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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Clin Lab Med 36 (2016) 693–707
http://dx.doi.org/10.1016/j.cll.2016.07.010 **labmed.theclinics.com**

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,

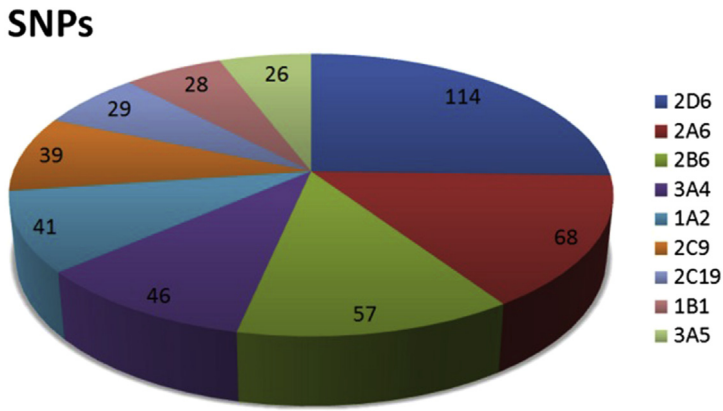

Fig. 1. SNPs in CYP. (*From* Preissner SC, Hoffmann MF, Preissner R, et al. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS One 2013;8(12):e82562; with permission.)

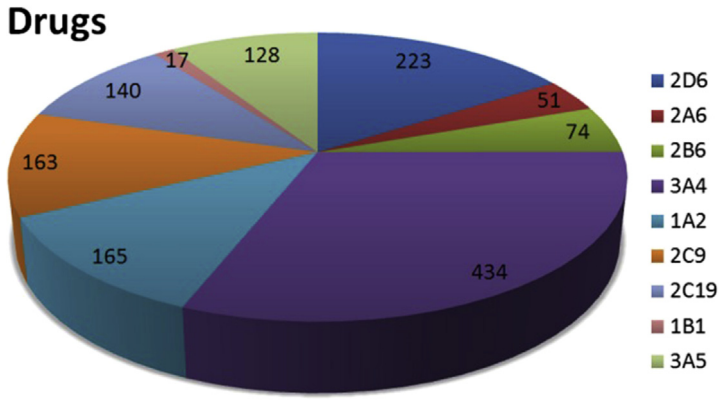

Fig. 2. Number of drugs metabolized per SNP. (*From* Preissner SC, Hoffmann MF, Preissner R, et al. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS One 2013;8(12):e82562; with permission.)

thus, affecting its metabolism. This is the core aspect of how PGx is integral to our study of toxicology.

Pharmacodynamics, on the other hand, is the affect the drug will have on the body, often with a focus at the organ or tissue site, and can be subject to drug concentration levels. Although pharmacokinetics also has a role at the tissue site, pharmacodynamics primarily focuses on the effect in relation to receptor binding, effect on the cell, secondary messenger, or positive/negative feedback inhibition/induction of receptors after drug/receptor binding. Thus, another separate topic is PGx and how SNPs affect coding for central nervous system receptors such as the μ-opioid and catechol-*O*-methyltransferase receptors, which is beyond the scope of general toxicology testing.

Table 1 is a chart containing the most common substrates categorized by the CYP enzymes. The most important aspect the reader must understand is this subject matter is continuously changing and is not an exact science. **Table 2** depicts the common inducers, whereas **Table 3** depicts inhibitors of select enzymes.

It is important to understand the interaction between the inducers, inhibitors, and the substrate before any SNP variations. This on its own is analogous to understanding the basics of microbiology before learning which antibiotic one would use to treat an infection and whether it should attack the cell membrane, cell wall, or DNA or if its action is bacteriostatic or bacteriocidal. PGx is similar, and the knowledge of the enzyme or substrate should be mastered before assessing genetic variations. In fact, most drugs are metabolized through CYP3A4 and 3A5, yet only 4 substrates are clinically affected by genetic variation (highlighted in **Table 1**) that we know of at this time.[2]

With respect to SNP variants, the phenotypic enzymatic activities that result from such are classified into 4 categories of metabolism based upon kinetics: rapid, normal, intermediate, or poor. The authors prefer to use this direct, more clinically applicable nomenclature because the current system tends to be redundant, less cohesive, and, at times, confusing. What the authors refer to as *rapid* is currently known as *ultrarapid*, whereas our reference to *normal* is currently labeled *extensive-normal*. Intermediate metabolizers vary, which makes it difficult for physicians to apply the clinical science. However, the authors refer the reader at this time to focus on the substrates, inducers, and inhibitors and the free link: Medscape's Drug Interaction checker (http://reference.medscape.com/drug-interactionchecker). Any health care professional may use the drug-interaction portion, which is the only site that currently provides PGx

Table 1
Phase I common substrates

CYP2C19		CYP2D6		CYP2C9	
Psychotropics	Proton pump	ADHD	Opioids	Hypoglycemics	NSAIDS
Amitriptyline (1°)	Omeprazole	Modafinil	*Hydrocodone*	Glipizide	Celecoxib
Clomipramine (2°)	Lansoprazole	*Amphetamine*	*Codeine (P)*	Glimepiride	Diclofenac
Imipramine	Pantoprazole	Atomoxetine	*Tramadol*	Tolbutamide	Meloxicam
Citalopram	Cardiovascular	*Methylphenidate*	*Oxycodone (2°)*	Glyburide	Naproxen
Escitalopram	Clopidogrel (P)	Psychotropics	β blockers	Anti-coagulants	Ibuprofen
Sertraline	Prasugrel	Aripiprazole	Carvedilol	S-warfarin	Indomethacin
Anticonvulsant	Other	Risperidone	Metoprolol	Diuretic	Anticonvulsant
Phenobarbital (<25%)	*Carisoprodol*	Haloperidol	Propranolol	Torsemide	Valproic acid
Diazepam	Proguanil/(P)	Thioridazine	Antiarrythmics	ARBs	Phenytoin (1°)
Clobazam (2°)	Atovaquone	Clozipine	Flecainide	Losartan (P)	Other
Phenytoin (2°)	Nelfinavir	Olanzapine (2°)	Propafenone	Irbesartan	Sildenafil
Oncology	Tolbutamide	Donepezil	Quinidine	Statins	Hypnotics
Cyclophosphamide (P)		Tricyclics	Oncology	Fluvastatin	*Zolpidem (2°)*
		Nortriptyline	Tamoxifen (P)	Rosuvastatin	
		Clomipramine (1°)	Doxorubicin		
		Desipramine	SNRIs		
		SSRIs	Duloxetine		
		Fluoxetine (1°)	Venlafaxine		
		Paroxetine (1°)			
		Sertraline			

CYP3A4/5		CYP1A2		CYP2B6
Psychotropics	Statins	Psychotropics	Ardiovascular	Opioids
Carbamazepine	**Atorvastatin**	Clomipramine	Mexiletine	*Methadone*
Aripiprazole	**Lovastatin**	Imipramine	Propranolol (2°)	
Quetiapine	**Simvastatin**	Fluvoxamine	Oncology	
Mirtazapine	Sex hormones	Antipsychotics	Erlotinib (2°)	
Trazodone	Finasteride	Haloperidol	Other	
Sertraline	Estradiol	Clozipine	Theophylline	
Oncology	Progesterone	Olanzapine	Caffeine	
Vincristine	Ethinylestradiol	Muscle relaxant	Zolmitriptan	
Vinblastine	Testosterone	Cyclobenzaprine	Ondansetron (2°)	
Imatinib	HIV	Tizanidine	Acetaminophen	
Erlotinib (1°)	Amprenavir	Hypnotics		
Doxorubicin	Efavirenz	*Zolpidem (2°)*		
Cardiovascular	Atripla			
Amlodipine	Atazanavir			
Diltiazem	Ritonavir			
Nifedipine	Opioids			
Verapamil	*Buprenorphine*			
Amiodarone	*Fentanyl*			
Other	*Methadone*			
Tacrolimus	*Oxycodone (1°)*			
Cyclosporin	Tranquilizers			
Hydrocortisone	*Alprazolam*			
Dexamethasone	*Midazolam*			
Ondansetron (2°)	Hypnotics			
Donepezil	*Zolpidem (1°)*			
Erythromycin	*Eszopliclone*			

Bold, affected by SNP in 3A4; italic, toxicology tested.

Abbreviations: (1°), primary metabolic pathway; (2°), secondary metabolic pathway; ADHD, attention deficit hyperactivity disorder; ARBs, angiotensin receptor blockers; HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

Table 2
Inducers

2C19	2D6	2C9	3A4	1A2	2B6
Carbamazepine	None known	Carbamazepine	Carbamazepine	Carbamazepine	Carbamazepine
Norethindrone		Phenytoin	Dexamethasone	Omeprazole	Phenytoin
Prednisone		Phenobarbitol	Glucocorticoids	Phenytoin	Phenobarbitol
Rifampicin		Rifampicin	Nafcillin	Phenobarbitol	Rifampicin
St John's Wort		St John's Wort	Nelfinavir	Polycyclic –aromatic/ hydrocarbons	St John's Wort
			Oxycarbazepine		
			Phenytoin		
			Phenobarbitol	Rifampicin	
			Progesterone		
			St John's Wort		
			Topiramate		

inducer/inhibitor clinical PGx information. This information should be interrogated before prescribing medications.

There are several databases that include SNPs, variants, the substrates, and quoted literature with the best aims at their functional variants (**Box 1**). However, there are discrepancies within the literature, in demographics, and over time as new publications arise. Thus, the viewer should not take any set publication as the gold standard by any means. The authors encourage the reader to search the listed databases and carefully review any publications including the type of study (isolated SNPs or genomewide association study using thousands of patients with a set marker and known trait) and inclusion of demographics.

CYP2C19 primarily only affects the metabolism of diazepam and the muscle relaxer carisoprodol as highlighted in **Table 1**. However, the current literature provides some laboratory evidence of the interaction of substrates and inhibitors/inducers, but there are not many significant studies showing clinical relevance in toxicology at this time.[3–5] It is suggested to check for interactions prior to prescribing these medications.

CYP2D6

Codeine (C) is the only formal opioid prodrug that has no analgesic effect until activated by the liver. The primary activation is phase I; (1) *O*-demethylation via

Table 3
Inhibitors

2C19	2D6	2C9	3A4/5	1A2	2B6
Fluoxetine	Bupropion	Fluconazole	Indinavir	Fluoroquinolones	Thiotepa
Fluvoxamine	Fluoxetine	Amiodarone	Nelfinavir	Fluvoxamine	Ticlopidine
Ketoconazole	Paroxetine	Isoniazid	Ritonavir	Ticlopidine	
Lansoprazole	Quinidine		Clarithromycin		
Omeprazole	Duloxetine		Erythromycin		
Ticlopidine	Chlorpheniramine		Itraconazole		
	Clomipramine		Ketoconazole		
	Doxepin		Nefazodone		
	Haloperidol		Grapefruit Juice		
	Methadone		Verapamil		
	Mibefradil		Diltiazem		
	Ritonavir		Amiodarone		
			Fluvoxamine		

Box 1
Databases of single nucleotide polymorphisms

Human CYP allele: http://www.cypalleles.ki.se/

PharmGKB: http://www.pharmgkb.org/

dbSNP: http://www.ncbi.nlm.nih.gov/projects/SNP/

1000 Genomes Project: http://browser.1000genomes.org/index.html

SNPedia: http://www.snpedia.com/index.php/SNPedia

Gene Cards: http://www.genecards.org/index.shtml

CYP2D6 to morphine (M) and (2) *N*-demethylation via CYP3A4 to norC. A blood sample will contain M and its metabolites along with norC, whereas oral fluid will reveal C and norC.

Urine drug testing is based on CYP2D6 activity and includes genetic variants or P450 inducers and inhibitors as follows:

A rapid 2D6 variant (*1/*2) will activate C into M exceeding the standard dosing. This dosing resulted in overdose of children, leading several children's hospitals to remove codeine from their formularies and a general review published by the Clinical Pharmacogenetics Implementation Consortium in 2012, updated in 2014.[6,7] Overall, the rapid variant SNP resulted in excess formation of M in mothers breast milk leading to overdose of neonates, in post-tonsillectomy patients with or without sleep apnea,[8] and even in some cases in which only 1 allele carried the *2 variant (heterozygous),[7] leading the FDA to come out with extensive black box warnings about codeine in the pediatric, neonatal/breast feeding population, along with the Consortium as noted. Similarly, any potential 2D6 inducer could have the same effect, although at this time there are no known in vivo or in vitro inducers of CYP2D6.

Hydrocodone (HC) undergoes (1) *O*-demethylation via 2D6 into hydromorphone (HM) and (2) *N*-demethylation by 3A4/5 into minimally active norHC. HM also undergoes phase II metabolism by UGT into HM-3-G.[9]

In blood and oral analysis, the primary metabolite is parent HC followed by norHC and significantly less HM.[10] The benefit of oral analysis is the consistent presence of norHC with an HC/norHC ratio of 1:16, and minimal HM, which helps delineate the patient is taking HC rather than HM.[11] Urine analysis finds 26% HC eliminated within 72 hours, with results as follows: (1) HC 9% to 12%, (2) norHC 5% to 19%, (3) HM-3-G 2% to 4%, and (4) 6 α and β Hydrocol 1% to 3%.[12] The importance of norHC in urine, as in oral fluid, is to delineate the use of HC versus ingestion of HM, which is always present in its conjugated form.[13]

Despite the phase I CYP2D6 metabolism of HC, a review of the literature and the Consortium have not found inhibitors[14] or PGx variants in either poor or rapid metabolizers to affect toxicology results from a laboratory metric of clinical relevance.[7]

Oxycodone (OC) primary metabolism (~85%) is *N*-demethylation by CYP3A4/3A5 to noroxycodone (NOC), which has minimal analgesic activity and secondarily (~15%) is *O*-demethylation by CYP2D6 to oxymorphone (OM), which has more analgesic activity than its parent compound. NOC then converts into noroxymorphone (NOM) via CYP2D6. OM and NOM undergo phase II conjugation to OM-3-G.[15] Finally, OC, NOC, and OM undergo some keto-reduction to the 6 α and β metabolites.[12,15] In both blood and oral fluid, the primary analytes found in descending order are OC, NOC, and OM, with blood/oral ratios fairly uniform.[16] Of importance is that oral testing finds NOC in 80%–90% of specimens, helping discern patients taking OC and not

OM.[16] One experimental urine study reported 8% free OC with 23% free NOC then 10.4% conjugated OM, 8.6% conjugated NOM, and approximately 6% of various keto metabolites.[17] The authors, having experience with millions of human pain management specimens and review of evidence-based clinical research, support urine metabolites as primarily free OC, NOC with conjugated OM to a lesser extent based on genetic variability, and inducers/inhibitors of CYP2D6 and 3A4.[18] Clinically, the message is (1) free OC and NOC; (2) conjugated OM, which varies with metabolism; (3) less NOM only 39% conjugated; and (4) creatinine correction, where applicable, should be done for final levels.[19]

OC would require both a grapefruit diet (3A4 inhibition) and a CYP2D6 poor metabolizer (*3-*9 homozygous variant) or inhibitorlike paroxetine (see **Table 2**) to create complete metabolic inhibition to create toxic levels of OC. This would appear in the urine as minimal OC, no NOC or OM, and with elevated OC in the plasma. An actual small clinical study proved the above case by combining itraconazole, a potent 3A4 azole antifungal with paroxetine, a strong 2D6 inhibitor. The study found a minimal pharmacokinetic effect with 2D6 inhibition alone, although not statistically significant. However, the combined 3A4/2D6 inhibition was significant in both pharmacokinetic and pharmacodynamic effects from OC-reduced metabolism.[20]

The opposite, however, in which a rapid 2D6 variant could potentially increase OM production by urine drug testing, or clinically, any evidence-based increased risk has not been found in the literature to date. Thus, the Consortium has not included OC in its warning or risk, stating the data are conflicting and attributes any current analgesia side effects to the parent compound.[7]

OM is primarily metabolized through conjugation, which is phase II, or UGT into OM-3-glucuronide (OM-3-G) and some keto-reduction into the 6α/β-hydroxy-OM (6-HOM) with urine as follows: greater than 40% OM-3-G, less than 5% free and conjugated 6-HOM, and less than 5% parent OM.[12] In plasma, one finds a similar result with primarily OM-3-G at 90% greater levels than free OM.[15] Any precision medicine in toxicology would be based on urine drug toxicology (UDT) as described in that section in this review.

3A4

As briefly noted during the introduction, precision medicine in toxicology primarily affects most metabolism through inhibitors and inducers through the 3A4 enzyme; similarly, currently only the 3 common statins and tacrolimus are known to be affected by SNPs. Fentanyl, methadone, tramadol, buprenorphine and OC are some of the key opiates metabolized by this enzyme.[15]

2B6

Methadone is a complex opiate consisting of dual activity based on the racemic stereoisomers: the (R) or "l"-isomer provides μ-opioid agonist activity for nociceptive pain, whereas the (S) or "d"-isomer provides *N*-methyl, D-aspartate receptor antagonist activity for neuropathic pain. Primary metabolism is *N*-demethylation by 3A4, 2B6 (and to a minor extent by 2D6 and 2C19) into 2- ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). In the urine, we commonly measure 2:1 EDDP to methadone, with the ratio increasing directly with urine pH. In a large series by Pesce and colleagues,[21] in part because of its lipophilic nature, they found a lack of consistency with the ratio in chronic pain patients as the dose varied,[22] although they were unable to conclude with certainty the causal relationship. However, an earlier PGx study showed a definite pharmacokinetic variation with the 2B6*6 allele as a poor metabolizer affecting methadone.[23]

Overall, the study found the (S) enantiomer was affected, which is associated more often with prolonged QT interval and respiratory depression, although because medications were a covariable, it could not rule out potential inhibitors. More recently, Levran and colleagues[24] excluded any medication confounders and accounted for ABCB1, an SNP variant, for the efflux p-glycoprotein blood–brain barrier transport protein associated with higher methadone dose requirements by the same author in 2008. In this study, Levran and colleagues[24] not only agreed with the findings of earlier study but actually found evidence-based clinical support for lower methadone dosing by the 2B6*6 homozygous allele.[24] Although a more recent study briefly attempted to state its inability to corroborate Levran's findings, it had multiple covariables, lacked the same power, and was not focused on the same specific aims but rather was more broadly focused.[25] The 2B6 data support the prior data with a scientifically sound stepwise research protocol within a set demographic profile and is a step toward isolating clinically relevant variant effects of phase I metabolism on methadone dosing.

Buprenorphine (Bup) is primarily N-dealkylated to norBup by 3A4 and 2C8. Bup and norBup undergo glucuronidation by UGT into Bup-G and norBup-G, however, not by UGT2B7 but primarily by UGT1A3.[26] In terms of 3A4, the important PGx for toxicology remains inducers and inhibitors. The most important aspects for this publication include use of the drug interaction tool. At the time of print, the authors are not aware of any EMR/EHR having PGx logic built into their system. Briefly, in pain management, it is gradually becoming more prevalent for multidisciplinary groups to have one or more physicians with a Bup "Data 2000" waiver, to prescribe Bup for opioid dependency. Otherwise, a transdermal patch using lower doses of Bup exists, which requires knowledge of precision medicine in toxicology.

The most common toxicology concern is false-negative findings in presumptive testing for Bup. Because even American Society of Addiction Medicine–certified physicians surveyed answered many questions incorrectly regarding immunoassay testing,[27] it can be inferred that most physicians would likely miss the approximately 20% to 25% false-negative rate from the average point-of-care on-site testing device used in the physician's office today. The reason for this is that Bup is quickly metabolized into the nor-form[28] then conjugated into the glucuronide format. In addition, many pain and even primary care patients will be on inducers (see **Table 2**) including carbamazepine, topiramate, glucocorticoids, and herbal supplements.

Patients in addiction medicine who may be simultaneously undergoing detoxification for benzodiazepine dependency along with opioid/opiates may utilize phenobarbital and Bup, respectively. If the phenobarbital is extended for a prolonged taper, it may induce CYP enzymes, 3A4, and 2C8, potentially reducing the Bup level, although no formal clinical studies have been done to support this. More common, however, is the opposite situation, in which inhibitors of 3A4 can lead to elevated doses of norBup. This situation occurs in comorbid diseases such as human immunodeficiency virus treatment or fungal infections. Thus, it is important to use the drug interaction tool on Medscape's site as noted.

At the time of this writing, there are both FDA approval of a new subcutaneous long-acting 8-mg Bup implant and approval of phase III clinical trials of a 28-day Bup subcutaneous injection. The injection has been published in a few pharmacokinetic studies, with data supporting steady levels achieving at least 70% receptor saturation, although PGx inducer/inhibitor data are pending.[29]

URINE DRUG TOXICOLOGY

Primary metabolism of morphine (M) is phase II glucuronide (G) conjugation via UGT using several variations of the enzyme to M-6-G (active), M-3-G (inactive), and other metabolites: M-3,6-G, norM (via CYP3A4 and CYP2C8), which are conjugated to norM-3-G and norM-6-G. Similarly, HM is primarily metabolized by UGT at the 3 position to HM-3-G, and some 6-keto-reductase into 6α and 6β hydromorphone as noted in prior discussion. Although one opioid review mentions HM-6-G,[30] which is a minimal amount verified by the original article,[15] conjugation into any 6-moeity is not supported because of the presence of a ketone at the 6 position,[31] which is the key differentiation between M (hydroxyl at 6) and HM. Blood concentration finds HM-3-G approximately 25 times the concentration of the parent HM, whereas oral fluid is highly variable and inconsistent with significantly lower required thresholds.[11]

Most data unfortunately are from HC studies, and a paucity of HM metabolism data in oral fluid exist at the date of this writing. Urine is at least 35% conjugated to HM-3-G and 6% free HM and the remainder as H-3-sulfate, H-3-glucoside, and the 6 keto forms, while chronic pain patients may find primarily HM-3-G without free HM.[12]

In renal failure, both M and HM, both conjugated into 3-glucuronide, can build up to potentially neurotoxic levels. One must take caution with M and HM in renally compromised patients, as M-3-G and HM-3-G levels, which lead to neuro-excitatory toxic responses, can be more common in those individuals.[32,33]

Despite all the metabolic findings, and one commercial laboratory offering PGx testing for UGT2B7 genetic SNP, aside from pharmacokinetic urine testing,[1] we were only able to find one evidence-based clinical study in which pharmacodynamics have been affected by UGT from PGx in advanced cancer patients with renal dysfunction,[34] in which, as noted above, M-3-G and HM-3-G may exhibit neurotoxic effects.

In addition to the common functional polymorphisms of the *p450* genes listed above (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and 3A5), there are additional variations that differ among populations (**Table 4**). For example, the CYP 2D6 variant 6*10 corresponds to decreased enzymatic activity and is found most common among Asians (50%) when compared with African and white populations, thus, warranting consideration of modifying the dosing of opiates such as C. Furthermore, the UDT results of such a patient prescribed C may only detect the presence of C and not show the characteristic metabolites of HC and M. This finding is in contrast to the 2D6 variant (*1/*2), representing a gene duplication, translating into increased enzymatic activity (ultrametabolizer) with respect to C to HC and M conversion. Such a UDT result may have no presence of C rather only HC, M, and HM, posing the inappropriate suspicion of diversion of C and surreptitious administration of M.

In summary, despite hundreds of publications over the past two decades rapidly expanding on precision medicine, there remains a pressing need for greater pronounced support towards the utility and application of genetic testing in the discipline of clinical toxicology. One can observe a similar pattern in its educational limitations.[35] Specifically, the core knowledge of precision medicine is tantamount to clinical decision making for toxicology and prescribing, especially at the time of this article based on the continued increase in combination opioid/opiate with benzodiazepine death rates.[36–38] It is imperative that precision medicine be part of the basic educational curriculum, specifically, key enzymes and their substrates, inducers, and inhibitors before being eligible to prescribe, and mandatory for any certification for a medical review officer.

Table 4
Common naturally occurring functional polymorphisms in the major cytochrome *P450* genes: Allele frequency and functional effects for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and 3A5

		Allele Frequency (%)[a]			
Common Allelic Variants	**Polymorphism/Substitution**	**Ca**	**As**	**Af**	**Functional Effect[b]**
CYP1A2					
CYP1A2[a]1C	−3860G> A	—	—	—	↓Inducibility
CYP1A2[a]1F	−163C> A	33	68	—	↑Inducibility
CYP1A2[a]1K	Haplotype (−63C> A, −739T> G, −729C> T)	0.5	—	—	↓Inducibility ↓Activity
CYP2B6					
CYP2B6[a]4	K262R	5	—	—	↑Activity
CYP2B6[a]5	R487C	11–14	1	—	↓Expression
CYP2B6[a]6	Q172H; K262R	16–26	16	—	↑Activity
CYP2B6[a]7	Q172H; K262R; R487C	13	0	—	↑Activity
CYP2C9					
CYP2C9[a]2	R144C	13–22	0	3	↓Activity
CYP2C9[a]3	I359L	3–16	3	1.3	↓Activity
CYP2C9[a]5	D360E	0	2	0	↓Activity
CYP2C19					
CYP2C19[a]2	Splicing defect; I331V	15	30	17	Abolished activity
CYP2C19[a]3	W212X; I331V	0.04	5	0.4	Abolished activity
CYP2C19[a]17	I331V	18	4	—	↑Transcription
CYP2D6					
CYP2D6[a]3	Frameshift	1–2	<1	—	Abolished activity (PM)

(*continued on next page*)

Table 4
(*continued*)

Common Allelic Variants	Polymorphism/Substitution	Allele Frequency (%)[a] Ca	As	Af	Functional Effect[b]
CYP2D6[a]4	Splicing defect	20–25	1	6–7	Abolished activity (PM)
CYP2D6[a]5	Gene deletion	4–6	4–6	4–6	Abolished activity (PM)
CYP2D6[a]10	P34S; S486T	<2	50	3–9	↓Activity (IM)
CYP2D6[a]17	T107I; R296C; S486T	<1	—	20–34	↓Activity (IM)
CYP2D6[a]41	R296C; splicing defect; S486T	1.3	2	5.8	↓Activity (IM)
CYP2D6[a]1 × N, N ≥2	Gene duplication	—	—	—	↑Activity (UM)
CYP2D6[a]2 × N, N ≥2	Gene duplication	—	—	—	↑Activity (UM)
CYP3A4					
CYP3A4[a]1B	5′ flanking region	2–9	0	35–67	Altered expression
CYP3A4[a]2	S222P	2.7–4.5	0	0	Substrate-dependent altered activity
CYP3A4[a]3	M445T	1.1	—	—	↓Activity
CYP3A4[a]17	F189S	2.1	—	—	↓Activity
CYP3A4[a]18	L293P	0	—	1	↑Activity
CYP3A5					
CYP3A5[a]3	Splicing defect	90	75	50	Abolished activity
CYP3A5[a]6	Splicing defect	0	0	7.5	Severely ↓activity
CYP3A5[a]7	346 frameshift	0	0	8	Severely ↓activity

↑, indicates increased; ↓, indicates decreased.

Abbreviations: Af, African; As, Asian; Ca, Caucasian (white); IM, intermediate metabolizer; PM, poor metabolizer; UM, ultra-rapid metabolizer.

[a] Allele frequency *data from* Refs.[39–45]

[b] Functional effect data are obtained from the Human Cytochrome P450 (CYP) Allele Nomenclature Committee website (http://www.cypalleles.ki.se/).

From Li J, Bluth MH. Pharmacogenomics and personalized medicine. In: McPherson RA, Pincus MR, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier: 2017; p. 1409–10; with permission.

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