



REVIEW ARTICLE

PHARMACOGENOMICS-GUIDED DRUG SAFETY: A REVIEW OF GENETIC SUSCEPTIBILITY TO ADVERSE DRUG REACTIONS AND PERSONALIZED PHARMACOVIGILANCE

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ABSTRACT

Pharmacogenomics is an emerging component of precision medicine that investigates how genetic variation influences drug response, treatment efficacy, and susceptibility to adverse drug reactions (ADRs). Interindividual differences in drug-metabolizing enzymes, transporters, drug targets, and immune-related genes can alter pharmacokinetics and pharmacodynamics, contributing to treatment failure, toxicity, and preventable medication-related harm. Pharmacogenomics-guided drug safety offers an opportunity to identify genetically susceptible patients before prescribing and to integrate genetic information into personalized pharmacovigilance. This review examines the major genetic determinants of ADRs, clinically relevant gene–drug associations, and the application of pharmacogenomic testing in routine clinical practice. Important examples include CYP2C19-related clopidogrel response, CYP2D6-associated variability in opioid metabolism, TPMT and NUDT15 variants associated with thiopurine toxicity, HLA-B*57:01-associated abacavir hypersensitivity, and HLA-B*15:02-associated carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis. Evidence-based prescribing guidelines and regulatory recommendations support the clinical utility of selected pharmacogenomic biomarkers, although implementation varies across healthcare systems. Integrating pharmacogenomic data with electronic health records, clinical decision-support systems, medication surveillance, and post-marketing safety databases may improve early identification of high-risk patients and strengthen adverse-event prevention. Nevertheless, challenges remain, including genetic diversity, unequal access to testing, interpretation of uncertain variants, data privacy, cost-effectiveness, and limited representation of some populations in genomic research. Pharmacogenomics should therefore complement, rather than replace, clinical assessment, therapeutic drug monitoring, and conventional pharmacovigilance. A coordinated, ethically responsible framework combining pre-emptive testing, evidence-based prescribing, and longitudinal safety monitoring could improve medication outcomes and support more individualized, equitable, and proactive drug-safety practices.

Keywords: Pharmacogenomics; pharmacovigilance; adverse drug reactions; pharmacogenetic testing; personalized medicine; drug safety; genetic polymorphism; precision prescribing; drug-induced hypersensitivity; clinical decision support.

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INTRODUCTION

Adverse drug reactions (ADRs) are an important cause of preventable morbidity, hospitalization, and increased healthcare expenditure. Although medicines undergo extensive evaluation before approval, clinical trials may not identify all safety risks because of limited sample sizes, restricted patient populations, and relatively short observation periods. Genetic variability is one of several factors contributing to differences in drug response among individuals. Pharmacogenomics examines how variations across the genome influence

drug disposition, therapeutic response, and toxicity, providing a scientific foundation for individualized prescribing [1,2].

Genetic variants can affect drug-metabolizing enzymes, membrane transporters, pharmacological targets, and immune recognition pathways. Consequently, patients receiving identical drug doses may experience different systemic drug concentrations or immune-mediated responses. These differences may increase the risk of severe toxicity in susceptible individuals or reduce therapeutic effectiveness in others [1,3].

Traditional pharmacovigilance primarily identifies and evaluates adverse events through spontaneous reporting, clinical observation, epidemiological investigations, and post-marketing surveillance. Integrating pharmacogenomic information into these activities may improve the identification of patients at increased genetic risk and help explain otherwise unpredictable reactions [4,5].

This review discusses the principal genetic mechanisms underlying ADR susceptibility, clinically actionable gene–drug associations, the role of pharmacogenomic testing in clinical practice, and the integration of genetic information into personalized pharmacovigilance. It also examines implementation barriers and future opportunities for safer, evidence-based, and equitable medication use.

2. GENETIC MECHANISMS UNDERLYING ADVERSE DRUG REACTIONS

2.1. Genetic variation in drug-metabolizing enzymes

Drug-metabolizing enzymes are major determinants of drug exposure. Variants in genes encoding cytochrome P450 enzymes can produce poor, intermediate, normal, rapid, or ultrarapid metabolizer phenotypes, depending on the gene and the individual's genotype. These differences can alter therapeutic effectiveness and toxicity [1,3].

For example, CYP2D6 influences the metabolism of several antidepressants, antipsychotics, and opioid analgesics. Poor metabolism of some active drugs may increase exposure and adverse effects, whereas ultrarapid metabolism of codeine can increase morphine formation and potentially cause life-threatening respiratory depression. Conversely, reduced CYP2C19 activity can impair the conversion of clopidogrel into its active metabolite, reducing platelet inhibition and increasing the risk of adverse cardiovascular outcomes [3,6].

2.2. Genetic variation in drug targets and transporters

Genetic variation in drug targets and transport proteins can influence therapeutic response and adverse-event susceptibility. Variants affecting transporters may alter drug absorption, distribution, tissue penetration, or elimination. Genetic differences in pharmacological targets may also influence the dose required to achieve a therapeutic effect or the likelihood of treatment-associated toxicity [1,3].

These associations are often drug-specific. Therefore, a genetic variant should not automatically be considered a predictor of toxicity for every medicine metabolized by the same pathway. Interpretation requires evidence regarding the particular drug, genotype, clinical outcome, and relevant patient characteristics.

2.3. Immune-mediated genetic susceptibility

Human leukocyte antigen (HLA) genes encode molecules involved in antigen presentation and immune recognition. Certain HLA alleles are strongly associated with specific drug-induced hypersensitivity

reactions, including severe cutaneous adverse reactions.

The association between HLA-B*57:01 and abacavir hypersensitivity is an established example of pharmacogenomic-guided prevention. Similarly, HLA-B*15:02 is associated with carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis, particularly in genetically susceptible populations. HLA-B*58:01 is associated with allopurinol-induced severe cutaneous adverse reactions [7–9].

These examples demonstrate that genetic testing can identify selected high-risk patients before drug exposure, allowing clinicians to consider alternative treatments when supported by clinical guidelines.

3. CLINICALLY RELEVANT PHARMACOGENOMIC BIOMARKERS

Pharmacogenomic biomarkers differ in their clinical validity, strength of evidence, and implications for prescribing. Some support drug avoidance or selection of an alternative medicine, while others guide dosage adjustment or closer monitoring. Regulatory labeling and professional guidelines provide complementary sources of prescribing recommendations [3,10].

Table 01: Major pharmacogenomic biomarkers associated with drug safety and adverse drug reactions

Gene/biomarker	Drug	Clinical implication of genetic variation	Potential safety intervention
CYP2C19	Clopidogrel	Reduced activation in intermediate and poor metabolizers may decrease antiplatelet efficacy	Consider an alternative antiplatelet agent when clinically indicated [6].
CYP2D6	Codeine	Ultrarapid metabolism may increase morphine exposure and respiratory toxicity	Avoid codeine in ultrarapid metabolizers according to applicable guidance [3].
TPMT	Azathioprine, mercaptopurine, thioguanine	Reduced enzyme activity increases the risk of thiopurine-related myelosuppression	Use genotype-informed dose reduction or an alternative regimen [11].

NUDT15	Thiopurines	Reduced function increases susceptibility to thiopurine-induced myelosuppression	Adjust treatment according to genotype and guideline recommendations [11].
HLA-B*57:01	Abacavir	Increased risk of potentially serious hypersensitivity	Screen before treatment and avoid abacavir in allele-positive patients [7].
HLA-B*15:02	Carbamazepine	Increased risk of Stevens–Johnson syndrome and toxic epidermal necrolysis	Test susceptible patients before treatment and select an alternative when indicated [8,9].
HLA-B*58:01	Allopurinol	Increased risk of severe cutaneous adverse reactions	Consider pretreatment testing in populations for whom testing is recommended [10].

Source: Compiled from published pharmacogenomic guidelines, clinical studies, and regulatory recommendations [3,6–11].

As summarized in Table 01, pharmacogenomic information can inform several distinct safety interventions, including avoiding a contraindicated drug, selecting an alternative therapy, adjusting the dose, and intensifying monitoring. The appropriate intervention depends on the specific gene–drug association and the strength of supporting evidence. Genetic results must be interpreted alongside renal and hepatic function, concomitant medications, clinical indication, and other patient-specific factors.

4. PHARMACOGENOMICS-GUIDED PERSONALIZED PHARMACOVIGILANCE

4.1. Pre-prescription risk assessment

Pre-prescription pharmacogenomic assessment aims to identify actionable genetic variants before a patient receives a medicine associated with a known risk. Testing may be performed reactively, when a particular

drug is being considered, or pre-emptively, with results stored for use across future prescribing decisions.

Pre-emptive testing can be particularly useful for patients likely to receive multiple medicines with established pharmacogenomic recommendations. However, the decision to test should be guided by clinical utility, the likelihood of future drug exposure, available evidence, and local practice recommendations [4,5].

4.2. Integration with electronic health records

Electronic health records (EHRs) can store validated pharmacogenomic results and make them available during prescribing. Clinical decision-support systems may generate alerts when a prescribed drug is associated with an actionable genetic result, suggest an alternative medicine, or recommend a genotype-informed dosage adjustment.

Such systems should prioritize clinically meaningful alerts and explain the recommended action. Poorly designed systems may generate excessive warnings, contributing to alert fatigue and reduced adherence to recommendations. Standardized terminology and updated clinical rules are therefore essential for safe implementation [4,5].

4.3. Integration with post-marketing surveillance

Conventional pharmacovigilance depends on reports from healthcare professionals, patients, manufacturers, and observational studies to identify and evaluate potential drug-safety signals. Incorporating relevant genetic information into adverse-event reports may help distinguish genetically susceptible subgroups and clarify mechanisms underlying severe or unexpected reactions [4,5].

For example, recording the relevant genotype, drug exposure, dosage, reaction phenotype, clinical outcome, and relevant concomitant medications could improve the interpretation of suspected pharmacogenomic ADRs. Such information may support the investigation of safety signals and the development of more targeted risk-minimization strategies.

Nevertheless, pharmacogenomic data should complement rather than replace conventional adverse-event reporting. A genetic association alone does not establish that a particular adverse event was caused by a medicine; clinical assessment and appropriate causality evaluation remain necessary.

5. BENEFITS OF PHARMACOGENOMICS-GUIDED DRUG SAFETY

The integration of pharmacogenomics into clinical care offers several potential benefits.

1. **Prevention of avoidable ADRs:** Identifying selected high-risk genotypes before treatment may prevent serious reactions, particularly when validated recommendations support avoiding a specific drug.
2. **Improved treatment selection:** Genetic information can help clinicians select medicines

with a more favorable expected safety and efficacy profile.

3. **Individualized dosing:** Genotype-informed dosing may reduce excessive drug exposure or inadequate therapeutic response for selected medications.
4. **Enhanced safety surveillance:** Incorporating genetic information into post-marketing reports may improve the characterization of susceptible subgroups and support more focused investigations.
5. **Improved clinical decision-making:** Linking genetic results to EHRs and validated clinical guidelines can facilitate consistent prescribing decisions [4,5,10].
6. Clinical evidence supports the value of selected interventions. The PREDICT-1 trial demonstrated that prospective HLA-B*57:01 screening substantially reduced immunologically confirmed abacavir hypersensitivity, illustrating how a validated genetic biomarker can translate into a practical drug-safety intervention [7].
7. These benefits should not be generalized to every available pharmacogenomic test. The clinical value of testing depends on the strength of the gene–drug association, the availability of an effective intervention, and the context in which the test is used.

6. CHALLENGES AND LIMITATIONS

6.1. Genetic diversity and population representation

The frequency of clinically relevant alleles varies among populations. Underrepresentation of certain ancestry groups in genomic research can limit the interpretation of test results and contribute to unequal access to effective pharmacogenomic care. For example, the distribution of NUDT15 variants differs across populations, demonstrating the importance of including diverse groups in research and clinical implementation [11].

6.2. Cost and accessibility

The cost of testing, limited laboratory infrastructure, reimbursement barriers, and shortages of trained healthcare professionals can restrict implementation. These challenges may be particularly significant in resource-constrained healthcare systems. Economic evaluations should consider not only testing costs but also potential reductions in severe ADRs, hospital admissions, and treatment failure [4,12].

6.3. Interpretation and clinical complexity

Genetic information does not fully determine an individual's drug response. Age, organ function, disease severity, drug interactions, adherence, and environmental factors can modify the effects of genetic variants. Furthermore, some gene–drug associations have limited evidence for specific clinical outcomes, making it inappropriate to use them as definitive predictors of toxicity [1,4].

6.4. Ethical, legal, and privacy concerns

Pharmacogenomic information may reveal inherited characteristics relevant beyond the immediate prescribing decision. Secure data storage, informed consent, appropriate access controls, and transparent policies for data sharing are essential. Clinical systems must also communicate uncertainty clearly and avoid discriminatory use of genetic information [5,12].

7. FUTURE PERSPECTIVES

Future pharmacogenomics-guided pharmacovigilance will likely involve greater integration of genomic data, clinical records, medication histories, and longitudinal safety outcomes. Standardized reporting of genotypes and phenotypes could improve the comparability of adverse-event reports across institutions and countries.

Artificial intelligence and machine-learning methods may help identify patterns involving multiple genetic variants, concomitant medicines, and patient characteristics. However, these approaches require representative datasets, independent validation, transparent evaluation, and safeguards against algorithmic bias [5,13].

Another important direction is the development of pre-emptive pharmacogenomic programs that make validated results available throughout a patient's healthcare journey. Such programs should include updated clinical decision-support rules, clear responsibility for interpreting results, and mechanisms for communicating relevant findings when patients move between healthcare providers.

In India and other genetically diverse countries, implementation should prioritize population-relevant evidence, equitable access to testing, and integration with existing pharmacovigilance infrastructure. Collaboration among clinicians, pharmacists, genetic laboratories, researchers, regulators, and patients will be important for translating genomic discoveries into effective clinical practice.

8. CONCLUSION

Pharmacogenomics-guided drug safety provides a promising approach to reducing genetically mediated adverse drug reactions and improving individualized treatment. Variants in drug-metabolizing enzymes, transporters, drug targets, and HLA genes can influence treatment outcomes and, for selected drug–gene pairs, identify patients who require alternative therapies, modified doses, or additional monitoring. As demonstrated by established examples involving abacavir, carbamazepine, clopidogrel, and thiopurines, pharmacogenomic testing can support clinically meaningful safety interventions.

Nevertheless, genetic testing cannot independently predict all adverse reactions and must be integrated with clinical assessment, laboratory monitoring, medication review, and conventional pharmacovigilance. Addressing implementation costs, population diversity, ethical concerns, and limitations in

clinical evidence will be essential. A coordinated approach combining validated genetic testing, electronic decision support, and continuous post-marketing surveillance could strengthen medication safety and advance more personalized, proactive, and equitable pharmacovigilance.

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