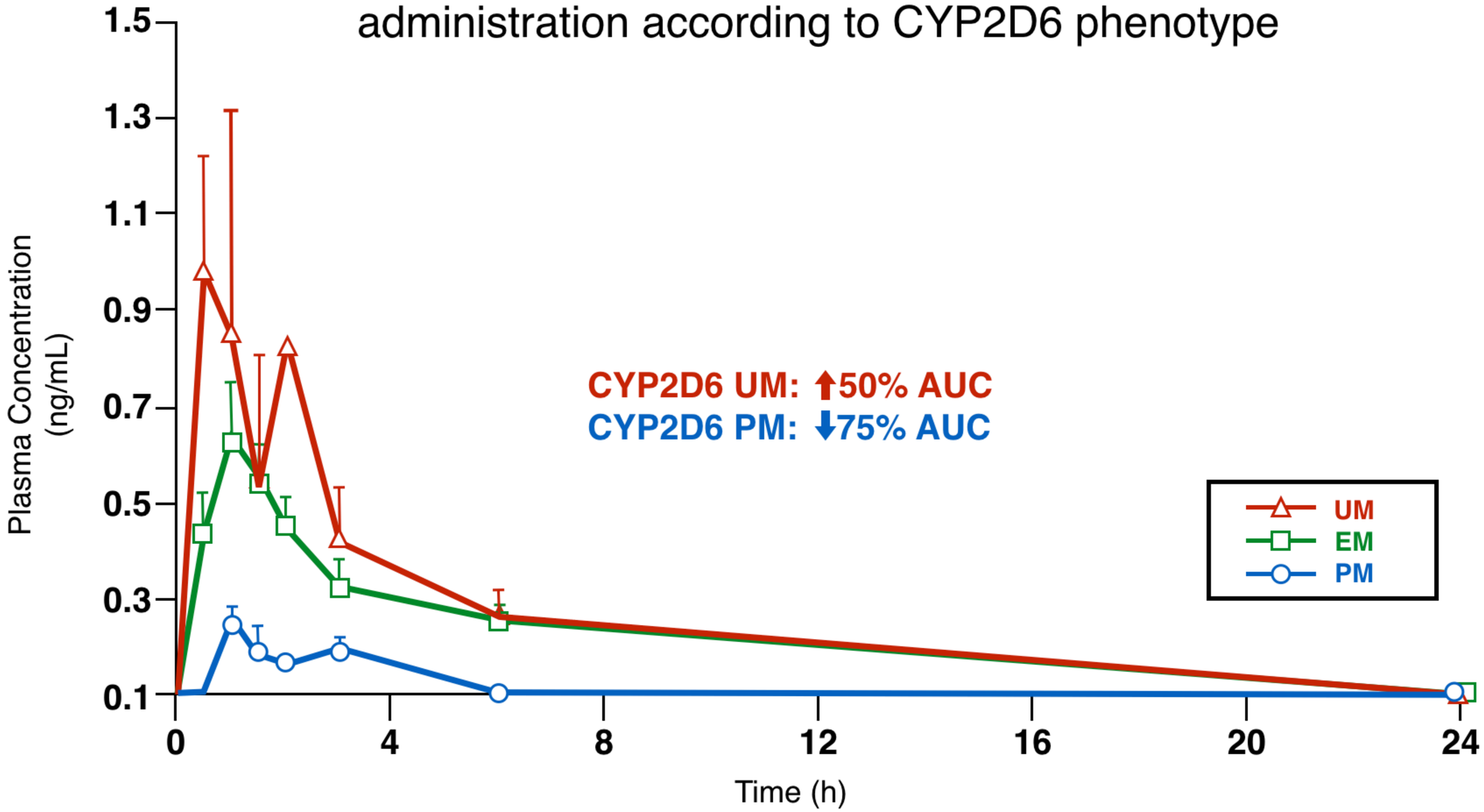
If CYP2D6 function is impaired, oxycodone is not converted to its active metabolite, but is instead converted by CYP3A4/5 into an inactive metabolite.



0.33x mu opioid receptor affinity

44x mu opioid receptor affinity

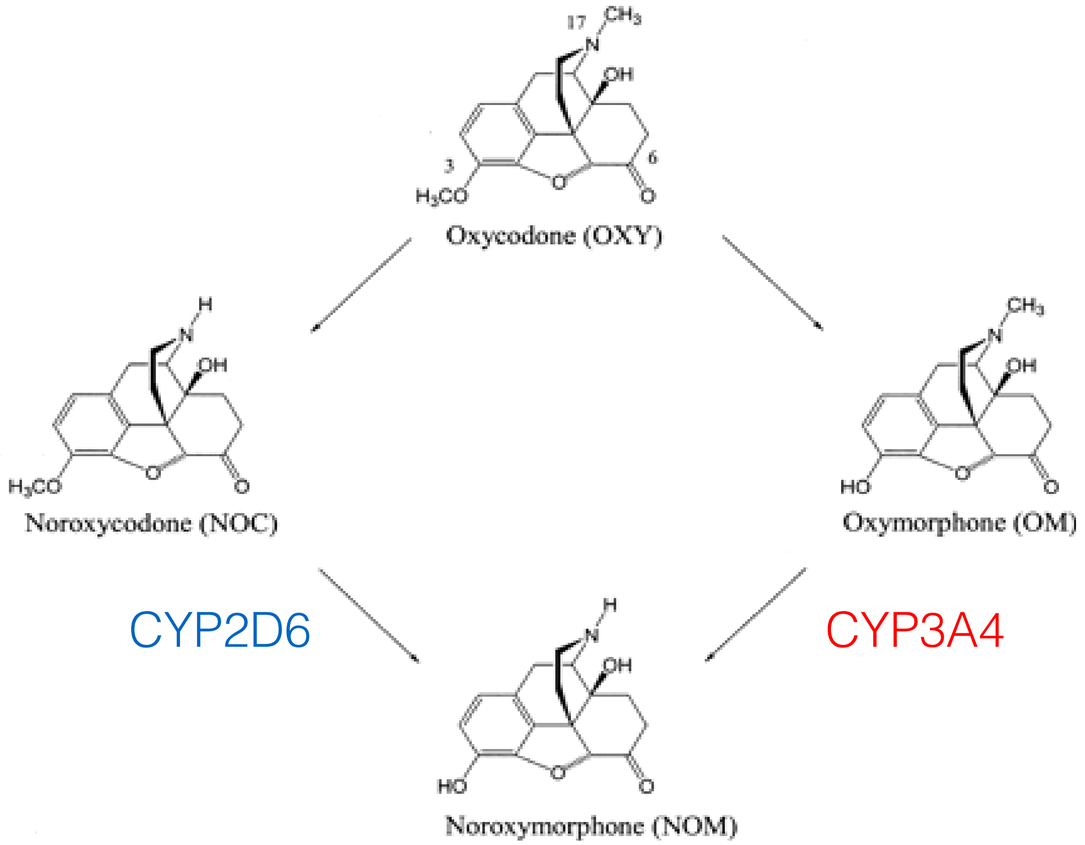
Oxymorphone concentrations following oxycodone administration according to CYP2D6 phenotype



Samer at al., Br J Pharmacol 2010, 167: 907-18

Secondary Metabolism of Oxycodone

The second step in oxycodone metabolism converts both primary metabolites into a relatively inactive metabolite secondary metabolite, noroxymorphone.

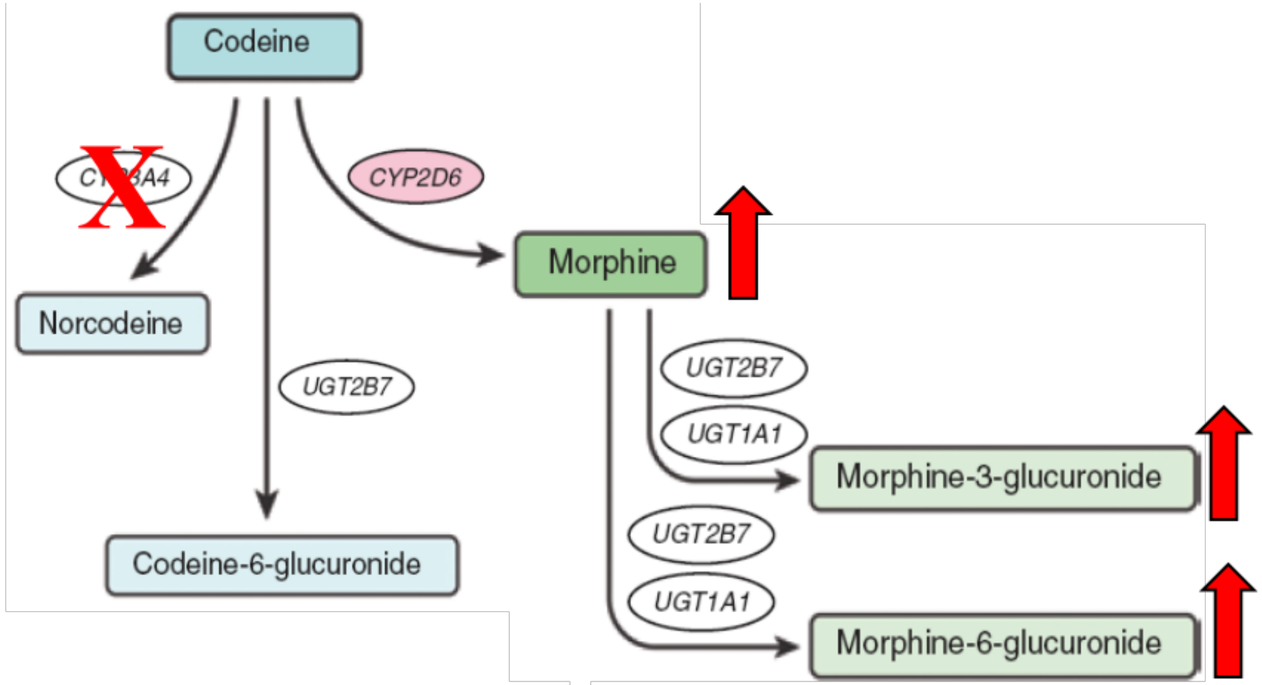


3x mu opioid receptor affinity

Opioid intoxication with codeine

- 62 yr male with CLL and pneumonia treated with clarithromycine, voriconazole and codeine for cough (25 mg 3x/day)
- Coma and respiratory failure on day 4 requiring ventilation and ICU transfer
  - Resolution after **naloxone**

- **CYP2D6** phenotype: **UM** **CYP3A** phenotype: **PM**
  - (CYP3A inhibition by clarithromycine and voriconazole)
  - Morphine values in blood **20-80-fold** higher than expected
  - **Acute renal failure** -> accumulation of morphine active metabolites



Gasche Y. et al NEJM 2004, 351: 2827-31

Opioid toxicity and CYP2D6 UM genotype

Case	Indication	Codeine Dose	Toxicity
Breastfed Newborn (13 days)	Episiotomy pain (mother)	2x30mg then 2x15 mg	**Death**
Breastfed Newborn	Severe muscle pain	120 mg/day	Mother: sedation, nausea, dizzy; Child: drowsy, poor feeding
Child (2 years)_	Tonsillectomy	10-12.5mg, q 4-6 h	**Death**
Child (29 months)	Tonsillectomy	1.75mg/kg	Apnea, unresponsiveness
Child (3 years)	Tonsillectomy	15mg, q 4-6 h	Severe respiratory depression
Child (4 years)	Adenotonsillectomy	8mg, q 5 h	**Death**
Child (5 years)	Adenotonsillectomy	12mg, q 4 h	**Death**
Male (33 years)	Dental pain	60mg	Euphoria, dizzy, blurred vision, epigastric pain

Dalen et al 1997, Koren et al 2006, Madadi et al 2007, Voronov et al 2007, Madadi et al 2009, Kelly et al 2012

Hawaii sues makers of Plavix
(Here come the lawyers!)
March 20, 2014

"The attorney general in Hawaii filed a lawsuit against the manufacturers of clopidogrel, claiming the companies deceptively marketed the antiplatelet drug by not disclosing its reduced efficacy in patients who are **poor metabolizers**.

Attorney General David M. Louie claimed that between 38 percent and 79 percent of Pacific Islanders and **40 percent to 50 percent of East Asians are poor metabolizers**. He argued that more than 1 million prescriptions for clopidogrel have been given for profits of more than $10 million since 1998."

http://www.cardiovascularbusiness.com/topics/practice-management/hawaii-sues-makers-plavix

Typical Pharmacogenetic Clinical Study Design

Cytochrome 2C19*17 Allelic Variant, Platelet Aggregation, Bleeding Events, and Stent Thrombosis in Clopidogrel-Treated Patients With Coronary Stent Placement

Dirk Sibbing, MD; Werner Koch, MD; Daniela Gebhard, MS; Tibor Schuster, MSc; Siegmund Braun, MD; Julia Stegherr, MS; Tanja Morath, MS; Albert Scho¨mig, MD; Nicolas von Beckerath, MD; Adnan Kastrati, MD

Background—The cytochrome P450 (CYP) 2C19 isoenzyme plays an important role in clopidogrel metabolization. A recently explored *CYP2C19*17* allelic variant has been linked to increased transcriptional activity, resulting in extensive metabolization of *CYP2C19* substrates, which may lead to an enhanced platelet response to clopidogrel treatment. The aim of this study was to assess the impact of *CYP2C19*17* on ADP-induced platelet aggregation, the risk of bleeding, and stent thrombosis in clopidogrel-treated patients undergoing percutaneous coronary intervention.

Methods and Results—The study population included 1524 patients undergoing percutaneous coronary intervention after pretreatment with 600 mg clopidogrel. Genotypes were determined with a TaqMan assay. ADP-induced platelet aggregation was assessed on a Multiplate analyzer. The primary clinical safety end point was the 30-day incidence of bleeding defined according to Thrombolysis in Myocardial Infarction criteria, and the primary clinical efficacy end point was the 30-day incidence of stent thrombosis. For both heterozygous (*wt/*17; n546) and homozygous (*17/*17; n76) allele carriers, significantly lower ADP-induced platelet aggregation values were found compared with wild-type homozygotes (*wt/*wt; n902; *P*0.039 and *P*0.008, respectively). *CYP2C19*17* allele carriage was significantly associated with an increased risk of bleeding; the highest risk was observed for *CYP2C19*17* homozygous patients (*P*0.01, $_2$ test for trend). Multivariate analysis confirmed the independent association of *CYP2C19*17* allele carriage with platelet aggregation values (*P*0.001) and the occurrence of bleeding (*P*0.006). No significant influence of *CYP2C19*17* on the occurrence of stent thrombosis was found (*P*0.79).

Conclusions—*CYP2C19*17* carrier status is significantly associated with enhanced response to clopidogrel and an increased risk of bleeding. (***Circulation*.2010;121:512-518.**)

Example of a genetic variant in a secondary metabolic pathway having serious adverse consequences

- ***Cuisset et al.*** **"*CYP2C19*2* and **17* Alleles Have a Significant Impact on Platelet Response and Bleeding Risk in Patients Treated With Prasugrel After Acute Coronary Syndrome" JACC: Cardiovascular Interventions, 5(12):1280-1287, 2012**
  - "The present study shows a significant influence of *CYP2C19*2* and **17* alleles on response to chronic treatment by prasugrel 10 mg daily and occurrence of bleeding complications."
- Prasugrel, like clopidogrel, is a pro-drug that is converted by CYP metabolism to its active form
  - clopidogrel is primarily activated by CYP2C19, however prasugrel is primarily activated by CYP3A4 and CYP2B6
- This study shows that variants of the gene for a secondary metabolic pathway can have significant clinical impact

Importance of Secondary Metabolic Pathways on Drug Safety

CYP2C19*2 and *17 Alleles Have a Significant Impact on Platelet Response and Bleeding Risk in Patients Treated With Prasugrel After Acute Coronary Syndrome

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Objectives The present study was designed to assess the effect of genetic variants on chronic biological response to prasugrel and bleeding complications.
Background *CYP2C19*2* loss-of-function allele and *CYP2C19*17* gain-of-function allele have been linked with response to clopidogrel, but preliminary data did not show any significant influence of these alleles on prasugrel effect.
Methods A total of 213 patients undergoing successful coronary stenting for acute coronary syndrome and discharged with prasugrel 10 mg daily were included. Prasugrel response was assessed at 1 month with the platelet reactivity index (PRI) vasodilator-stimulated phosphoprotein (VASP) and high on-treatment platelet reactivity (HTPR) defined as PRI VASP 50% and hyper-response as PRI VASP 75th percentile (PRI VASP 17%). *CYP2C19*2* and *CYP2C19*17* genotyping were performed.
Results Carriers of loss-of-function **2* allele had significantly higher PRI VASP than noncarriers (33 15% vs. 27 14%, p 0.03) and higher rate of HTPR (16% vs. 4%, p 0.01). Conversely, carriers of **17* gain-of-function allele had significantly lower PRI VASP than noncarriers (25 13% vs. 31 15%, p 0.03, p 0.03), lower rate of HTPR (1% vs. 10%, p 0.02), higher rate of hyper-response (34% vs. 21%, p 0.02), ***and higher rate of bleeding complications than noncarriers: 23% versus 11%, (odds ratio [95% confidence interval]: 2.5 [1.2 to 5.4]; p 0.02).*** No significant influence of genotypes on platelet reactivity assessed by adenosine diphosphate–induced platelet aggregation was observed.
Conclusions The present study shows a significant influence of *CYP2C19*2* and **17* alleles on response to chronic treatment by prasugrel 10 mg daily and occurrence of bleeding complications.

(J Am Coll Cardiol Intv 2012;5:1280–7)

Activation of the prodrug prasugrel by a secondary metabolic pathway

doubled ***the risk of a bleed***

Problems in translating existing research into the clinic

- Almost all clinical PGx studies examine only one gene and its impact on one drug
  - Not looking at all relevant PGx information (secondary metabolic pathways become important if the primary pathway is impaired (and sometimes even when the primary pathway is not impaired – see prasugrel and CYP2C19)
  - PGx information is biological information, the more information the physician has to make a treatment decision, the more informed the decision and the better the decision

Proper Evidentiary Requirements for PGx Adoption

There has been much attention to the gaps in evidence that preclude translating genomic testing into clinical use, particularly for disease risk (EGAPP, 2014). However, there are multiple examples of using genomic testing to inform treatment decisions (Bielinski et al., 2014; Gottesman et al., 2013; Hoffman et al., 2014; Johnson et al., 2013; O'Donnell et al., 2014; Pulley et al., 2012; Shuldiner et al., 2014), and in many instances, there is sufficient evidence to justify using genetic testing to inform choice or dosage of medications.

Prescribing decisions are routinely made on the basis of imperfect evidence and on extrapolations between solid evidence of mechanisms underlying interpatient variability in drug response and unstudied clinical scenarios."

from Relling and Veenstra, *"Implementation of Pharmacogenomics: Evidence Needs"* a discussion paper from the Institute of Medicine of the National Academies, published Feb. 26, 2015 by the National Academy of Sciences

Proper Evidentiary Requirements for PGx Adoption (*cont.)*

- "for many pharmacogenetic traits, the mechanisms are well understood, and randomized controlled trials are not necessary. Many actionable genetic variants affect drugs on a pharmacokinetic basis, analogous to the effects measured by using creatinine to assess renal or bilirubin to assess hepatic function. Thus, many pharmacogenetic prescribing recommendations can be based on underlying pharmacokinetic evidence."

rom Relling and Veenstra, *"Implementation of Pharmacogenomics: Evidence Needs"* a discussion paper from the Institute of Medicine of the National Academies, published Feb. 26, 2015 by the National Academy of Sciences

Prominent Clinical Studies in Pharmacogenetics

Objectives:

Multiple studies compared medication management guided by pharmacogenetic testing to trial-and-error (treatment as usual) in patients with depression

Outcomes:

Prescribing guided by PGx testing demonstrated a statically significant improvement in patient outcomes by:

(1)Reducing depression symptoms[1]
(2)Decreasing time to symptom relief[2]
(3)Increasing patient satisfaction with their medication[3]

An additional study by the same group also proved that healthcare costs decreased by $5,188 on average per patient when prescribed genetically optimal medications[4]

1 Hall-Flavin DK, Winner, JG, Allen JD, Jordan JJ, Nesheim RS, Snyder KA, Drews MS, Eisterhold LL, Biernacka JM, Mrazek DA. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012;2:e 172.
2 Hall-Flavin DK, Winner JG, Allen JD, Carhart JM, Proctor B, Snyder KA, Drews MS, Eisterhold LL, Geske J, Mrazek DA. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenetics and Genomics. 2013;23(10):535-548.
3 Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM. A prospective, randomized double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discovery Med. 2013;16(89): 219-227.
4 Winner JG, Allen JD, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry. 2013;3:e300. doi:10. 1038/tp.2013.2.

When is PGx testing currently warranted?

- Disease states for which current standard of care often results in poor outcomes (e.g. adverse effects, lack of efficacy)
- Disease states for which treatment failures can have serious consequences (e.g. schizophrenia, anticoagulant prophylaxis, cancer)
- Drugs and drug classes that have high failure rates (e.g. antidepressants, antipsychotics)
- Drugs and drug classes that have narrow therapeutic windows and associated serious adverse events (e.g. opiates, cancer meds, warfarin, clopidogrel)

When is PGx testing currently warranted? *(cont.)*

- Patients on multiple medications
  - Underlying genetic-derived alterations of metabolic capacity can exacerbate drug-drug interactions and associated adverse effects
- Patients that have impaired excretion ability (e.g. renal impairment)
- Patients exhibiting inadequate therapeutic response or tolerability issues with standard doses of current medication

Realizing the Promise of PGx in Clinical Practice

- The greatest utility of PGx is in *prospective drug selection*
- The more relevant genes tested, the more information the physician has to make an optimal drug selection
  - ***One gene, one drug doesn't provide adequate guidance***
  - ***Combinatorial PGx enables the clinical integration of multiple genes into drug selection***
- Education of physicians on how to use PGx information
  - Most physicians are unfamiliar with PGx, but do understand the general principles of pharmacology