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Pharmacogenomics as a Tool in Addressing Genetic Variation-Dependent Adverse Drug Reactions

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Abstract
Adverse drug reactions (ADRs) are a cause of discontinuing drug development and withdrawal from market, as well as a very common source of morbidity and mortality. Genetic variables may be the primary predictor of drug response for certain medications, but they are estimated to account for 15–30% of the variability in drug response. Many factors can contribute to adverse drug reactions, including genetics and drug targeting/delivery. Genetic markers, such as single nucleotide polymorphisms (SNPs) in drug-metabolizing enzymes, drug targets, and human leukocyte antigen (HLA) genotypes, have been associated with an increased risk of ADRs. Pharmacogenomics is the study of the genetic variation in the way that different people react to different pharmaceuticals, including variations in the risk of adverse drug reactions, dose requirements, and efficacy. The implementation of genetic data for predicting responses to medications and ADRs is becoming a reality in clinical practice, offering the potential to reduce the incidence of ADRs and improve patient outcomes. As pharmacogenomic research continues to advance, it holds great promise for enhancing drug safety and efficacy, ultimately leading to more tailored and effective therapeutic interventions.

Keywords: Adverse drug reaction, Pharmacogenomics, Genetic variation, Clinical practice, and Drug classes

INTRODUCTION
A significant issue in clinical practice and drug development is the individual diversity in therapeutic response. It may result in therapeutic failure or unfavorable drug reactions in specific patients or patient subpopulations (Severino and Del zompo, 2004). Unwanted and negative consequences brought on by the usage of pharmaceuticals are referred to as adverse drug reactions (ADRs) (Wei *et al.,* 2012). From minor side effects to serious problems that might result in morbidity and mortality, these reactions can range widely. Patient safety and healthcare expenditures are significantly impacted by ADRs (Ferrara *et al*., 2022). For instance, individuals who experience ADRs could need additional diagnostic procedures, specialized advice, or additional medications to treat the side effects (Patton and Borshoff, 2018). As a result, they present problems to the healthcare system in terms of patient well-being and medical expenses. Pharmacogenomics offers important insights into the role of genetics in

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drug response that can enhance patient outcomes, avoid serious side events, and lower treatment costs (McInnes *et al*., 2021).

An individual's susceptibility to ADRs can be affected by genetic polymorphisms in drug-metabolizing enzymes, transporters, and drug targets (Langmia *et al*., 2021). By tailoring pharmacological therapy based on a patient's genetic profile, personalized medicine techniques can be used to lower the likelihood of adverse drug reactions (Pirmohammed *et al*., 2014). Drug selection, dosing, and monitoring can identify genetic markers associated with ADRs, enabling healthcare providers to make informed decisions about drug selection, dosage, and monitoring decisions can be made by healthcare professionals with the use of pharmacogenomic testing, which can uncover genetic markers linked to ADRs (Krebs and Milani, 2019). The requirement for evidence-based recommendations and ethical issues with implementation are still issues (Reilling and Evans, 2015). Despite these difficulties, pharmacogenomics is increasingly moving toward proactive testing and application, serving as a foundation for precision medicine and enhancing the usage of drugs (Adams *et al*., 2018). Pharmacogenomics presents prospects to improve medication therapy and outcome prediction in the context of global precision medicine, while also addressing the problems (Rajman *et al.,* 2017).

Adverse Drug Reactions

Adverse drug reactions are reactions that are harmful and unintentional and occur at doses normally used in human subjects (Severino and Del zompo, 2004). ADRs can be categorized in a number of ways depending on various characteristics. ADRs can be classified in one classification system according to the severity of the ADR, which can range from mild to moderate, severe, and life-threatening (Coleman and Pontefract, 2016). This classification aids medical practitioners in determining the severity of the response and the most effective therapy techniques (Coleman and Pontefract, 2016). ADRs are frequently divided into two main categories. Type A reactions are frequently dose-dependent and predictable based on the mode of pharmacological processes. On the other hand, type B reactions, which make up about 15% of ADRs, are known as idiosyncratic, unpredictable, and dose-independent reactions (Wei *et al*., 2012). Many factors, such as a drug's known pharmacologic activity, drug interactions, toxicity, drug delivery off target, and drug hypersensitivity, might be linked to ADRs (Khan, 2016).

Pharmacogenomics

Pharmacogenomics is a field of study that examines how an individual's genetic makeup influences their response to medications (McInnes *et al*., 2021). Genetic variations in drug-metabolizing enzymes, transporters, receptors, and other drug targets have been associated with differences in drug efficacy and toxicity among individuals (Becker *et al*., 2009). The scope of pharmacogenomics extends to various aspects of healthcare, including drug discovery, personalized medicine, disease prevention, and insights into disease mechanisms (Mancinelli *et al*., 2000). Pharmacogenomics facilitates the development of customized therapeutics and individualized drug selection, dosage, and monitoring by discovering genetic markers linked to drug response (Pirmohamed, 2014). It has the potential to improve treatment outcomes, reduce adverse drug reactions, and optimize medication use (Giudicessi *et al*., 2017). Pharmacogenomics also plays a role in addressing health disparities by considering genetic variations that may differ among ethnic groups (Martin *et al*., 2017). The field continues to evolve with advancements in technology, data sharing, and the development of guidelines and resources for healthcare professionals. One crucial element that determines whether variations in genetic polymorphisms will be clinically significant is

the therapeutic index of a medication (Evans and Reiling, 2009). However, small differences in concentrations due to polymorphisms may matter if a medication has a limited therapeutic window (Chang *et al.,* 2020). The application of pharmacogenomics in personalized medicine allows for tailored drug selection, dosage adjustments, and monitoring to optimize treatment outcomes and minimize the risk of adverse drug reactions (Mosa *et al*., 2020).

Genetic Variations and Adverse Drug Reactions

Molecular basis of genetic variability in drug metabolism

The result of variances in the genome's DNA sequence is genetic diversity. Genes can exist in various (mutagenized) versions known as alleles due to variations in DNA sequences (Meyer, 2000). An individual's phenotype refers to the observable traits, such as drug responsiveness or drug metabolism ability, that are derived from specific sets of alleles that make up their genome (Amur *et al.,* 2010). According to Hinds *et al*. (2005), genetic polymorphism occurs when two or more alleles occur at a locus, with the rare allele having a frequency of at least 1% or higher in a particular population. A frame shift can be created by insertions and deletions, and this typically also results in a non-functional protein. On the other hand, through altering transcriptional control or *mRNA* stability, single nucleotide polymorphisms (SNPs) in promoters, splice sites, and untranslated regions may change the expression and consequently the amount of a gene product (Conne *et al*., 2010). Polymorphisms can impact translation efficiency and splicing errors can be caused by changes in splice site sequences (Nebert *et al.,* 2009). Furthermore, a gene's product could be enhanced by a duplication of the gene or missing due to a deletion of the gene (Duan *et al*., 2013).

Genetic variations in drug-metabolizing enzymes

An extensive array of enzymes, many of which exhibit genetic variation, contribute to the metabolism of xenobiotic substances, including pharmaceuticals and carcinogens (Nebert *et al*., 2009). The metabolic transformation of drugs typically occurs in two distinct phases. Phase I drug metabolizing enzymes (DMEs), predominantly cytochromes P450 (CYPs enzymes e.g., CYP2D6, CYP2C19, CYP2C9), introduce reactive electrophilic groups into xenobiotic molecules (Sauver *et al.,* 2017). Subsequently, these modified xenobiotics undergo conjugation reactions with endogenous compounds mediated by Phase II DMEs, such as UDP-glucuronosyltransferases (UGTs), N-acetyltransferases (NATs), glutathione S-transferases (GSTs), and others. A specific drug's rate of metabolism can vary between Poor Metabolizers (PM) and Ultra Rapid Metabolizers (UM) by a factor of 1000 (Frederiksen, 2020). A typical population-based dose may result in a greater risk for adverse effects (ADR) in these patients because of high plasma levels in PM or resistance to therapy in UM (Crews *et al.,* 2012). As a result, dose modifications may be necessary. CYP2D6, a member of the cytochrome P450 family, is one of the most extensively studied drug-metabolizing enzymes (Khan, 2016). Its metabolic activity exhibits significant variability among ethnic groups, with allelic variations leading to a 100-fold difference in metabolism rates. Approximately 7% of Western Europeans are CYP2D6 poor metabolizers, necessitating lower drug dosages, while an estimated 20 million individuals are ultra-rapid metabolizers who fail to respond to standard treatment (Wei *et al*., 2012). Codeine, a drug that relies on CYP2D6 for bioactivation and conversion to morphine, illustrates this variability (Sauver *et al.,* 2017). Poor metabolizers experience minimal therapeutic benefit from codeine, whereas ultra-rapid metabolizers (CYP2D6∗1/∗1 and ∗1/∗2) exhibit increased morphine conversion, leading to severe or fatal toxic side effects following standard doses (Crews *et al*., 2012).

Genetic variations in drug transporters

Drug transporters are important molecules that affect how medications are absorbed, distributed, and eliminated from the body (Woodahl *et al.,* 2004). P-glycoprotein (P-gp), encoded by the ABCB1 gene, serves as a crucial efflux transporter, characterized by its broad substrate range and widespread tissue distribution (Cascorbi, 2011). Genetic polymorphisms of ABCB1 can lead to variations in P-gp expression or function (Eichelbaum *et al.,* 2014). Genetic variations in P-gp, notably the C3435T polymorphism, have been associated with altered expression and function of drugs contributing to variability in drug absorption and disposition in different individuals and races (Zawadzka *et al.,* 2020). Polymorphisms in ABCB1 gene, a synonymous mutation C3435T (rs1045642) was discovered to increase serum concentration of clopidogrel and 2-oxo clopidogrel (a dual antiplatelet therapy employed in management of patients after acute myocardial infarction) in patients with ABCB1 polymorphic C alleles as opposed to patients with the T alleles who show lower expression of P-gp activity (Stokanovic *et al*., 2015) and correlated with increased risk of atorvastatin-induced muscle side effects (Lalatović *et al*., 2023). ABCB1 C3435T polymorphism was observed to enhance the elimination of risperidone, trazodone and dehydro-aripiprazole (antidepressants and antipsychotics) from plasma circulation hence affecting drug disposition (Saiz-Rodriguez *et al*., 2018). Patients with C allele in C3435T polymorphism of MDR1 gene has been associated with increased risk of drug resistant epilepsy in children (Stasiolek, 2016). The weekly maintenance dose of warfarin needed for embolic atrial fibrillation and deep vein thrombosis patients was discovered to be significantly lower in patients with the *ABCB1 3435CT* or *TT* polymorphism type than in those with the *ABCB1 3435CC* type (Lee and An, 2022). The presence of homozygous or heterozygous T allele which reduces activity of P-gp predisposed the patients to less elimination of warfarin (Lee and An, 2022). In Chinese Han patients with refractory lupus nephritis, a homozygote T allele was associated with increased P-gp expression, while MDR1 CC and CT genotype with lower P-gp expression (Zhou *et al*., 2021). In a case of cancer, TT genotype increases the risk of lung cancer, associated with accumulation of carcinogenic xenobiotics (Zawadzka *et al*., 2020). Beyond P-glycoprotein, other transporters, including organic anion and cation transporters (OAT, OCT, SLC22A), organic anion transport proteins (OATP, SLCO, formerly SLC21A), and MRPs (ABCCs), also members of the ATP-binding cassette (ABC) family, contribute to drug disposition and show significance in drug delivery and response (Tarasova *et al.,* 2012). A number of OCT1 variations have been linked to decreased or impaired drug absorption. In a clinical trial including healthy participants, those with OCT1 polymorphisms (OCT1-R61C, G401S, M420del, and G465R) showed higher plasma glucose levels following metformin administration than those with the wild-type OCT1 sequence (Becker *et al*., 2009). These individuals also showed lower metformin absorption in cellular experiments (Becker *et al*., 2009). In another clinical trial involving individuals with type-II diabetes mellitus, only the intronic variant rs622342 of all examined variants was linked to metformin's ability to lower blood glucose levels. The rs36056065 variant leads to the formation of a truncated protein, which has been linked to adverse gastrointestinal side effects in patients receiving metformin treatment (Lozano *et al*., 2018).

Genetic variation in drug targets

Drug targets can be broadly categorized into three main groups: the direct protein target of the drug, components of signal transduction cascades or downstream proteins, and proteins involved in disease pathogenesis (Shyamveer *et al.,* 2023). Genetic variability within drug target pathways can significantly modulate pharmacodynamics, potentially influencing the efficacy of drug therapy, particularly in the context of G-protein-coupled receptors (GPCRs) (Yang *et al.,* 2021). These variations hold the potential to influence receptor expression,

function, and drug response, underscoring the need for genetic assessment in both drug development and clinical practice (Eichelbaum *et al.,* 2014). The existence of genetic variation in GPCR drug targets has been well established, with certain variants demonstrated to lead to altered or adverse drug responses (Hauser, 2018). In a single individual, one-third of the GPCR pharmacological targets has 68 missense variants present in the coding regions. Of these, eight variations on average per person have been clinically linked to altered response to drugs (Sriram and Insel, 2018). For example, in women with polycystic ovary syndrome (PCOS), the heterozygous A307T polymorphism (minor allele frequency) in the follicle stimulating hormone receptor (FSHR) gene is linked to an increased responsiveness to exogenous follicle stimulating hormone (FSH) (Laven, 2019). Parkinson disease patients who are carriers of the G9S variant in the dopamine receptor 3 (DRD3) gene exhibit an elevated risk of gastrointestinal toxicity associated with Levodopa (a dopamine replacement) therapy (Auton *et al*., 2015).

Pharmacogenomic Associations with Specific ADRS in Different Drug Classes

The HapMap project, employing genome-wide association studies, and subsequently the 1000 Genome Project, utilizing next-generation sequencing technologies, delved into the realm of rare genetic variants, further expanding our understanding of the genetic determinants of drug response. The knowledge gained from these studies, particularly the identification of genomic biomarkers, has been instrumental in unraveling the genetic basis of inter-individual variation in drug metabolizing enzymes.

Anticoagulants

Blood coagulation is a tightly regulated process controlled by a series of enzymatic reactions (cascade) that can be originated by two primary pathways: extrinsic and intrinsic. Both pathways meet on a common pathway, eventually leading to the creation of the key enzyme, thrombin. This protease cleaves soluble fibrinogen into its insoluble form, fibrin. Spontaneously polymerizing into a meshwork, fibrin provides a structural scaffold for platelet aggregation, stabilizing the initial plug formed at sites of vascular injury (Rasche, 2001). However, several endogenous anticoagulant pathways exist to counterbalance this procoagulant response and maintain hemostasis. Notably, the protein C (PC) and protein S (PS) pathway, along with the serine protease inhibitor antithrombin (AT), serve as crucial regulators to prevent excessive clot formation and potentially harmful thrombotic events (Esmon, 2003). Disruption of the procoagulant or anticoagulant pathways is mechanism of action of pharmacological anticoagulants (Roemisch *et al*., 2002). The most significant ADR associated with anticoagulants is bleeding, which can occur as a result of excessive anticoagulation (Andrade and Sharma, 2016). By suppressing the coagulation cascade, these medications increase the risk of spontaneous bleeding, which can manifest as mild bruising, nosebleeds, or even life-threatening intracranial hemorrhages (Suarez-Kurtz and Botton, 2015). The severity and frequency of bleeding depend on several factors, including the type and dosage of anticoagulant, coexisting medical conditions, and medication interactions. This risk is further compounded by drug interactions, as certain medications can potentiate the anticoagulant effect, leading to an increased risk of bleeding. Adverse cutaneous reactions that have been reported with traditional anticoagulants such as warfarin and heparin, as well as with newer direct oral anticoagulants (DOACs) like dabigatran and rivaroxaban are; heparin-induced thrombocytopenia, leukocytoclastic vasculitis, urticaria angioedema and so on (Vu and Gooderham, 2017). Warfarin acts as a vitamin K antagonist, inhibiting the production of key coagulation factors and anticoagulant proteins (Johnson *et al*., 2011).

However, this inhibition occurs at different rates for different proteins due to their varying half-lives. Notably, the procoagulant factors FVII and protein C (PC) have relatively short half-lives of 5 and 8 hours, respectively (Scarff *et al*., 2002). In contrast, the anticoagulant protein 'protein S' (PS) and the coagulation factors II, IX, and X have significantly longer half-lives, ranging from 24 to 72 hours (Vu and Gooderham, 2017). Loss-of-function genetic variants of CYP2C9*2/*3 may impair warfarin metabolism and have been associated with over-coagulation and an increased risk of bleeding (Avery *et al*., 2011). However, carriers of the VKORC1 variation rs9923231 have decreased VKORC1 liver expression and increased warfarin sensitivity. On the other hand, uncommon mutations in VKORC1 have been linked to resistance to warfarin therapy and a higher chance of unfavorable ischemia events (Johnson *et al*., 2011). Some adverse drug interactions associated with anticoagulants occur in instances of combination therapy of anticoagulants like warfarin with antiplatelet therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) or selective serotonin reuptake inhibitors (SSRI) (Andrade and Sharma, 2016) along with anticoagulants raises the risk of bleeding, especially upper gastrointestinal hemorrhage and cerebral haemorrhage (in the case of SSRI) (Bakhriansyah *et al.,* 2017). Selective cyclooxygenase-2 (COX-2) enzyme inhibitors result in less bleeding than with nonspecific COX-1 inhibitors, however, the risk of bleeding remains higher than that of NSAID nonusers (Bakhriansyah *et al*., 2017). In Brazilian populations, specific polymorphisms have been identified to influence warfarin and clopidogrel response, highlighting the potential for personalized medicine approaches (Hirata *et al.,* 2021). CYP2C92, CYP2C93, and VKORC1 rs9923231 are associated with increased warfarin sensitivity and lower dose requirements. Carriers of CYP4F2 rs2108622 variant exhibit warfarin resistance and require higher doses (Johnson *et al.,* 2011). Identifying such individuals allows for personalized dose adjustments to ensure adequate anticoagulation. Age, gender, body weight, co-medications, food interactions, and other factors contribute significantly (up to 63%) to warfarin dose variability (Storelli *et al*., 2016). These factors should be carefully considered alongside pharmacogenomic data for optimal dosing. CYP2C19*2, PON1 rs662, and ABCC3 rs757421 polymorphisms have been linked to altered platelet responsiveness or clopidogrel pharmacokinetics in individuals with coronary artery disease or acute coronary syndrome (Stokanovic *et al.,* 2015). The glycoprotein receptor complex IIb/IIIa (integrin αIIbβ3) exhibits quantitative and/or qualitative abnormalities as a result of mutations in the ITGA2B and ITGB3 genes (Alharbi *et al*., 2022). This reduces platelet aggregation and causes Glanzmann's thrombasthenia (GT) (Alharbi *et al*., 2022).

Antidepressants

Adverse drug reactions associated with antidepressants pose significant clinical challenges and can manifest in various forms, including liver injury, increased risk of adverse outcomes in older individuals, movement disorders, and even rare events such as suicidal ideation and behavior (Uher *et al.,* 2009). Antidepressants can also lead to drug-induced liver injury, with some medications inhibiting or inducing CYP450 enzyme activity, potentially increasing the risk of hepatic toxicity, with reported cases of fulminant hepatic failure leading to transplantation or death (Voican *et al*., 2014). Adverse effects of antidepressants like selective serotonin reuptake inhibitors can have significant implications, particularly in older individuals, due to factors such as comorbidity, physiological changes, and polypharmacy (Coupland *et al.,* 2011). These adverse effects can also manifest as poor tolerability in youth at risk for bipolar disorder, as evidenced by decreased right amygdala activation in response to emotional distracters. In addition to the physical manifestations of ADRs, the impact of antidepressants on mental health and behavior is also a significant concern (Nery *et al*., 2021). For instance, decreased right amygdala activation in response to emotional distracters has been associated with experiencing antidepressant-related adverse reactions in at-risk youth,

highlighting the potential impact on brain functional activation (Nery *et al*., 2021). Additionally, Williams *et al*. (2015) suggested that amygdala reactivity to emotional faces may help predict general and medication-specific responses to antidepressant treatment, indicating the potential of amygdala probes in informing the personal selection of antidepressant treatments. The selection of important gene variants when prescribing antidepressants is a critical aspect of personalized medicine. Studies (e.g. Uher *et al*., 2009; Kao *et al.,* 2019; Brown *et al*., 2022) have highlighted several key genetic variants that play a significant role in predicting antidepressant response and guiding prescribing decisions. Additionally, genes such as CYP2C19 and CYP2D6, as well as SLC6A4 and HTR2A, have been identified as important targets for pharmacogenomic testing to derive antidepressant prescribing recommendations (Brown *et al*., 2022). Moreover, studies have investigated the association of specific genetic variants with antidepressant treatment response, such as genes related to the neurotrophic pathway (BDNF, VEGFA), corticotropin-releasing factor system (CRH, CRHR1, CRHR2) and serotonin signaling (HTR2A) (Kao *et al*., 2018). These genetic variants have shown potential in predicting treatment outcomes and guiding antidepressant selection. Additionally, machine learning algorithms applied to large datasets with genetic, clinical, and demographic features have been proposed to improve the accuracy of antidepressant prescription (Taliaz *et al*., 2021). Pharmacogenomic biomarkers have been explored as a source of evidence for the effectiveness and safety of antidepressant therapy, aiming to identify genetic variations that influence individual responses to antidepressants (Correia *et al.,* 2022). Moreover, combinatorial pharmacogenomic testing has been suggested to contribute to the better selection of antidepressant therapy, potentially improving treatment outcomes (Vojvodic *et al*., 2021). However, the emerging focus on pharmacogenomics in the context of antidepressant treatment also raises considerations regarding the benefits and barriers of pharmacogenomics-guided treatment for major depressive disorder (Ahmed *et al.,* 2018).

Antivirals

Antiviral drugs, particularly those used in the context of COVID-19 treatments (Nobari *et al.,* 2020) like Paxlovid™ and Lagevrio® have been associated with dermatological reactions (Pupo-Correia *et al.,* 2022). Some of the documented effects of antiviral drugs owing to gene variations in patients are depicted in Table 1. Dermatological side effects have also been reported in the context of antiviral treatments for various conditions, including chronic hepatitis C (Gabar *et al*., 2019; Chinudomporn *et al.,* 2021), as evidenced by a case report of alopecia areata following hepatitis C virus treatment (Eroglu, 2021). Furthermore, the use of antiviral drugs in COVID-19 patients has been associated with concerns regarding psychiatric symptoms and behavioral effects, indicating the need for comprehensive management of potential adverse effects (Zhang *et al*., 2020).

Table 1: Gene variations mitigating adverse drug reactions to antivirals

Antiviral drugs	Gene Variations	Effects	References
Acyclovir	HLA-B*57:01	Increased risk of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS)	Baldo and Pham, 2021
Abacavir	HLA-B*57:01	Increased risk of hypersensitivity reaction	Quiros-Roldan *et al*, 2020
Nevirapine	HLA-DRA*01:01	Increased risk of SJS/TEN	Castro *et al*., 2015
Ribavirin	ITPA*28	Increased risk of anemia and neutropenia	Sakamoto *et al*., 2010
Ritonavir	CYP3A422 and CYP3A53	Reduced clearance, leading to increased drug exposure and potential for interactions with other medications	Saravolatz *et al*., 2023
Saquinavir	CYP3A56 and CYP3A422	Reduced clearance, leading to increased drug exposure and potential for interactions with other medications	Sharma *et al*., 2020

Opioids

Adverse drug reactions (ADRs) associated with codeine and tramadol are of significant clinical concern. Codeine, a weak opioid, is known to cause adverse effects such as constipation, euphoria, nausea, drowsiness, and potentially fatal anaphylaxis (Crews *et al*., 2012). Furthermore, codeine's metabolism to morphine can lead to serious or fatal adverse reactions, particularly in ultra-rapid metabolizers, such as neonates and children, necessitating restrictions on its use in these populations (Seif-Barghi et al., 2015). Additionally, codeine use has been associated with gastrointestinal side effects and respiratory depression in patients with severe chronic obstructive pulmonary disease (Crews *et al*., 2012). The hypersensitivity reactions to codeine can manifest as various dermatological conditions, including generalized maculopapular eruptions, bullous eruptions, fixed drug eruptions, drug-induced hypersensitivity syndrome, and even toxic epidermal necrolysis (Yoo *et al*., 2014). OCT1 genotypes play a significant role in the pharmacokinetics of intravenously administered morphine. The presence of defective OCT1 variants is associated with a reduced clearance of morphine, potentially leading to an increased incidence of drug-induced toxicity episodes (Tarasova *et al*., 2012; Eapen-John *et al*., 2022). OAT3-I305F variant, have been associated with a significantly lower renal clearance of cefotaxime antibiotics (Yee *et al*., 2013). On the other hand, tramadol, while structurally similar to codeine, exhibits a different profile of adverse events, particularly in relation to addiction. Studies have reported the unlikelihood of developing drug abuse with tramadol, distinguishing it from traditional opioids like codeine (Duehmke *et al*., 2017). However, tramadol is associated with side effects such as drowsiness, headache, and digestive problems, which are common adverse effects similar to other opiate agonists (Duehmke *et al*., 2017). Ultra-rapid metabolizers (UMs) due to CYP2D6 gene duplication may experience exaggerated and potentially dangerous opioidergic effects, leading to poor pain control and increased adverse reactions related to opioid use (McDonough, 2021). Specifically, individuals lacking CYP2D6 activity (poor metabolizers, PM) may suffer from poor analgesia from codeine, while UMs may experience severe adverse events due to increased opioidergic effects (Radford *et al*., 2019). The association between CYP2D6 phenotype and adverse outcomes related to opioid medications has been examined, with UMs being at risk of adverse drug reactions due to altered CYP2D6 function (Radford *et al*., 2019). The Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines

recommend against the administration of codeine to ultra-rapid CYP2D6 metabolizers due to the higher risk of adverse drug reactions (Lopes *et al*., 2020).

Antipsychotics

The metabolism of antipsychotic medications is influenced by genetic variation, particularly in genes encoding cytochrome P450 (CYP) enzymes. CYP2D6, responsible for the oxidative metabolism of a significant proportion of antidepressants and antipsychotics, plays a crucial role in the metabolism of these medications (Samer *et al*., 2013). For instance, poor metabolizers of CYP2D6 may experience toxic effects at standard doses of antipsychotics metabolized by this enzyme, while ultra-rapid metabolizers may not respond adequately to these medications (Arranz *et al*., 2011). Additionally, genetic variations in other CYP enzymes, such as CYP1A2, CYP2C9, CYP2C19, and CYP3A4, have also been implicated in the metabolism of atypical antipsychotic drugs, further highlighting the influence of genetic polymorphisms on drug metabolism and response (Nebert *et al*., 2009; Frederiksen *et al*., 2020). Approximately 70% to 80% of the variability in clozapine plasma concentration can be attributed to variability in CYP1A2 activity (Marcos-Vadillo *et al*., 2022). CYP2D6 polymorphism may affect transcription factor binding, with the T allele associated with greater expression of the gene and less weight gain, highlighting the potential clinical implications of genetic variations in drug metabolism (Eum *et al*., 2016). Individuals with poor CYP2D6 activity (PMs) are prone to therapeutic failure due to inadequate drug clearance, while those with ultra-rapid metabolism (UMs) may require higher dosages to achieve desired therapeutic effects (Wei *et al*., 2012). This is exemplified by risperidone, where PMs may not experience sufficient therapeutic benefit, whereas UMs require increased doses to achieve efficacy (Yau *et al*. 2023).

Anticonvulsants

Genetic variation significantly influences the metabolism of anticonvulsants, impacting drug efficacy and safety. The metabolism of anticonvulsants such as carbamazepine, phenobarbital, phenytoin, and primidone are affected by genetic variations in the cytochrome P-450 enzyme system (Leckband *et al*., 2013). These anticonvulsants have been associated with metabolic changes that may contribute to cardiovascular risk, highlighting the impact of genetic variation on drug metabolism and potential adverse effects. Carbamazepine, an anticonvulsant medication, is associated with a range of adverse effects (Ksouda *et al*., 2017). These adverse effects include aplastic anemia, hyponatremia, leucopenia, osteoporosis, and hypersensitivity reactions such as maculopapular eruptions (MPEs), hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced liver injury (Leckband *et al*., 2013). Additionally, carbamazepine therapy is associated with cutaneous adverse reactions in up to 10% of patients, and it has been reported to cause severe cutaneous adverse reactions, including SJS and TEN (Yip and Pirmohamed, 2017). Furthermore, carbamazepine has been linked to neurological adverse drug reactions, such as neurological drug reactions and neurological side effects, and it is also associated with hematological disorders, including aplastic anemia, agranulocytosis, pancytopenia, and thrombocytopenia (Farooq *et al*., 2019). Other reported adverse effects of carbamazepine include angioedema, DRESS syndrome, and hepato-splenomegaly, as well as reductions in the plasma concentration of other medications, such as haloperidol, when used in combination (Karuppannasamy *et al*., 2019). The presence of the human leukocyte antigen (HLA)-B*1502 allele has been strongly associated with the occurrence of these severe adverse reactions during carbamazepine treatment, particularly in the Asian population (Wang *et al*., 2011). Additionally, the HLA-A*3101 allele has been implicated in the development of drug reaction with eosinophilia and systemic symptoms (DRESS) secondary to carbamazepine

(Ksouda *et al.,* 2017). Genetic variation has been linked to adverse effects of both phenytoin and primidone. For phenytoin, CYP2C9*3 has been identified as a significant genetic variant associated with increased plasma concentrations and severe cutaneous adverse reactions (Chang *et al.,* 2020). This variant can lead to reduced drug clearance, increasing the risk of adverse effects (Franco and Perucca, 2015). Similarly, a study on phenytoin-induced gingival enlargement found a homomutant presentation of the CYP2C9*2 gene, suggesting a potential role of genetic variation in this adverse effect as well (Balakrishnan, 2020).

Pharmacogenomic Testing and Clinical Implementation

Pharmacogenomic testing methods play a crucial role in personalized medicine, aiming to optimize drug selection and dosing based on an individual's genetic makeup. These methods encompass a range of approaches and considerations, as evidenced by the literature. Pharmacogenomics is able to analyse individual genetic variations by several testing methods highlighted as follows:

Single-gene tests

This type of test focuses on analyzing specific genes known to influence the metabolism or response to a particular medication. Examples include CYP2D6 testing for antidepressants and HLA-B*1502 for carbamazepine, where variations can predict potential adverse reactions or therapeutic failure. Single-gene tests are often the first step in pharmacogenomic testing, offering targeted information for specific medication decisions (Haidar *et al.,* 2022). The use of single-gene tests to analyze specific genes influencing drug metabolism and response has been a key focus in pharmacogenetics.

Panel tests

These tests analyze a panel of genes simultaneously, providing a broader picture of an individual's predisposition to metabolize and respond to various medications (Williams, 2020). This approach is particularly useful for individuals taking multiple medications or for those with complex medical conditions requiring multiple drug therapies. Examples include panels for pain management, cardiovascular medications, and psychotropic medications (Brown *et al.,* 2014). Zeuli (2023) demonstrated its potential in people with HIV, with the panel offering explanations for prior medication failures and adverse effects. Williams (2020) validated broad-based panels, with the former focusing on genes responsible for drug absorption, distribution, metabolism, and excretion, and the latter on 106 SNPs involved in drug response. However, despite these advancements, van der Wouden (2020) highlighted several barriers to the routine implementation of panel testing in primary care, including unclear procedures, reimbursement issues, and infrastructure inefficiencies.

Whole-exome sequencing (WES)

This test analyzes the coding regions of all genes in the human genome, providing the most comprehensive overview of an individual's genetic makeup (Srivastara *et al.,* 2014). WES offers valuable insights into potential drug interactions and adverse reactions based on an individual's unique genetic profile (Dewey *et al.,* 2016).

Whole-genome sequencing (WGS)

Similar to WES, WGS analyzes the entire human genome, including both coding and non-coding regions (Malone, 2020). This provides the most comprehensive genomic information, potentially revealing unforeseen genetic variations that may impact drug response.

Direct-to-consumer tests

These tests are available directly to consumers without the need for a healthcare professional's involvement. Direct-to-consumer **(**DTC) tests often offer broader genetic information, including insights into ancestry and other health-related traits (Rahma *et al.,* 2020). Commercially available pharmacogenomic tests encompass a wide array of genes, with varying levels of evidence for their associations with disease risk, underscoring the complexity of interpreting test results and the need for robust counseling and patient education (Zierhut *et al*., 2017). The need for pharmacogenomic education among pharmacists and healthcare professionals has been emphasized, with a focus on improving knowledge and confidence in responding to questions regarding pharmacogenomics and its use (Loudon *et al*., 2021).

CONCLUSION

In conclusion, the implications of pharmacogenomics in addressing ADRs are profound, offering the potential for personalized medicine and improved patient outcomes through tailored pharmacogenomic approaches. By leveraging on genetic information to predict individual responses to medications, pharmacogenomics holds the promise of minimizing ADRs, optimizing drug efficacy, and enhancing patient safety. The integration of pharmacogenomic data into clinical decision-making has the capacity to revolutionize drug therapy, leading to more precise and individualized treatment strategies. As pharmacogenomic research continues to advance, it is essential to recognize the transformative impact of personalized medicine in mitigating ADRs and improving patient care.

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