# Precision Medicine in Toxicology

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**KEYWORDS**

• Precision medicine • Pharmacogenetics • Pharmacogenomics • Toxicology
• Metabolism • Cytochrome

**KEY POINTS**

- Precision medicine applies primarily to pharmacokinetics in toxicology and relates to basic hepatic metabolism, the common substrates, inducers and inhibitors of cytochrome P450 along with genetic variants which affect enzyme function.
- Mastering hepatic metabolism through an understanding of the genetics behind Phase I, or oxidation/reduction and some Phase II, or conjugation, enhances the scientific and clinical application of common drug toxicology.
- Evidence based research and clinical correlations conclude that knowledge of inducers and inhibitors, in conjunction with genetic variations, are integral components for applied precision medicine in toxicology.

## INTRODUCTION

Precision medicine, also referred to as *personalized medicine,* is a recently assigned banner to depict the amalgam of the disciplines of pharmacogenetics and pharmacogenomics (PGx) as they apply to clinical medicine. The US Food and Drug Administration (FDA) has amassed a large almost decade old Web site of data under its Drugs tab (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/default.htm) devoted to this topic, primarily as it relates to adverse drug reactions. This review is principally devoted to the metabolism of substances commonly measured by toxicology testing that may be used to avoid misuse or abuse and result in deleterious clinical effects. These include the opioids, opiates, sedatives/hypnotics (benzodiazepines and others), cannabinoids, cocaine, and psychostimulants. This article reviews (1) the phase I, or P450 direct enzyme-mediated oxidative/reduction pathway and (2) the phase II, or conjugation pathway. Next, this

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article reviews single nucleotide polymorphisms (SNPs), or isolated regions of the DNA, in various regions including the promoter, and their activity, including terminology and known metabolic pathways' effects on substrates. Subsequently, this report addresses the inducers and inhibitors of the enzymes affecting the phase I metabolism, which can, in certain respects, play a more significant role than the SNPs.

A clinical summary supports the minimal role PGx variant SNP testing has on opioid pharmacodynamics and the significant role it carries in psychiatric toxicology and the knowledge of inhibitor/inducer PGx required for appropriate pain management and addiction toxicology today.

Phase I metabolism covers the cytochrome P450 (CYP) enzymes that include oxidative, reduction and hydrolysis of drugs into a more polar metabolite, usually active, by adding –OH, –SH or $–NH_2$ moieties. A common example would be *O or N*-demethylation of oxycodone by CYP2D6 and CYP3A4, respectively. These are catalyzed by the common CYP hepatic enzymes that can be affected by SNPs. However, not every enzyme may be affected by a SNP, and not every medication or drug may be affected, especially if it is metabolized by several enzyme pathways. The more common CYP enzymes affecting metabolism for purposes of substances tested by toxicology for this series are as follows: CYP2C19, CYP2D6, CYP2C9, CYP3A4 and 3A5, CYP1A2, and CYP2B6. Although there are others, these are the primary ones of study for our purpose. **Fig. 1** shows the most common CYP enzymes, and **Fig. 2** shows the number of drugs metabolized per CYP enzyme.

Phase II metabolism represents a subsequent conjugation of either parent drug or metabolite that has already undergone phase I metabolism into an even more polar, hydrophilic moiety. The new structure usually undergoes renal excretion. This conjugation is done by glucuronidation, sulfation, or hydroxylation. One of the common enzymes is UDP-glucuronosyltransferase (UGT), which exists in multiple subclasses, including a major one affecting opioid toxicology, UGT2B7*2, and its metabolism of morphine,[1] which is reviewed toward the end of this article.

Pharmacokinetics is the primary concern of this review and deals with the absorption, metabolism, distribution, and excretion of a drug. Toxicology testing depends on all these factors, as we measure analytes in the plasma, oral fluid, urine, sweat, hair, or other matrices. PGx affects the metabolism of the compound either through an SNP variation or because another drug either induced or inhibited the same enzyme,

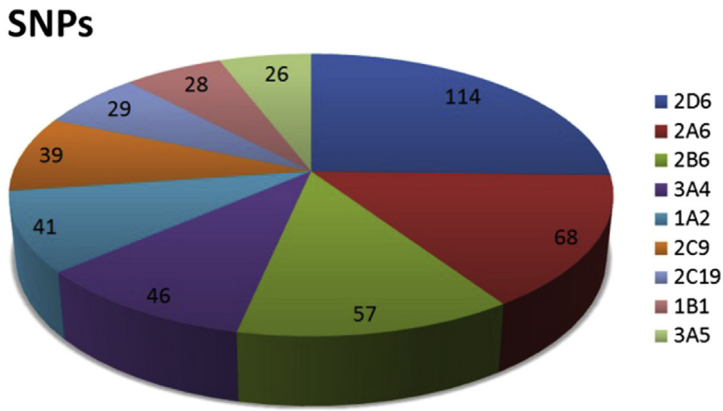


**Fig. 1.** SNPs in CYP. (*From* Preissner SC, Hoffmann MF, Preissner R, et al. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS One 2013;8(12):e82562; with permission.)