Pharmacogenomics of adverse drug reactions: implementing personalized medicine

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Pharmacogenomics aims to investigate the genetic basis of inter-individual differences in drug responses, such as efficacy, dose requirements and adverse events. Research in pharmacogenomics has grown over the past decade, evolving from a candidate-gene approach to genome-wide association studies (GWASs). Genetic variants in genes coding for drug metabolism, drug transport and more recently human-leukocyte antigens (HLAs) have been linked to inter-individual differences in the risk of adverse drug reactions (ADRs). The tight association of specific HLA alleles with Stevens–Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity syndrome and drug-induced liver injury underscore the importance of HLA in the pathogenesis of these idiosyncratic drug hypersensitivity reactions. However, as with the search for the genetic basis for common diseases, pharmacogenomic research, including GWAS, has so far been a disappointment in discovering major gene variants responsible for the efficacy of drugs used to treat common diseases. This review focuses on the pharmacogenomics of ADRs, the underlying mechanisms and the potential use of genomic biomarkers in clinical practice for dose adjustment and the avoidance of drug toxicity. We also discuss obstacles to the implementation of pharmacogenomics and the direction of future translational research.

INTRODUCTION

Pharmacogenetics is an area of research that addresses the genetically determined variation in how individuals respond to specific drugs, in terms of differences in dose requirement, efficacy and the risk of adverse drug reactions (ADRs). Pharmacogenomics, in addition to addressing variability in DNA, is also concerned with gene expression profiling. In line with the increasing use of functional genomics, pharmacogenetics and pharmacogenomics have been used interchangeably (1,2).

Genetically determined variations affecting inter-individual responses to drugs can be grouped, in a broad sense, into germ-line genetic variants and somatic mutations as occur in tumor tissues. Germ-line genetic variants—mainly in genes encoding drug-metabolizing enzymes, drug transporters, drug targets and human-leukocyte antigen (HLA)—are reported to be responsible for many of the observed inter-individual differences in drug efficacy, the risk for ADRs, or both. The different somatic mutations in cancer have allowed the development of new anti-cancer agents aimed at treating patients whose cancer carries the targeted mutations, so-called targeted therapies. The pharmacogenetics of targeted anti-cancer therapy has been extensively reviewed recently (3).

Since the completion of the Human Genome Project, pharmacogenomics has been touted as the field with greatest clinical potential to radically improve patient care through the implementation of personalized medicine. The terms personalized medicine and pharmacogenomics are often used together, as both aim to maximize therapeutic benefit and avoid ADRs. In addition to improving patient care, pharmacogenetics-based personalized approaches have the potential to save money by improving the cost-effectiveness of health care delivery. There are many commonly prescribed drugs that fail to work for some patients. For example, many patients with high cholesterol fail to respond to statins, and many hypertensive patients do not respond to beta-blockers (4). The ability to prescribe drugs only to individuals identified as responders would significantly reduce wasted medical costs.
Furthermore, by not prescribing drugs to those genetically at risk for ADRs, the costs associated with caring for patients with untoward drug toxicities could be eliminated.

ADRs are a major clinical problem that accounts for 6.7% of all hospitalizations and ranks between the fourth and sixth most common cause of inpatient death in western countries, posing challenges to the healthcare system in terms of both patient wellbeing and medical costs (5,6). ADRs are also a major burden for the pharmaceutical industry. From 1990 to 2012, there have been 43 drugs withdraw from the market due to severe ADRs (7). ADRs are often classified into two groups. Type A reactions are predictable by the mode of pharmacological mechanisms and are often dose-dependent. In contrast, type B reactions, which account for ~15% of ADRs, are historically referred to as unpredictable, dose-independent, idiosyncratic reactions (8,9).

Recent pharmacogenomic studies that have evolved from a candidate-gene approach to the genome-wide association study (GWAS) have greatly advanced the discovery of genes associated with inter-individual differences in drug response, especially genes that predispose individuals to ADRs and, to a lesser extent, genes responsible for drug efficacy. These studies also have advanced our understanding of the underlying mechanisms of ADRs and drug efficacy. Based on these discoveries, the Food and Drug Administration (FDA) has relabeled over 100 approved drugs to include genetic information. A list of valid genomic biomarkers for clinical guidance can be found on the FDA website 'Table of Pharmacogenomic Biomarkers in Drug labels' (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). Here, we summarize recent important findings that advance our knowledge of the genetic contribution to inter-individual variability in drug efficacy and ADRs. We focus on the pharmacogenomics of ADRs, especially on genes coding for drug metabolizing enzymes, drug transporters and HLAs, as well as the potential use of these genomic biomarkers in clinical practice for dose adjustment and for preventing drug toxicity. We also discuss key challenges for the implementation of pharmacogenomics and the direction for future translational research.

**DRUG-METABOLIZING ENZYMES**

Before genome-wide technologies were available, early pharmacogenomic studies relied on candidate-gene approaches; thus, genes affecting drug metabolism and detoxification were obvious candidates. As a result, numerous metabolic biomarkers have been identified (Fig. 1). As of July 2012, 67 drugs with valid metabolic biomarkers for dosage adjustment have been listed in the Table of Pharmacogenomic Biomarkers in Drug Labels; of these, 87% have genetic tests approved or cleared by the FDA. However, for most there are no guidelines to direct the clinical use of this genetic information (10). Among these drugs, ~25% are metabolized by cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) and their rates of metabolism can vary >100-fold depending on allelic variability in different ethnic groups (11). Seven percent of Western Europeans are CYP2D6 poor metabolizers who require lower prescribing doses, whereas an estimated 20 million individuals are ultra-rapid metabolizers who experience no response to standard treatment (12).

For example, one meta-analysis demonstrated a reduction in ~50% in the average dose for most tricyclic antidepressants in patients who are CYP2D6 poor metabolizers (CYP2D6*3/3) (13). In the case of codeine, which requires CYP2D6 for bioactivation and conversion to morphine, poor metabolizers experience little therapeutic effect, whereas morphine conversion is increased in ultra-rapid metabolizers (CYP2D6*16*1 and *1/*2), which results in severe or life threatening toxic side effects following standard doses (14).

Clopidogrel is a thienopyridine antiplatelet drug used to prevent recurrent thrombosis in patients with myocardial infarction and percutaneous coronary intervention with stent implantation. However, responses to clopidogrel vary widely, both inter-individually and inter-ethnically. Several genes have been investigated, but variations in the CYP2C19 gene appear to be the most consistent genetic determinants for differences in response to clopidogrel treatment. Patients who carry the reduced function alleles CYP2C19*2 are at higher risk for major cardiovascular events compared with non-carriers (15).

Another important drug-metabolizing enzyme is thiopurine S-methyltransferase (TPMT), which metabolizes 6-mercaptopurine and azathioprine (16). TPMT-deficient patients carrying the non-functional alleles TPMT*2, TPMT*3A and TPMT*3C are at high risk of severe hematologic toxicity, and homozygous-TPMT-deficient patients require substantial dose reductions. Reliable TPMT genotyping tests with high sensitivity (90%) and specificity (99%) are commercially available and allow proper dose adjustment (17). Similarly, patients with a polymorphism that results in decreased expression of uridine diphospho glucuronosyltransferase 1A1 (UGT1A1) are at a risk for neutropenia following the initiation of irinotecan treatment (18). The homozygous and heterozygous genotypes of UGT1A1*28 present the most significant risk, and a reduced initial dose of irinotecan is suggested for these patients.

In addition to the metabolizing enzymes that affect drug pharmacokinetics, there are genetic variants that influence drug pharmacodynamics. One successful example of a drug for which both pharmacokinetic and pharmacodynamic biomarkers are used for individualized dose prediction is warfarin. Warfarin is the most commonly prescribed anticoagulant.
Despite its clinical effectiveness, warfarin has a narrow therapeutic index and shows large inter-individual variability (19). Warfarin overdose is often associated with major bleeding complications (20). Both candidate-gene and GWA studies have confirmed that dose requirement of warfarin is primarily determined by CYP2C9, coding for the enzyme that metabolizes the potent S-isomer of warfarin, and vitamin K epoxide reductase enzyme complex subunit 1 (VKORC1), encoding the warfarin target protein (21–24). It is now recognized that compared with wild-type CYP2C9*1, the non-synonymous polymorphisms CYP2C9*2 and *3 coding variants with reduced enzymatic activity and prolonged warfarin half-life have a significant clinical influence on warfarin sensitivity and severe bleeding events. On the other hand, the non-coding polymorphism of VKORC1 at the promoter region, a guanine to adenine substitution (G→A) at position −1639, decreases expression of the gene and the availability of vitamin K. Recently, a large collaborative study with multi-ethnic groups, the International Warfarin Pharmacogenetics Consortium, established a warfarin dosing algorithm that incorporates the clinical factors and genotypes of CYP2C9 and VKORC1 to more accurately predict warfarin doses (25,26). A large prospective randomized multicenter double-blinded study comparing the genotype guided dosing of warfarin with other approaches is ongoing (http://clinicaltrials.gov/ct2/show/NCT01124058).

ENZYMES IN INBORN ERRORS OF METABOLISM

Enzymes affecting drug metabolism can also be found in two classical inborn errors of metabolism, dihydropyrimidine dehydrogenase (DPD) deficiency and glucose-6-phosphate dehydrogenase (G6PD) deficiency. DPD is the rate-limiting enzyme involved in the catabolism of thymidine and uracil. It is also the main enzyme involved in the degradation of structurally related compounds like 5-fluorouracil (5-FU) or its prodrug capecitabine, two widely used anticancer drugs. A decrease in DPD activity can result in toxicity to 5-FU and capecitabine; therefore, these drugs should not be used in DPD-deficient patients (27,28). G6PD deficiency is characterized by abnormally low levels of G6PD, a metabolic enzyme involved in the pentose phosphate pathway. The most notable symptom of G6PD deficiency is hemolytic anemia caused by ingestion of drugs, food and other trigger substances that cause oxidative stress. Of the many drugs known to cause hemolytic anemia in patients with G6PD deficiency, chloroquine, dapsone and rasburicase are the three for which the FDA recommends screening for G6PD deficiency before beginning treatment. Rasburicase is a recombinant uricase recently approved for the management of high uric acid levels associated with chemotherapy for certain type of cancer. Patients deficient in G6PD have an impaired ability to reduce hydrogen peroxide formed as a major byproduct of the rasburicase-catalyzed oxidation of uric acid to allantoin.

DRUG TRANSPORTERS

Drug transporters represent another class of genes affecting drug pharmacokinetics. These are mainly classified into two major superfamilies: the efflux transporter ATP-binding cassette (ABC) and the influx transporter solute carrier (SLC) transporters (29). For instance, genetic variants of ABCB1, encoding p-glycoprotein (Pgp) associated with multiple drug resistance, may account for a difference of 25% in the renal clearance of cyclosporine (30). In fact, the functional polymorphism ABCB1 34355TT is strongly associated with cyclosporine-induced nephrotoxicity (31). Similarly, subjects with Q141K variant of ABCG2, which codes for breast cancer resistance protein, are at risk of gefitinib-induced diarrhea (32).

Statins, or HMG-CoA reductase inhibitors, are one of the most commonly prescribed classes of drug for reducing cholesterol levels and preventing cardiovascular events (33). However, patients treated with a statin are at risk for muscle complications, including myopathy or fatal rhabdomyolysis. A recent GWAS study identified a strong association between simvastatin-induced myopathy and the SLC organic anion transporter family member 1B1 (SLCO1B1), which encodes the organic anion-transporting polypeptide (OATP1B1). Homozygous CC of the SNP rs4363657 accounts for an 18% cumulative risk of myopathy (34). In addition, clinical studies have shown that the C allele of rs4149056 SLCO1B1 is also associated with higher blood statin concentrations and increased risk of myopathy (35). However, the association of rs4149056 in SLCO1B1 with simvastatin-induced myopathy is not highly predictive for other statins, suggesting that this association may not be a class effect (36,37). Consequently, genotyping of SLCO1B1 may be a clinically useful tool for personalized dose regulation in preventing simvastatin-induced myopathy (38).

HUMAN LEUKOCYTE ANTIGENS

The HLA system has been a major focus for Type B ADRs, i.e. those associated with drug hypersensitivity reactions, including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypersensitivity syndrome (HSS) and drug-induced liver injury. Ample evidence supports the view that drug hypersensitivity is mediated by adaptive immunity, which involves MHC-restricted drug presentation, activation and clonal expansion of T cells. The specific MHC molecules involved have been identified, for example, HLA-B*5701 in abacavir-induced drug hypersensitivity and HLA-B*1502 in carbamazepine (CBZ)-induced SJS (see Table 1 for the list of ADRs with HLA association).

The HLA/ADR association is known to be phenotype specific. In the case of CBZ-induced cutaneous ADRs, studies in Han Chinese demonstrate that CBZ-SJS/TEN is highly associated with HLA-B*1502, whereas CBZ-induced maculopapular eruption and HSS are not. Instead, induced maculopapular eruption is associated with SNPs in the HLA-E region and HLA-A*3101, and HSS is associated with the MHC class II genes (39). Likewise, HLA-DRB1*0301 is related to aspirin-induced asthma, while HLA-DRB1*1302 and HLA-DQB1*0609 are associated with aspirin-induced urticaria/angioedema and asthma (40,41). The discrepancy of HLA association in hypersensitivities induced by the same drug may contribute to distinct pathogenesis of particular disease phenotypes. It should be noted that the HLA
association in CBZ-induced cutaneous ADRs seen in Japanese and Caucasian patients does not show phenotypic specificity (42,43).

It is also widely recognized that the genetic association can also be ethnicity specific, which could be due to difference in allele frequency. In populations such as Japanese and Caucasians, where the *HLA-B*^1502^ allele is very low to absent, the susceptibility to CBZ-SJS is not associated with *HLA-B*^1502^. It is instead associated with *HLA-A*^3101^, which is present at a higher allelic frequency in Japanese (9.1%) and Caucasians (5%), but is found in only 1.8% of Africans (44). These studies illustrate that ancestry plays an important role in the biomarker assessment of drug hypersensitivity.

The physiological role of HLA is to present an antigen to the T cell receptor, thereby initiating the T cell-mediated immune response (45). The strong association between HLA alleles and ADRs implies a causal relationship of HLA in the development of drug hypersensitivity, with the offending drug in the role of antigen. In support of this view, drug-specific CD8\(^+\) cytotoxic T cells activated in a HLA class I-restricted pathway were found in the blister fluid of drug-induced SJS/TEN patients (46). Currently, there are two drug-presentation hypotheses, the hapten concept and p–i concept (the direct pharmacological interaction of a drug with immune receptors) (Fig. 2). According to the hapten concept, chemically reactive drugs or metabolites covalently bind a protein or peptide to become neo-epitopes (47). An example is the covalent binding of penicillin to lysine residue of serum albumin and its presentation by HLA through the classical processing-required pathway to trigger T cell activation, eliciting penicillin allergy (48). Conversely, the p–i concept proposes a direct interaction between drugs and immune receptors, such as the T-cell receptor or drug with immune receptors (e.g. hydrogen bonding).

The tight HLA association in certain drug-induced hypersensitivity reactions (odds ratio >100, Table 1) provides a plausible basis for further development of such a test to identify individuals at risk of developing these life-threatening conditions. In fact, the FDA has recommended HLA-B^1502^ genetic screening before prescribing CBZ to reduce the risk of SJS and TEN and HLA-B^5701^ testing to avoid abacavir-induced hypersensitivity, in patients with ancestry from areas in which those HLA-B alleles are prevalent. Recent prospective studies using HLA genotyping as a screening tool before abacavir or CBZ treatment have illustrated the remarkable capability of HLA screening to prevent these severe

Table 1. Serious adverse drug reactions with HLA association

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA allele</th>
<th>Severe ADR</th>
<th>Ethnicity</th>
<th>OR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HLA-B^*5701</td>
<td>HSS</td>
<td>Western Australian</td>
<td>117</td>
<td>(57)</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>HLA-B^*5801</td>
<td>SCAR</td>
<td>Han Chinese</td>
<td>580</td>
<td>(58)</td>
</tr>
<tr>
<td>Aminopenicillin</td>
<td>HLA-A^*2016</td>
<td>SJS/TEN</td>
<td>Japanese</td>
<td>41</td>
<td>(59)</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>HLA-A^*1502</td>
<td>DILI</td>
<td>European</td>
<td>80</td>
<td>(60)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>HLA-DRB1^*1501</td>
<td>Urticaria</td>
<td>Korean</td>
<td>4</td>
<td>(40)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B^*1502</td>
<td>SJS/TEN</td>
<td>Han Chinese</td>
<td>2504</td>
<td>(63)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>HLA-DRB5^*0201</td>
<td>Agranulocytosis</td>
<td>Caucasian</td>
<td>22</td>
<td>(64)</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>HLA-B^*5701</td>
<td>DILI</td>
<td>Caucasian</td>
<td>81</td>
<td>(65)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>HLA-B^*3801</td>
<td>DILI</td>
<td>European</td>
<td>32</td>
<td>(60)</td>
</tr>
<tr>
<td>Lumiracoxib(^b)</td>
<td>HLA-DRB1^*1501-DQB1^*0602-DRB5^*0101</td>
<td>DILI</td>
<td>Multiple populations</td>
<td>5</td>
<td>(66)</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>HLA-B^*5901</td>
<td>SJS/TEN</td>
<td>Korean</td>
<td>250</td>
<td>(67)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>HLA-Cw8-B14</td>
<td>DILI</td>
<td>Italian Sardinian</td>
<td>15</td>
<td>(68)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>HLA-Cw8</td>
<td>DILI</td>
<td>Japanese</td>
<td>6.2</td>
<td>(69)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>HLA-B^*3505</td>
<td>DILI</td>
<td>Thai</td>
<td>49</td>
<td>(70)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>HLA-DRB1^*0101</td>
<td>DILI</td>
<td>Western Australian</td>
<td>18</td>
<td>(71)</td>
</tr>
<tr>
<td>Oxicams</td>
<td>HLA-B^*7301</td>
<td>SJS/TEN</td>
<td>European</td>
<td>152</td>
<td>(60)</td>
</tr>
<tr>
<td>Phenytin</td>
<td>HLA-B^*1502</td>
<td>SJS/TEN</td>
<td>Thai</td>
<td>36</td>
<td>(72)</td>
</tr>
<tr>
<td>Sulfoxmethoxazole</td>
<td>HLA-B^*3802</td>
<td>SJS/TEN</td>
<td>European</td>
<td>76</td>
<td>(60)</td>
</tr>
<tr>
<td>Ximelagatran(^b)</td>
<td>HLA-DRB1^*0701</td>
<td>DILI</td>
<td>Northern European</td>
<td>4</td>
<td>(73)</td>
</tr>
</tbody>
</table>

\(\text{cADR, cutaneous adverse drug reaction; DILI, drug-induced liver injury; HSS, hypersensitivity syndrome; SCAR, severe cutaneous adverse drug reaction; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; NA, not available; OR, odds ratio.}

\(\text{*Withdrawn from the markets.}\)
ADR, indicating that personalized medicine and pharmacogenomics are extremely useful in the right clinical setting. These studies have made genetic testing to prevent drug toxicity a clinical reality.

**TRANSLATING PHARMACOGENOMICS FINDINGS INTO CLINIC**

Table 2 lists some pharmacogenomic tests for drugs currently in use that have practical value in predicting ADRs and/or drug efficacy. These are based on well-defined genetic variants that are known to have reproducible and significant consequences for drug therapy. These tests have high predictive values (either high negative predictive value, high positive predictive value or both), and a causal relationship between genetic variations and drug response and clinical utility have been established. Many of the tests also have clinical guidelines for dose adjustment and alternative medications assembled by The Clinical Pharmacogenomics Implementation Consortium (Table 2). The biomarkers include the genetic variants in the above-mentioned drug metabolizing enzymes, inborn errors of metabolism, drug transporters and HLA alleles. The tests are available commercially as well as in academic settings. In addition, the costs of the tests may be reimbursed by third-party payers, for example, Taiwan National Health Insurance pays for the HLA-B*1502 test for all new CBZ users, some private insurance companies in the USA and Australia pay for the HLA-B*5701 test for abacavir users, and more recently, US Medicare pays for the CYP2C19 test for clopidogrel treatment. The tests are also available as an FDA-approved panel, including a pharmacogenetic test that covers all gene variants of CYP2D6 and CYP2C19 (Roche Amplichip CYP450 Test). However, the implementation of the vast information generated from the chip is still problematic. CYP2D6 metabolizes more than 100 commercially available drugs; with the exception of codeine and doxepin, the need for dose adjustment for these drugs is unclear. Thus, further research is required on how to best use the information from these gene chips.

**CHALLENGES AND FUTURE DIRECTIONS**

It is well recognized that genetics can affect clinical outcomes of drug therapy. The greatest obstacle to the clinical implementation of genetic biomarker tests is that, with the exception of those listed in Table 2, few of them have sufficient sensitivity, specificity and predictive value to be clinically useful as screening tools to predict drug efficacy and prevent ADRs. This is especially true for the genes responsible for drug efficacy, as thus far pharmacogenomic studies on the efficacy of drugs used to treat common diseases have been disappointing. Taking statins again as an example, there is large variability in the clinical response to statin treatment. Genetic variants in HMGCR and APOE have been reported to influence the lipid-lowering response after stain therapy (52,53). However, conflicting results have also been reported for both APOE and for HMGCR (54,55). GWAS so far have identified multiple loci; however, each locus plays only a small role and none of the loci, alone or in combination, has shown clinical utility.

There are several reasons for the slow progress of the pharmacogenomic study of drug efficacy for common diseases. First, the causes of common diseases are multifactorial, involving both genetic and environmental factors, and in most
cases genetic determinants underlying the disease pathogenesis are unknown. Thus, drugs used to treat these common diseases, such as statins, may target only one of the factors/pathways. If the cause of elevated blood lipid levels for an individual is not targeted by a statin, a statin would be ineffective. To better understand the mechanisms of drug efficacy and identify clinically useful biomarkers requires a better understanding of the diseases. Secondly, the effects of many drugs are influenced by drug–drug or drug–diet interactions. Drug efficacy may be modulated by concomitant drugs or diet, making it difficult to control pharmacogenomic studies. Similarly, common diseases are also largely influenced by both environment and diet. If life style and diet are not modified accordingly, common diseases are also largely influenced by both environmental factors will reveal functional variants not only for epigenetics, proteomics and metabolomics, and a detailed description of clinical phenotypes/endophenotypes as well as combined data from GWAS, next generation sequencing, drug–drug or drug–diet interactions. Drug efficacies may be modulated by concomitant drugs or diet, thus allowing for personalized therapy. Pharmacogenomics can also help reveal pathogenic mechanisms of disease. The clinically useful pharmacogenomic tests currently available are directed more at predicting drug toxicities and dose adjustment. More research will be needed to identifying genetic determinants of responders and non-responders, especially for drugs used to treat common complex diseases.}

**Conflict of Interest statement.** Y.-T.C. is an inventor of ‘Risk Assessment for Adverse Drug Reactions’ which has been licensed to PharmiGene, Inc. Y.-T.C. Chairs the Scientific Advisory Board of PharmiGene, Inc.

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**REFERENCES**


### Table 2. Clinical useful pharmacogenomic tests in predicting drug efficacy and adverse drug reactions

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Drugs</th>
<th>Clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Celecoxib</td>
<td>Consider starting treatment at the lowest recommended dose in poor metabolizers (CYP2C9*3/3) to avoid adverse cardiovascular and gastrointestinal events.</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>Poor metabolizers (CYP2C9*3/3) should administrated with caution to avoid adverse cardiovascular and gastrointestinal events.</td>
</tr>
<tr>
<td>CYP2C9+VKORC1</td>
<td>Warfarin&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Dose adjustment based on CYP2C9 and VKORC1 genotypes to achieve efficacy and avoid bleeding complications.</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Clopidogrel&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Poor metabolizers (CYP2C19*2/2) should take alternative therapy to avoid bleeding complications.</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codeine&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Ultra-rapid metabolizers (CYP2D6&lt;sup&gt;*&lt;/sup&gt;1/1 and *1/2) should avoid usage due to potential for toxicity.</td>
</tr>
<tr>
<td>DPD deficiency</td>
<td>Doxepin</td>
<td>Poor metabolizers (CYP2D6*3/3) should reduce dose by 60% to avoid arrhythmia and myelosuppression.</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Capecitabine</td>
<td>Avoid usage in G6PD deficient patients to prevent hemolysis.</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
<td>Avoid usage in G6PD deficient patients to prevent hemolysis.</td>
</tr>
<tr>
<td>HLA-B&lt;sup&gt;*&lt;/sup&gt;1502</td>
<td>Carbamazepine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Avoid usage in HLA-B&lt;sup&gt;*&lt;/sup&gt;1502 carriers to prevent SJS/TEN.</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Avoid usage in HLA-B&lt;sup&gt;*&lt;/sup&gt;1502 carriers to prevent SJS/TEN.</td>
</tr>
<tr>
<td>HLA-B&lt;sup&gt;*&lt;/sup&gt;5701</td>
<td>Abacavir&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Avoid usage in HLA-B&lt;sup&gt;*&lt;/sup&gt;5701 carriers to prevent hepatotoxicity.</td>
</tr>
<tr>
<td>HLA-B&lt;sup&gt;*&lt;/sup&gt;5801</td>
<td>Allopurinol</td>
<td>Avoid usage in HLA-B&lt;sup&gt;*&lt;/sup&gt;5801 carriers to prevent severe cutaneous ADRs.</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Simvastatin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dose adjustment based on SLCO1B1 genotype (C allele of rs4149056 SLCO1B1) to avoid myopathy.</td>
</tr>
<tr>
<td>TPMT</td>
<td>Azathioprine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dose adjustment based on TPMT genotype to achieve efficacy and avoid bone-marrow suppression (non-functional alleles TPMT&lt;sup&gt;a&lt;/sup&gt;2, TPMT&lt;sup&gt;a&lt;/sup&gt;3A, and TPMT&lt;sup&gt;a&lt;/sup&gt;3C).</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Mercaptopurine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dose adjustment based on UGT1A1 genotype (UGT1A1&lt;sup&gt;a&lt;/sup&gt;28) to achieve efficacy and avoid neutropenia.</td>
</tr>
</tbody>
</table>

ADR, adverse drug reaction; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; HLA, human-leukocyte antigen; SJS, Stevens–Johnson syndrome; SLCO1B1, solute carrier organic anion transporter family, member 1B1; TEN, toxic epidermal necrolysis; TPMT, thiopurine S-methyltransferase; UGT, UDP-glucuronosyltransferase.<br>

<sup>a</sup>Guidelines provided.


