Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

# Pharmacogenomics in Emergency Care: Actionable Genetic Variability, Drug-Related Toxicity, and Precision Prescribing

**Dayanna Estefania Fernández Astudillo**
*Universidad Catolica de Cuenca*
edayafernandez0203@gmail.com
https://orcid.org/0009-0001-3604-2793

**Elsa Noralma Lucas Parrales**
*Universidad Estatal del Sur de Manabí- Carrera de Laboratorio Clínico*
elsa.lucas@unesum.edu.ec
https://orcid.org/0000-0002-7651-2948

**Cristian David Castro Hernandez**
*Universidad Antonio Nariño*
Cristian24ccx@gmail.com
https://orcid.org/0009-0006-1248-3398

***Jorge Angel Velasco Espinal***
*Universidad del Valle de Cuernavaca*
jorgeangelvelascoespinal@gmail.com
https://orcid.org/0009-0000-3567-0774

**María Alejandra Galindo Van Strahlen**
*COLSANITAS*
mgalindov4@gmail.com
https://orcid.org/0009-0002-6525-379X

***Alexa Fernanda Uriostegui Navarro***
*Universidad del Valle de Cuernavaca*
fernavarro0401@gmail.com
https://orcid.org/0009-0007-9161-3177

**Sebastián Prieto Rueda**
*Hospital La Misericorida Calarca*
sprieto65142@gmail.com
https://orcid.org/0009-0002-7763-0126

**Daniel Alberto Madrid González**
*Universidad del Valle de Cuernavaca*
drmadirdgonzalez@gmail.com
https://orcid.org/0000-0002-4453-8625

**Received:** 22-Sep-2026 | **Accepted:** 22-Sep-2026 | **Published:** 28-Sep-2026

*** Corresponding Author:** edayafernandez0203@gmail.com

**How to cite this article:** Fernández Astudillo, D. E., Castro Hernandez, C. D., Galindo Van Strahlen, M. A., Prieto Rueda, S., Lucas Parrales, E. N., Velasco Espinal, J. A., Uriostegui Navarro, A. F., & Madrid González, D. A. (2026). Pharmacogenomics in Emergency Care: Actionable Genetic Variability, Drug-Related Toxicity, and Precision Prescribing. México. *International Science Journal* "TheSci". 4 (1) 369-403. Quality Consulting Instituto de Educación Capacitación y Certificación de México. https://ieccmexico.com/thesci

**Copyright (c).** 2026 Fernández Astudillo, D. E., Castro Hernandez, C. D., Galindo Van Strahlen, M. A., Prieto Rueda, S., Lucas Parrales, E. N., Velasco Espinal, J. A., Uriostegui Navarro, A. F., & Madrid González, D. A.; This is an open access article distributed under the terms of the Attribution 4.0 International (CC BY-NC-SA 4.0). *International Science Journal* "TheSci". Mexico Review/ Vol. 4, N. 1 / pp. 369-403/ July-December 2026 / e-ISSN: 3122-3591 / p-ISSN: 3122-3753. Research Article

## ABSTRACT

Pharmacogenomic variability represents an increasingly relevant determinant of therapeutic response, drug toxicity, and treatment failure in emergency and internal medicine. This study analyzed the clinical applicability of actionable gene–drug interactions associated with acute pharmacological decision-making, severe adverse drug reactions, and the potential integration of genomic information into emergency-care workflows. A structured integrative review based on the Scientific Method was conducted using pharmacogenomic guidelines, implementation studies, regulatory resources, and clinically oriented evidence. Particular attention was given to associations involving CYP2D6, CYP2C19, CYP2C9, VKORC1, G6PD, RYR1, CACNA1S, HLA-B, SLCO1B1, TPMT, and NUDT15. The evidence demonstrated that pharmacogenomic-guided prescribing can be associated with measurable differences in medication safety. In the

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

PREPARE study, clinically relevant adverse drug reactions occurred in 21.0% of patients managed with genotype-guided treatment compared with 27.7% receiving standard care. In an emergency department cohort, actionable pharmacogenomic variants were identified in 99% of patients, while clinically relevant gene–drug pairs were detected in 53%. The analyzed interactions were mainly associated with altered drug metabolism, modified pharmacological sensitivity, severe genetically mediated adverse reactions, and delayed toxicities capable of producing acute-care presentations. Pharmacogenomic information showed potential utility for medication selection, dose modification, drug avoidance, risk stratification, and prevention of recurrent adverse events. Nevertheless, its clinical value depends on integration with renal and hepatic function, comorbidities, drug interactions, disease severity, and conventional emergency assessment. Preemptive testing integrated into electronic health records appears to be one of the most feasible models for emergency implementation because it allows actionable results to be available before time-sensitive treatment decisions. Pharmacogenomics may therefore contribute to a more preventive, individualized, and precise approach to medication safety in acute care, although prospective emergency-specific studies, interoperable systems, population-diverse validation, and equitable access remain necessary for broader implementation.

***KEYWORDS***

*pharmacogenomics, pharmacogenetics, emergency medicine, precision medicine, adverse drug reactions, gene–drug interactions, personalized therapy, drug toxicity, pharmacogenomic testing, preemptive pharmacogenomics, clinical decision support, medication safety*

## INTRODUCTION

Pharmacological treatment in emergency medicine is characterized by the need to make therapeutic decisions within limited timeframes and frequently under conditions of incomplete clinical information. Patients presenting to emergency departments may require analgesics, antiplatelet agents, anticoagulants, antimicrobials, anticonvulsants, cardiovascular drugs, or other medications whose therapeutic effects and toxicity profiles can vary considerably among individuals. Although age, renal and hepatic function, comorbidities, drug–drug interactions, and previous exposure remain essential determinants of pharmacological response, inherited genetic variation has emerged as another clinically relevant factor capable of modifying drug metabolism, transport, pharmacodynamic activity, and susceptibility to adverse drug reactions. Pharmacogenomics (PGx) seeks to characterize these gene–drug relationships and translate them into individualized therapeutic decisions that improve efficacy while reducing preventable toxicity [18], [19].

The relevance of pharmacogenomics becomes particularly evident in acute care because conventional dosing approaches are generally based on population averages and may not adequately represent patients with functionally important genetic variants. Polymorphisms affecting cytochrome P450 enzymes, drug transporters, immune-related human leukocyte antigen (HLA) molecules, pharmacological targets, and enzymes responsible for cellular protection may substantially modify exposure to commonly prescribed drugs. Consequently, two patients receiving the same medication at the same dose may experience markedly different clinical outcomes: one may obtain an appropriate therapeutic effect, another may show insufficient response, and a third may develop severe or potentially life-threatening toxicity. Such variability creates a significant challenge for emergency and internal medicine, where delayed therapeutic efficacy or unexpected toxicity can rapidly influence morbidity, hospital admission, intensive monitoring requirements, and subsequent treatment decisions [2], [18].

Evidence obtained directly from emergency departments supports the clinical significance of this problem. The ADRED study evaluated pharmacogenomic characteristics among patients presenting with adverse drug reactions and demonstrated that genetically determined metabolic profiles could contribute to clinically relevant drug-related events, including bleeding associated with clopidogrel exposure and CYP2C19 activity [2]. These findings are especially important because emergency departments frequently represent the point at which serious adverse drug reactions first become clinically apparent. Genetic information available before or during an acute encounter could therefore provide additional context for interpreting apparently unexplained therapeutic failure, excessive pharmacological response, or

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

severe toxicity. Nevertheless, pharmacogenomic information has historically been underused in emergency settings, partly because most implementation programs have been developed in outpatient care, specialty clinics, or preemptive precision-medicine initiatives rather than in acute-care workflows.

Recent evidence, however, suggests that this scenario may be changing. A 2026 emergency department cohort evaluating multigene preemptive pharmacogenomic testing identified actionable genetic variants in almost all tested patients and relevant gene–drug pairs in more than half of the cohort, supporting the feasibility and potential clinical utility of incorporating previously generated or rapidly accessible PGx information into emergency care [1].

These findings complement larger implementation studies outside the emergency department. In a multicenter European trial involving a 12-gene pharmacogenetic panel, genotype-guided prescribing significantly reduced clinically relevant adverse drug reactions compared with standard treatment, providing evidence that preemptive multigene testing can translate genomic information into measurable improvements in medication safety [3]. Together, these studies suggest that the clinical question is no longer limited to whether pharmacogenomics can influence drug response, but increasingly concerns how genomic information can be integrated into real-world decision-making processes in which therapeutic choices must often be made rapidly.

Several gene–drug interactions are particularly relevant to acute and emergency medicine. CYP2D6 variation, for example, alters the metabolic activation of codeine and tramadol, leading to substantial differences in analgesic response and toxicity risk. Poor metabolizers may obtain insufficient analgesia, whereas individuals with increased CYP2D6 activity can generate higher concentrations of active opioid metabolites, potentially increasing the risk of clinically significant adverse effects. The Clinical Pharmacogenetics Implementation Consortium (CPIC) therefore provides genotype-guided therapeutic recommendations for selected opioid therapies [4]. In cardiovascular emergencies, CYP2C19 is similarly relevant because clopidogrel requires metabolic bioactivation. Intermediate and poor CYP2C19 metabolizers demonstrate reduced formation of the active metabolite, decreased platelet inhibition, and an increased risk of adverse cardiovascular and cerebrovascular outcomes under specific clinical circumstances, leading to established pharmacogenomic recommendations for antiplatelet selection [5].

Other pharmacogenomic associations are linked not merely to differences in efficacy but to severe adverse reactions. Variants affecting CYP2C9 and VKORC1 can modify anticoagulant response and warfarin dose requirements [9], while G6PD deficiency can markedly increase susceptibility to oxidative drug-induced hemolysis. Current CPIC recommendations categorize medications according to their potential risk in individuals with G6PD deficiency and recommend avoidance or additional precautions for clinically significant exposures [8]. Likewise, pathogenic variants in RYR1 and CACNA1S are associated with susceptibility to malignant hyperthermia following exposure to triggering anesthetic agents or succinylcholine, representing a pharmacogenomic relationship with immediate relevance to emergency airway management, anesthesia, and urgent procedural care [7].

Immune-mediated pharmacogenomic associations further illustrate the potential severity of genetically influenced adverse drug reactions. Specific HLA variants are strongly associated with hypersensitivity syndromes and severe cutaneous adverse reactions produced by selected medications. Established examples include HLA-related risk associated with carbamazepine and oxcarbazepine [10], allopurinol [11], and abacavir [12]. Although genetic testing is ideally performed before exposure to these medications, emergency physicians may encounter patients during the acute manifestation of drug hypersensitivity, Stevens–Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, or other severe presentations. In these circumstances, recognition of a potential gene–drug association may support etiological assessment, documentation of drug intolerance, subsequent pharmacological avoidance, and counseling regarding future medication selection.

Despite the expanding number of evidence-based pharmacogenomic recommendations, several barriers continue to limit their systematic application in acute care. Conventional genotyping may not provide results within the timeframe required for an immediate emergency intervention, and interpretation of genetic variants requires integration with clinical factors rather than isolated use of genotype data. Additionally, phenotype prediction can be modified by drug interactions, organ dysfunction, polypharmacy, ancestry-related allele-frequency differences, and discrepancies among

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

testing platforms. Pharmacogenomics should therefore not be conceptualized as a replacement for clinical assessment, therapeutic drug monitoring, or standard emergency protocols, but rather as an additional layer of precision capable of refining treatment decisions when validated gene–drug information is available. The development of electronic clinical decision-support systems, standardized CPIC and Dutch Pharmacogenetics Working Group recommendations, integration of pharmacogenomic results into electronic health records, and broader use of preemptive multigene panels may reduce some of these limitations [15], [16], [17], [19].

This distinction is particularly relevant when considering the practical model most likely to succeed in emergency departments. Rather than performing de novo genetic testing for every acute prescription, one potential strategy involves preemptive pharmacogenomic profiling, in which clinically actionable genetic results are generated before an emergency occurs and remain accessible within the patient's electronic medical record. When the patient later requires urgent treatment, the emergency physician can retrieve the information immediately and determine whether a relevant gene–drug interaction exists. The recent demonstration that multigene PGx information can be incorporated into emergency department workflow supports the feasibility of this approach [1]. At the same time, regulatory resources and curated pharmacogenomic databases, including PharmGKB and pharmacogenetic associations recognized by the U.S. Food and Drug Administration, provide frameworks for distinguishing clinically actionable associations from relationships that remain primarily investigational [18], [20].

Within this context, the central research question of the present study is **to what extent clinically actionable pharmacogenomic information can contribute to the identification of therapeutic variability and serious adverse drug reactions in emergency medicine, and which gene–drug relationships currently offer the greatest potential for integration into acute clinical decision-making**. It is hypothesized that clinically validated pharmacogenomic variants are associated with meaningful differences in drug efficacy and toxicity for several medications relevant to emergency and internal medicine, and that systematic identification of these variants could improve medication selection, dosing, risk stratification, and prevention of severe adverse reactions, particularly when genomic information is available preemptively.

To address this question, the study adopts a structured integrative approach combining contemporary pharmacogenomic evidence with clinically oriented analysis of actionable gene–drug interactions. Particular attention is given to associations supported by established pharmacogenomic guidelines and implementation studies, including genes involved in drug metabolism, pharmacodynamic response, immune-mediated hypersensitivity, hemolytic susceptibility, and anesthesia-related complications. Evidence is examined according to its potential relevance to emergency presentations, therapeutic variability, severity of adverse reactions, availability of genotype-guided recommendations, and feasibility of integration into acute-care workflows. This design allows the investigation to connect molecular mechanisms with practical clinical scenarios while distinguishing established therapeutic applications from areas in which evidence or implementation remains limited.

Accordingly, the objective of this study is not only to describe the molecular basis of pharmacogenomic variability but also to evaluate its potential clinical role within emergency medicine. By integrating knowledge from internal medicine, emergency care, and medical genetics, the study seeks to identify the principal pharmacogenomic interactions capable of influencing urgent therapeutic decisions, characterize their relationship with serious adverse drug reactions and treatment failure, and examine current possibilities for implementing precision pharmacotherapy in acute-care environments. Such an approach may contribute to a transition from predominantly reactive management of adverse drug events toward a more preventive model in which genomic information becomes one component of individualized and safer pharmacological decision-making.

## DEVELOPMENT

### Pharmacogenomic Basis of Therapeutic Variability in Acute Care

Interindividual variability in pharmacological response represents one of the most complex challenges in clinical medicine. Even when patients receive an identical medication at an equivalent weight-adjusted dose, substantial differences may occur in plasma drug concentrations, therapeutic effectiveness, duration of action, and toxicity.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Traditionally, this variability has been attributed to age, body composition, renal and hepatic function, comorbidities, adherence, concomitant medications, and environmental exposures. However, genomic variation can substantially modify several of these processes and contribute to clinically important differences that cannot be adequately predicted using conventional clinical variables alone [18], [19].

Pharmacogenomic variation influences both pharmacokinetics and pharmacodynamics. From a pharmacokinetic perspective, polymorphisms in genes encoding metabolic enzymes and transport proteins can modify absorption, distribution, metabolism, and elimination. The cytochrome P450 enzyme system is particularly relevant because several of its isoenzymes metabolize medications frequently encountered in internal and emergency medicine. CYP2D6, CYP2C19, and CYP2C9 illustrate how genetic variation can classify individuals into different predicted metabolic phenotypes, ranging from poor to ultrarapid metabolism. These phenotypes can substantially alter exposure to active drugs or, in the case of prodrugs, the generation of active metabolites [4]–[6].

Pharmacodynamic variability is equally relevant. Variants affecting receptors, enzymes, ion channels, immune-response molecules, or other drug targets may alter the intensity of therapeutic or toxic responses without necessarily changing circulating drug concentrations. In this context, pharmacogenomics extends beyond the concept of accelerated or reduced metabolism and includes genetically mediated hypersensitivity, altered coagulation, skeletal-muscle hypermetabolism, hemolysis, myotoxicity, and other clinically relevant phenotypes [7]–[13].

This distinction has particular importance in emergency medicine. In acute care, therapeutic decisions are frequently made before a complete medication history, previous adverse-event record, or longitudinal clinical information can be obtained. Moreover, the clinical consequences of an inappropriate therapeutic response may emerge rapidly. Failure of antiplatelet therapy in a patient with an acute coronary syndrome, excessive anticoagulant sensitivity, insufficient opioid analgesia, drug-induced hemolysis, or a severe immune-mediated reaction may require urgent diagnostic and therapeutic interventions. Pharmacogenomic information therefore has the potential to function as an additional risk-modifying variable within a broader precision-medicine model.

**CYP2D6 and Variability in Opioid Response**

The relationship between *CYP2D6* and selected opioids provides one of the clearest examples of pharmacogenomic variability relevant to acute pain management. CYP2D6 metabolizes numerous medications and exhibits extensive genetic polymorphism. Depending on the combination of inherited alleles, patients may be classified into poor, intermediate, normal, or ultrarapid metabolizer phenotypes [4].

Codeine and tramadol are particularly important because part of their analgesic activity depends on CYP2D6-mediated formation of pharmacologically active metabolites. Codeine is converted to morphine, whereas tramadol is metabolized to O-desmethyltramadol. Reduced CYP2D6 activity can therefore result in inadequate active-metabolite formation and insufficient analgesia despite administration of apparently appropriate doses. At the opposite extreme, increased CYP2D6 activity may result in higher or faster formation of active metabolites, potentially increasing opioid-related toxicity [4].

This phenomenon is relevant to emergency departments because analgesia is frequently initiated before long-term follow-up is possible. In a patient with an actionable CYP2D6 result already documented in the electronic medical record, selection of an opioid that is not substantially dependent on CYP2D6 could potentially avoid ineffective treatment or excessive exposure. Nevertheless, genotype should be interpreted together with respiratory status, concomitant sedatives, renal function, opioid tolerance, age, and other factors that determine opioid safety. Pharmacogenomic information therefore modifies rather than replaces conventional clinical risk assessment.

The CYP2D6 phenotype can also be influenced functionally by concomitant medications. Potent CYP2D6 inhibitors may cause a patient with a genetically normal metabolic capacity to exhibit a functional phenotype resembling reduced metabolism, a phenomenon commonly referred to as phenoconversion. This illustrates one of the central principles of clinical pharmacogenomics: genotype establishes biological potential, but actual drug response results from the interaction between inherited variation and the patient's current physiological and pharmacological environment.

**CYP2C19 and Antiplatelet Therapy in Cardiovascular and Neurovascular Emergencies**

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The *CYP2C19*–clopidogrel interaction has direct relevance to both emergency medicine and internal medicine. Clopidogrel is a prodrug that requires hepatic bioactivation, and CYP2C19 contributes substantially to the formation of its active metabolite. Patients carrying no-function alleles may display intermediate or poor metabolizer phenotypes, resulting in lower active-metabolite concentrations and reduced inhibition of platelet aggregation [5].

Clinical evidence has associated CYP2C19 intermediate and poor metabolism with increased risk of adverse cardiovascular outcomes in clopidogrel-treated patients, particularly among individuals with acute coronary syndromes undergoing percutaneous coronary intervention. CPIC consequently recommends consideration of alternative P2Y12 inhibitors in selected clinical situations when CYP2C19 loss-of-function phenotypes are identified [5]. Evidence has also expanded toward neurovascular indications, including ischemic stroke and transient ischemic attack, although therapeutic decisions must continue to account for indication-specific evidence, bleeding risk, contraindications, and accessibility of alternative agents.

From an emergency perspective, this gene–drug interaction demonstrates why pre-existing pharmacogenomic data may be particularly valuable. Waiting for conventional genotyping after presentation with an acute coronary syndrome may be incompatible with the timeframe of immediate antiplatelet therapy. Conversely, when CYP2C19 status has been determined preemptively and is readily available in the electronic health record, genotype-informed selection can be incorporated without delaying standard emergency treatment.

The example also illustrates the importance of distinguishing pharmacogenomic actionability from genetic determinism. CYP2C19 genotype is an important contributor to clopidogrel response but does not explain all variability. Diabetes, obesity, smoking, adherence, concurrent medications, platelet biology, disease severity, and procedural factors continue to influence clinical outcomes [5]. Genomic information is therefore most useful when integrated into a multidimensional model of therapeutic decision-making.

**Anticoagulation and Genetically Determined Bleeding Risk**

Anticoagulants represent another therapeutically important area because the consequences of excessive or insufficient anticoagulation may include major bleeding, thrombosis, stroke, or recurrent embolic events. Warfarin has a narrow therapeutic index and considerable interindividual variability in dose requirement. Variants in *CYP2C9*, which contributes to warfarin metabolism, and *VKORC1*, which encodes the pharmacological target of warfarin, account for an important component of this variability. Other genetic factors, including *CYP4F2*, may further influence dose requirements [9].

Reduced-function CYP2C9 variants can decrease warfarin clearance and prolong the time required to achieve a stable anticoagulant response. Variants affecting VKORC1 can modify sensitivity to the drug. When these factors are not recognized, standard initial doses may produce excessive anticoagulation in susceptible individuals. Pharmacogenetically informed dosing algorithms therefore combine genotype with clinical variables such as age, body size, interacting medications, and treatment indication [9].

In the emergency department, pharmacogenomic testing is not a substitute for measurement of the international normalized ratio or established bleeding-management protocols. Its relevance is instead contextual. Genetic information may contribute to understanding unusual dose sensitivity, support subsequent dose individualization after stabilization, and help prevent recurrence after an anticoagulant-related adverse event. This distinction between immediate emergency management and prevention of subsequent toxicity is essential when evaluating the realistic role of pharmacogenomics in acute care.

**Genomic Predisposition to Severe Adverse Drug Reactions**

The greatest clinical value of pharmacogenomics may occur when genetic variation predicts adverse reactions that are uncommon but potentially catastrophic. In these situations, the objective is not merely to optimize drug concentration but to prevent exposure in genetically susceptible individuals.

One important example involves glucose-6-phosphate dehydrogenase deficiency. G6PD is essential for maintaining protection against oxidative stress in erythrocytes. Individuals with reduced enzymatic activity can develop acute hemolysis after exposure to specific oxidative medications. CPIC recommendations classify drug exposures according

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

to the strength of evidence and potential risk in individuals with genetically predicted G6PD deficiency [8]. Emergency manifestations may include abrupt anemia, jaundice, dark urine, weakness, tachycardia, or other consequences of intravascular or extravascular hemolysis. In such cases, genetic susceptibility provides a mechanistic explanation for toxicity and has implications for future avoidance of triggering agents.

Another highly relevant example is malignant hyperthermia susceptibility associated predominantly with pathogenic variation in *RYR1* and, less frequently, *CACNA1S*. Exposure of genetically susceptible individuals to potent volatile anesthetic agents or succinylcholine can precipitate an uncontrolled hypermetabolic skeletal-muscle response characterized by increasing carbon dioxide production, muscle rigidity, hyperthermia, acidosis, rhabdomyolysis, hyperkalemia, and potentially cardiovascular collapse [7]. CPIC guidance indicates that individuals with recognized pathogenic variants associated with malignant hyperthermia susceptibility should be considered at risk when exposure to triggering agents is contemplated [7].

This interaction can be clinically relevant during urgent airway management or emergency procedures. Succinylcholine remains an agent that may be considered for rapid neuromuscular blockade in selected settings, meaning that previously documented susceptibility has immediate consequences for drug selection. Because acute malignant hyperthermia requires immediate recognition and treatment, pharmacogenomic knowledge in this context represents a form of preventive information rather than a diagnostic requirement during the crisis itself.

**HLA Variation and Immune-Mediated Drug Toxicity**

Human leukocyte antigen variation represents a different pharmacogenomic mechanism. Rather than primarily affecting metabolism, certain HLA alleles influence immune recognition of drug-related antigens and can markedly increase susceptibility to severe hypersensitivity reactions. Some of the best-established relationships involve carbamazepine, oxcarbazepine, allopurinol, and abacavir [10]–[12].

Selected HLA genotypes are associated with severe cutaneous adverse reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis. These conditions may initially present to emergency services with fever, painful skin lesions, mucosal involvement, blistering, epidermal detachment, or systemic manifestations. Because mortality and long-term complications can be substantial, prevention through genotype-guided drug avoidance is preferable to recognition after the reaction has developed.

The association between *HLA-B* variants and carbamazepine-related severe cutaneous reactions is particularly relevant because carbamazepine may be used in patients with epilepsy, neuropathic pain, or psychiatric conditions [10]. Similarly, *HLA-B*58:01 is strongly associated with severe allopurinol hypersensitivity, providing a basis for genotype-informed avoidance in susceptible individuals [11]. *HLA-B*57:01 testing before abacavir initiation has become an established example of pharmacogenomics successfully preventing a serious drug hypersensitivity syndrome [12].

These relationships demonstrate that the value of genetic information extends beyond choosing a dose. In certain circumstances, the appropriate pharmacogenomic intervention consists of avoiding the drug altogether and selecting a therapeutically appropriate alternative.

**Additional Gene–Drug Relationships With Potential Acute-Care Relevance**

Other pharmacogenomic associations may indirectly generate emergency presentations. Variants in *SLCO1B1*, and to a lesser extent *ABCG2* and *CYP2C9*, influence susceptibility to statin-associated musculoskeletal adverse effects [13]. Although most statin-related symptoms are not medical emergencies, severe muscle injury and rhabdomyolysis can produce acute kidney injury, electrolyte disturbances, and systemic complications requiring urgent treatment. Recognition of genetic susceptibility may therefore contribute to prevention in patients requiring long-term lipid-lowering therapy.

Similarly, *TPMT* and *NUDT15* variation can substantially alter thiopurine metabolism. Reduced enzymatic activity increases the risk of severe myelosuppression when standard thiopurine doses are administered. Contemporary CPIC guidance recommends genotype- or phenotype-informed dose modification for susceptible individuals [14]. Severe neutropenia, infection, anemia, or thrombocytopenia can ultimately produce emergency presentations, demonstrating how pharmacogenomic prevention initiated in chronic care can reduce acute-care complications.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The clinical relevance of pharmacogenomics in emergency medicine therefore should not be restricted to medications administered inside the emergency department. A significant proportion of pharmacogenomically mediated emergencies arise from medications initiated previously in outpatient, inpatient, oncological, neurological, psychiatric, cardiovascular, or primary-care settings. The emergency department becomes the location where treatment failure or toxicity is recognized. This broader perspective connects pharmacogenomics with medication reconciliation, differential diagnosis, toxicology, internal medicine, and post-discharge prevention.

**Evidence for Preemptive Pharmacogenomic Testing**

A central question is whether pharmacogenomics can produce measurable improvements in patient safety when applied systematically. Large-scale implementation evidence increasingly supports the clinical utility of preemptive testing. In the multicenter PREPARE study, Swen *et al.* evaluated a 12-gene pharmacogenetic panel across seven European countries. Among patients with actionable gene–drug interactions, clinically relevant adverse drug reactions occurred in 21.0% of genotype-guided patients compared with 27.7% under standard care, corresponding to an odds ratio of 0.70 [3]. Across the wider study population, the same relative reduction was observed, supporting the feasibility of panel-guided prescribing across different healthcare settings.

These findings are important because they shift pharmacogenomics from theoretical association toward measurable clinical prevention. Rather than evaluating one genetic variant and one medication in isolation, preemptive panels create a genomic resource that may remain useful throughout the patient's life. A result generated for one therapeutic indication can subsequently influence medications prescribed by multiple specialties.

This model may be particularly advantageous in emergency medicine. Reactive testing performed only after an adverse event has occurred has limited preventive value for that initial event. Similarly, ordering a genetic test after an emergency medication is required may be clinically impractical if the result takes hours or days. Preemptive testing changes the temporal relationship: genetic information is generated before the acute event and stored for later use.

The emerging feasibility of this strategy in emergency care was illustrated in a 2026 cohort study involving 100 patients who underwent a 16-gene pharmacogenomic panel within an emergency department workflow. Actionable genetic variants were identified in 99% of tested patients, and existing gene–drug pairs were identified in 53%; most individuals with actionable findings carried multiple relevant variants [1]. Although this was a single-center retrospective study and does not establish that every identified variant requires an immediate medication change, it demonstrates the potentially high prevalence of clinically interpretable pharmacogenomic information among patients encountered in acute care.

**From Genetic Result to Emergency Clinical Decision**

The presence of a pharmacogenomic variant does not automatically imply that an emergency intervention must be modified. Clinical actionability depends on several sequential factors: the validity of the gene–drug association, the patient's predicted phenotype, the medication being considered, the indication, available alternatives, severity of the clinical situation, concomitant medications, organ function, and strength of the therapeutic recommendation.

Resources such as CPIC, the Dutch Pharmacogenetics Working Group, PharmGKB, and regulatory pharmacogenetic information provide structured frameworks for translating laboratory results into prescribing recommendations [18]–[20]. CPIC guidelines are particularly designed to answer a practical question: when a patient's genotype is already known, how should that information be used to guide medication therapy? [19]. This approach is highly compatible with emergency decision support because it separates the question of whether a patient should be tested from the question of what clinicians should do with an available result.

For practical integration, genomic information must therefore be converted into concise clinical guidance. An emergency physician cannot be expected to manually interpret raw variants during a time-sensitive resuscitation. Electronic health records can instead link a previously validated genotype with the medication order and generate a relevant alert, phenotype interpretation, or alternative recommendation. Ideally, this information should be selective rather than excessive, because large numbers of low-priority alerts can contribute to alert fatigue and reduce clinical adherence.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Clinical pharmacologists, geneticists, pharmacists, emergency physicians, internists, laboratory specialists, and information-technology teams consequently have complementary roles in pharmacogenomic implementation. Genetic laboratories must provide accurate allele detection and phenotype assignment; pharmacists and clinical pharmacologists can evaluate gene–drug and drug–drug interactions; genetic specialists contribute to interpretation of complex results; and emergency clinicians determine whether genomic information is relevant to the immediate clinical context.

**Limitations and Challenges of Pharmacogenomics in Emergency Medicine**

Despite its potential, routine pharmacogenomic application in emergency care faces important limitations. The first is turnaround time. Conventional genomic testing may not provide information rapidly enough to influence a medication that must be administered within minutes. Preemptive testing partially addresses this limitation, whereas rapid point-of-care genotyping may eventually expand the number of acute scenarios in which newly obtained results can inform treatment.

A second limitation is incomplete genetic representation. Allele frequencies differ among populations, and evidence supporting some pharmacogenomic associations has been generated disproportionately in populations with European ancestry. Application of limited genotyping panels may fail to detect rare or population-specific variants, creating the possibility of incorrect phenotype assignment. Implementation strategies must therefore consider genetic diversity and avoid assuming that a panel validated in one population provides equivalent coverage in another [17].

Third, the genotype is only one determinant of phenotype. Renal impairment, hepatic dysfunction, inflammation, critical illness, age, drug interactions, nutritional status, and other environmental factors can modify pharmacokinetics independently of inherited variation. For this reason, a genotype-guided recommendation should never override an immediate contraindication or a clinically evident physiological abnormality.

The interpretation of pharmacogenomic findings also requires differentiation between strongly validated actionable associations and exploratory genetic relationships. Commercial panels can contain numerous variants for which evidence varies substantially in quality. Using broad genetic reports without evidence-based filtering could lead to unnecessary medication changes or false reassurance. The most defensible acute-care applications are therefore those supported by reproducible evidence and established clinical guidelines.

Ethical and operational considerations are also relevant. Genetic data are persistent, potentially useful for decades, and may contain information beyond the immediate prescribing decision. Healthcare systems must establish appropriate procedures for consent, privacy, data security, result portability, patient education, and equitable access. The usefulness of preemptive pharmacogenomics would be substantially reduced if results were inaccessible when patients receive care outside the institution where testing was originally performed.

**Integration of Internal Medicine, Emergency Medicine, and Genetics**

The intersection between internal medicine, emergency medicine, and genetics provides a particularly appropriate framework for pharmacogenomic implementation. Internal medicine contributes comprehensive evaluation of multimorbidity, polypharmacy, organ dysfunction, and chronic pharmacotherapy. Emergency medicine provides the acute-care environment in which treatment failure and severe adverse drug reactions frequently become clinically apparent. Medical genetics and pharmacogenomics contribute an additional explanatory layer capable of identifying inherited susceptibility to abnormal drug response.

The strongest clinical model is therefore not a genome-centered replacement of conventional medicine, but an integrated system in which genomic information complements physiological, laboratory, pharmacological, and clinical data. A patient with gastrointestinal bleeding while receiving anticoagulant therapy still requires conventional stabilization and evaluation; a patient with suspected malignant hyperthermia requires immediate emergency treatment regardless of whether a genetic result is available; and a patient with severe cutaneous drug hypersensitivity requires withdrawal of the suspected agent and supportive management. Pharmacogenomic information becomes valuable because it can explain susceptibility, refine future prescribing, identify medications that should be avoided, and potentially prevent recurrence.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Current evidence supports a transition from exclusively reactive pharmacogenomics toward preemptive identification of actionable variants. The approximately 30% relative reduction in clinically relevant adverse drug reactions observed with a multigene pharmacogenetic strategy in the PREPARE trial [3], together with recent evidence demonstrating the feasibility and high yield of pharmacogenomic assessment within an emergency department population [1], provides a rationale for further evaluation of genomic information as a component of medication safety.

Accordingly, pharmacogenomics in emergency medicine should be understood as a continuum extending from prevention to acute recognition and subsequent risk reduction. Before an emergency occurs, genomic information may guide medication selection and decrease exposure to genetically inappropriate therapies. During the acute episode, previously available results may support rapid therapeutic decisions or contribute to the identification of an adverse drug reaction. After stabilization, pharmacogenomic interpretation may influence medication reconciliation, discharge prescriptions, specialist follow-up, and prevention of future events. This longitudinal model provides the conceptual basis for examining how actionable genetic information can be translated into safer, more individualized pharmacotherapy across emergency and internal-medicine settings.

## GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

### General Objective

To **analyze and integrate** the clinical relevance of pharmacogenomic variability in emergency medicine, identifying actionable gene–drug interactions associated with therapeutic failure and severe adverse drug reactions, and evaluating their potential incorporation into acute-care decision-making through evidence-based pharmacogenomic recommendations.

### Specific Objectives

**Cognitive domain**

1. To **identify** the principal pharmacogenomic variants associated with clinically relevant differences in drug metabolism, therapeutic response, and toxicity in medications commonly encountered in emergency and internal medicine.
2. To **describe** the molecular and pharmacological mechanisms through which variants in genes such as *CYP2D6, CYP2C19, CYP2C9, VKORC1, G6PD, RYR1, CACNA1S, HLA-B, SLCO1B1, TPMT,* and *NUDT15* modify drug efficacy or the probability of adverse reactions.
3. To **differentiate** pharmacokinetic, pharmacodynamic, and immune-mediated mechanisms responsible for interindividual variability in drug response.
4. To **analyze** the clinical implications of actionable gene–drug relationships in emergency scenarios, including inadequate analgesia, antiplatelet treatment failure, excessive anticoagulation, hemolysis, malignant hyperthermia, severe cutaneous adverse reactions, myotoxicity, and drug-induced myelosuppression.
5. To **compare** conventional pharmacological decision-making with genotype-informed strategies in order to determine the additional clinical information provided by pharmacogenomic testing.
6. To **evaluate** the strength and clinical applicability of current pharmacogenomic recommendations derived from recognized clinical guidelines, implementation studies, and validated pharmacogenomic databases.
7. To **interpret** available evidence regarding preemptive pharmacogenomic testing and its potential contribution to reducing clinically relevant adverse drug reactions.
8. To **determine** which pharmacogenomic associations currently have the greatest potential for practical integration into emergency and acute-care medicine.

**Psychomotor domain**

9. To **organize** clinically relevant gene–drug information into structured categories according to mechanism, predicted phenotype, associated medication, potential adverse effect, and recommended therapeutic action.
10. To **construct** a clinically oriented framework for the interpretation of pharmacogenomic results in emergency medicine, integrating genetic findings with pharmacological, biochemical, and clinical variables.
11. To **apply** evidence-based pharmacogenomic recommendations to representative acute-care scenarios in order to establish possible therapeutic modifications, drug avoidance strategies, or alternative medication selection.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

12. To **develop** a systematic process for recognizing pharmacogenomic information that may be relevant during medication reconciliation, emergency prescribing, adverse drug reaction assessment, and discharge planning.
13. To **integrate** pharmacogenomic results with clinical decision-support principles that could be incorporated into electronic medical records or medication-alert systems.

**Affective domain**

14. To **recognize** the importance of pharmacogenomic variability as a component of individualized and safer pharmacological care.
15. To **value** the interdisciplinary collaboration between emergency physicians, internists, geneticists, pharmacists, clinical pharmacologists, laboratory specialists, and information-technology professionals in the interpretation and implementation of pharmacogenomic information.
16. To **promote** responsible use of genetic information by considering patient privacy, informed consent, data protection, equity, accessibility, and the limitations of genomic testing.
17. To **adopt** a critical perspective regarding the interpretation of pharmacogenomic findings, distinguishing validated and clinically actionable associations from preliminary or insufficiently supported genetic relationships.
18. To **support** the incorporation of precision-medicine principles into emergency care without replacing conventional clinical judgment, physiological assessment, laboratory monitoring, or established emergency-treatment protocols.
19. To **appraise** the potential of pharmacogenomics to shift medication safety from a predominantly reactive model toward a preventive approach based on early identification of patients at increased genetic risk.

## OBJECT OF STUDY

The object of study of this research is the **clinical impact of actionable pharmacogenomic variability on therapeutic response, adverse drug reactions, and medication-related risk in patients requiring emergency or acute medical care**.

The phenomenon under investigation comprises the relationship between inherited genetic variants and clinically significant differences in drug metabolism, pharmacodynamic response, immune-mediated toxicity, and susceptibility to severe adverse events. Particular attention is directed toward pharmacogenomic interactions involving genes with established clinical relevance, including *CYP2D6, CYP2C19, CYP2C9, VKORC1, G6PD, RYR1, CACNA1S, HLA-B, SLCO1B1, TPMT,* and *NUDT15*, as well as other variants supported by validated clinical pharmacogenomic recommendations.

The study focuses on patients who may require urgent pharmacological treatment or who may present to emergency services because of therapeutic failure, unexpected drug toxicity, severe hypersensitivity, excessive pharmacological response, inadequate treatment effect, or medication-related complications. Although the analysis is centered on emergency medicine, it also incorporates the perspective of internal medicine because many pharmacogenomically influenced adverse events originate from chronic treatments initiated before the acute episode.

The pharmacological system under investigation includes medications that are either commonly used in acute care or capable of producing emergency presentations when genetically mediated variability alters their efficacy or safety. These include selected opioids, antiplatelet agents, anticoagulants, nonsteroidal anti-inflammatory drugs, anesthetic agents, neuromuscular blockers, anticonvulsants, urate-lowering therapies, antiretrovirals, statins, and thiopurines.

The principal unit of analysis is the **clinically actionable gene–drug interaction**. Each interaction is evaluated according to the genetic variant involved, predicted phenotype, pharmacological mechanism, medication affected, possible therapeutic consequence, severity of the associated adverse event, availability of evidence-based recommendations, and potential relevance to emergency decision-making.

The population of interest is therefore not defined by a single diagnosis but by the presence of a medication exposure or potential pharmacological intervention in which genomic variability may influence clinical outcomes. This includes patients with acute cardiovascular, neurological, hematological, toxicological, anesthetic, infectious, or pain-related conditions, as well as individuals presenting with suspected adverse drug reactions.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

A secondary component of the object of study is the healthcare system through which pharmacogenomic information can be translated into clinical action. This includes preemptive genetic testing, laboratory reporting, electronic medical records, clinical decision-support systems, pharmacogenomic databases, and professional guidelines designed to convert genotype information into therapeutic recommendations.

Accordingly, the study evaluates pharmacogenomics not only as a molecular phenomenon but also as a clinical decision-support strategy. The investigation examines how genetic information can contribute to medication selection, dosing, contraindication recognition, adverse-event prevention, post-event interpretation, and long-term risk reduction.

The boundaries of the study are restricted to pharmacogenomic associations with sufficient clinical evidence to support interpretation or therapeutic guidance. Exploratory genetic associations without established clinical utility are considered only when necessary to contextualize current limitations and future research directions. The study does not attempt to replace standard emergency assessment, toxicological evaluation, therapeutic drug monitoring, or conventional laboratory testing with genomic information.

## METHODOLOGY

### Study Design

This study was designed as a **structured integrative review based on the Scientific Method**, aimed at evaluating the clinical relevance of pharmacogenomic variability in emergency medicine, with particular emphasis on therapeutic response, severe adverse drug reactions, and the potential implementation of actionable genomic information in acute-care settings.

The Scientific Method was selected because it provides a sequential and reproducible framework for identifying a clinical problem, formulating a research question, collecting relevant evidence, analyzing observed relationships, and generating conclusions based on verifiable information. This methodological framework was complemented by an integrative evidence approach that allowed the inclusion of pharmacogenomic guidelines, clinical implementation studies, observational investigations, regulatory resources, and clinically relevant reviews.

The methodological process was organized around five fundamental components: identification of the clinical problem, formulation of the research question and hypothesis, systematic identification of relevant evidence, structured analysis of gene–drug interactions, and integration of findings according to their applicability in emergency medicine.

### Research Question

The principal research question was formulated as follows:

**To what extent can clinically actionable pharmacogenomic information contribute to the identification of therapeutic variability and severe adverse drug reactions in emergency medicine, and which gene–drug interactions currently present the greatest potential for integration into acute clinical decision-making?**

This question guided the selection, classification, and interpretation of the evidence included in the study.

### Working Hypothesis

The working hypothesis established that **clinically validated pharmacogenomic variants are associated with significant differences in drug efficacy and toxicity and that their identification may contribute to safer and more individualized pharmacological decision-making in emergency medicine, particularly when genomic information is available before the acute event or can be accessed rapidly through electronic health records**.

### Sources of Information

Scientific evidence was identified through recognized biomedical and pharmacogenomic information sources. The principal sources considered for the study included:

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

- PubMed/MEDLINE;
- Clinical Pharmacogenetics Implementation Consortium (CPIC);
- Pharmacogenomics Knowledgebase (PharmGKB);
- U.S. Food and Drug Administration pharmacogenomic resources;
- peer-reviewed journals specializing in clinical pharmacology, pharmacogenomics, internal medicine, emergency medicine, genetics, and precision medicine.

Particular priority was given to original investigations, clinical implementation studies, consensus recommendations, and pharmacogenomic guidelines with direct therapeutic implications.

The reference framework consisted of the previously selected scientific literature related to emergency pharmacogenomics, pharmacogenetic implementation, adverse drug reactions, and clinically actionable gene–drug interactions [1]–[20].

**Search Strategy**

The literature search was structured using combinations of controlled and free-text terms related to pharmacogenomics, emergency medicine, adverse drug reactions, therapeutic variability, and clinically actionable genetic variants.

Representative search terms included:

"pharmacogenomics," "pharmacogenetics," "emergency medicine," "emergency department," "adverse drug reactions," "drug toxicity," "precision medicine," "gene–drug interaction," "preemptive pharmacogenomics," "clinical implementation," "CYP2D6," "CYP2C19," "CYP2C9," "VKORC1," "G6PD," "RYR1," "CACNA1S," "HLA-B," "SLCO1B1," "TPMT," and "NUDT15."

Boolean operators were used to combine concepts, for example:

**(pharmacogenomics OR pharmacogenetics) AND (emergency medicine OR emergency department) AND (adverse drug reaction OR toxicity OR therapeutic response)**

Additional targeted searches were performed for individual gene–drug associations when clinically relevant information was required.

**Eligibility Criteria**

Evidence was considered eligible when it met one or more of the following criteria:

1. It evaluated a pharmacogenomic association with established or potentially relevant clinical implications.
2. It involved medications frequently used in emergency or internal medicine, or medications capable of producing complications requiring emergency treatment.
3. It provided genotype-based therapeutic recommendations.
4. It examined severe or clinically significant adverse drug reactions.
5. It assessed the implementation of pharmacogenomic testing in clinical practice.
6. It originated from recognized pharmacogenomic organizations, regulatory agencies, or peer-reviewed scientific publications.
7. It provided information relevant to medication selection, dosage modification, drug avoidance, risk stratification, or prevention of pharmacological complications.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Evidence was excluded when it was limited to experimental molecular findings without clear clinical translation, involved associations without sufficient supporting evidence, duplicated information already represented by higher-quality sources, or lacked relevance to acute clinical decision-making.

**Selection of Pharmacogenomic Associations**

Gene–drug interactions were selected according to their potential clinical relevance rather than exclusively according to the prevalence of the genetic variant.

Priority was assigned to associations meeting at least one of the following conditions:

- risk of a severe or potentially life-threatening adverse reaction;
- clinically meaningful alteration in therapeutic efficacy;
- availability of an evidence-based pharmacogenomic recommendation;
- relevance of the medication to emergency or internal medicine;
- potential for therapeutic modification based on genotype;
- feasibility of using previously available genetic information during acute care.

Based on these criteria, particular attention was directed toward associations involving *CYP2D6, CYP2C19, CYP2C9, VKORC1, G6PD, RYR1, CACNA1S, HLA-B, SLCO1B1, TPMT,* and *NUDT15* [4]–[14].

**Data Extraction**

Relevant information from each selected source was organized using a standardized analytical framework. The following variables were considered:

- gene or genetic variant;
- medication or pharmacological class;
- predicted phenotype;
- principal pharmacokinetic or pharmacodynamic mechanism;
- expected change in therapeutic response;
- associated adverse drug reaction;
- severity of the potential clinical consequence;
- emergency-medicine relevance;
- availability of genotype-guided recommendations;
- possible therapeutic intervention;
- evidence supporting clinical implementation.

This structure facilitated comparison between heterogeneous pharmacogenomic associations and allowed the findings to be evaluated according to their practical relevance in acute care.

**Clinical Classification of Gene–Drug Interactions**

For analytical purposes, gene–drug relationships were grouped into four principal categories.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The first category included **alterations in drug metabolism**, such as CYP2D6-associated opioid response and CYP2C19-associated clopidogrel activation.

The second category comprised **variations in pharmacological sensitivity or dose requirement**, including the influence of CYP2C9 and VKORC1 on warfarin therapy.

The third category included **genetically mediated severe adverse drug reactions**, such as G6PD-related hemolysis, RYR1- or CACNA1S-associated malignant hyperthermia, and HLA-associated hypersensitivity reactions.

The fourth category incorporated **pharmacogenomic relationships capable of producing delayed complications with potential emergency presentation**, including statin-associated muscle toxicity and thiopurine-related myelosuppression.

This classification allowed pharmacogenomic associations to be interpreted according to their mechanism and clinical manifestation rather than solely by gene nomenclature.

**Assessment of Clinical Actionability**

Clinical actionability was evaluated according to whether genetic information could reasonably modify a therapeutic decision.

An interaction was considered highly actionable when genomic information could support one or more of the following interventions:

- selection of an alternative medication;
- avoidance of a potentially harmful drug;
- adjustment of initial or maintenance dosage;
- intensification of clinical or laboratory monitoring;
- identification of patients at increased risk of severe toxicity;
- interpretation of an unexpected adverse drug reaction;
- prevention of recurrent exposure.

Recommendations supported by CPIC or equivalent evidence-based pharmacogenomic frameworks were given greater interpretative weight than exploratory associations [4]–[14], [19].

**Evaluation of Emergency-Medicine Relevance**

The relevance of each gene–drug interaction to emergency medicine was assessed through five clinical dimensions:

**1. Immediacy:** whether the pharmacological consequence could influence an acute therapeutic decision.

**2. Severity:** whether the associated outcome could produce hospitalization, organ dysfunction, life-threatening toxicity, or treatment failure.

**3. Therapeutic modifiability:** whether an alternative medication, dose adjustment, or preventive intervention was available.

**4. Accessibility of genomic information:** whether genetic results could realistically be available before or during the emergency encounter.

**5. Continuity of care:** whether identifying the interaction could prevent recurrent adverse events after discharge.

This approach allowed differentiation between pharmacogenomic information that is biologically relevant and information that is also practically useful in emergency care.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

**Analysis of Implementation Feasibility**

Implementation was analyzed at three levels.

At the **patient level**, the study considered whether genomic information could improve medication safety, reduce exposure to inappropriate therapy, or explain previous adverse reactions.

At the **clinical level**, attention was given to the ability of physicians, pharmacists, and genetic specialists to interpret pharmacogenomic findings and translate them into therapeutic decisions.

At the **health-system level**, analysis included preemptive testing, integration with electronic medical records, clinical decision-support alerts, availability of validated laboratory testing, and interoperability of genomic results.

Preemptive pharmacogenomic testing was considered particularly relevant because genetic information generated before an acute episode can remain available throughout the patient's lifetime and may therefore be accessed without delaying emergency treatment [1], [3], [15]–[17].

**Evidence Integration**

The extracted information was synthesized using a **qualitative comparative approach**. Evidence was not evaluated exclusively according to the number of studies available but according to the consistency of the pharmacogenomic association, existence of clinical recommendations, severity of the associated outcome, and potential to modify clinical management.

Findings from clinical implementation studies were compared with guideline recommendations to determine whether theoretical pharmacogenomic actionability had demonstrated applicability in real healthcare environments.

Particular attention was given to the multicenter PREPARE study, which demonstrated a reduction in clinically relevant adverse drug reactions through a multigene pharmacogenetic strategy [3], and to recent emergency department research evaluating the feasibility and clinical utility of multigene pharmacogenomic testing [1].

**Control of Methodological Bias**

Several strategies were incorporated to reduce interpretative bias.

Priority was given to peer-reviewed publications, evidence-based clinical guidelines, recognized pharmacogenomic databases, and regulatory information. When multiple publications described the same association, sources with greater methodological quality, updated recommendations, or direct clinical applicability were prioritized.

Exploratory associations were not interpreted as clinically equivalent to guideline-supported gene–drug interactions. Similarly, genetic information was evaluated together with conventional clinical variables because pharmacological response can be modified by renal function, hepatic function, age, inflammation, drug–drug interactions, and other non-genetic factors.

No pharmacogenomic association was considered sufficient by itself to replace standard diagnostic or therapeutic protocols in emergency medicine.

**Ethical Considerations**

Because pharmacogenomic information constitutes genetic health information, its clinical application requires consideration of confidentiality, informed consent, appropriate interpretation, data protection, and equitable access.

The analysis therefore incorporated the principle that genetic results should be used only when their clinical significance is sufficiently supported and when interpretation contributes to patient safety. Particular attention was given to avoiding deterministic interpretation of genotype because the presence of a genetic variant does not necessarily imply that an adverse clinical event will occur.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The proposed pharmacogenomic model is based on the integration of genetic information with clinical assessment rather than isolated genomic decision-making.

**Reproducibility**

To facilitate replication, the methodological framework specifies the databases and pharmacogenomic resources to be consulted, representative search terms, eligibility criteria, principal variables for data extraction, analytical categories, and criteria used to determine clinical actionability.

Future researchers can reproduce the approach by applying the same search strategy, selecting gene–drug interactions according to the defined eligibility criteria, extracting the established clinical variables, and evaluating each association according to evidence strength, clinical severity, therapeutic modifiability, and relevance to emergency medicine.

## PHASES OF DEVELOPMENT

### Phase 1. Identification and Delimitation of the Clinical Problem

The first phase consisted of defining the central clinical problem: the considerable interindividual variability observed in drug efficacy and toxicity among patients receiving similar pharmacological treatments.

This variability was analyzed from the perspective of emergency and internal medicine, where therapeutic decisions frequently occur under time constraints and where unexpected treatment failure or serious adverse reactions may have immediate clinical consequences.

The problem was delimited specifically to genetically influenced pharmacological variability. Therefore, the analysis focused on cases in which inherited genetic differences may modify drug metabolism, pharmacological activity, immune-mediated reactions, or susceptibility to severe toxicity.

During this phase, three principal dimensions of the problem were established:

1. variability in therapeutic effectiveness;
2. occurrence of clinically relevant or severe adverse drug reactions;
3. limited integration of pharmacogenomic information into acute-care decision-making.

The clinical relevance of the problem was supported by studies demonstrating the presence of actionable pharmacogenomic variants among emergency department patients and by implementation trials showing that genotype-guided prescribing can reduce clinically relevant adverse drug reactions [1]–[3].

### Phase 2. Formulation of the Research Question and Hypothesis

After delimiting the problem, the principal research question was formulated to determine whether clinically actionable pharmacogenomic information could improve understanding of therapeutic variability and severe adverse drug reactions in emergency medicine.

The research question was structured around three components: the presence of genetic variability, its effect on pharmacological response, and the possibility of translating this information into clinical action.

The working hypothesis proposed that validated pharmacogenomic variants are associated with clinically significant differences in drug response and toxicity and that their systematic identification could contribute to safer medication selection, dosing, monitoring, or avoidance.

At this stage, the study also established that pharmacogenomic information should be interpreted as a complementary clinical tool rather than as an isolated determinant of therapeutic decisions.

### Phase 3. Definition of the Analytical Framework

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The third phase established the variables and conceptual categories used to analyze the evidence.

The principal unit of analysis was defined as the **actionable gene–drug interaction**.

For each interaction, the following components were examined:

- gene involved;
- relevant genetic variant or predicted phenotype;
- medication or drug class;
- pharmacological mechanism;
- expected therapeutic effect;
- potential adverse reaction;
- severity of clinical consequences;
- availability of an evidence-based recommendation;
- possible therapeutic modification;
- relevance to emergency care.

This analytical framework made it possible to compare heterogeneous pharmacogenomic relationships using common clinical criteria.

**Phase 4. Identification and Selection of Scientific Evidence**

The fourth phase involved identifying scientific evidence relevant to pharmacogenomics, emergency medicine, adverse drug reactions, and clinical implementation.

The search strategy included scientific publications indexed in biomedical databases, recognized pharmacogenomic guidelines, implementation studies, and regulatory resources.

Priority was given to CPIC recommendations, PharmGKB resources, peer-reviewed clinical studies, and investigations evaluating pharmacogenomic implementation [18]–[20].

Targeted searches were additionally performed for clinically relevant genes and pharmacological pathways, including *CYP2D6, CYP2C19, CYP2C9, VKORC1, G6PD, RYR1, CACNA1S, HLA-B, SLCO1B1, TPMT,* and *NUDT15*.

Evidence was selected according to predefined inclusion and exclusion criteria, prioritizing associations with demonstrated clinical relevance and avoiding isolated genetic findings without sufficient therapeutic applicability.

**Phase 5. Extraction and Organization of Pharmacogenomic Data**

After the selection process, information from each source was extracted using a structured approach.

Data were organized according to the gene involved, medication affected, predicted phenotype, pharmacological mechanism, clinical consequence, and recommended therapeutic action.

This phase allowed the transformation of molecular pharmacogenomic information into clinically interpretable categories.

For example, CYP2D6-related opioid variability was analyzed according to predicted metabolic phenotype and its possible association with inadequate analgesia or increased active-metabolite exposure [4]. CYP2C19-related clopidogrel response was evaluated in relation to reduced bioactivation and impaired antiplatelet effect [5].

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Similarly, G6PD deficiency, malignant hyperthermia susceptibility, and HLA-associated hypersensitivity reactions were categorized as pharmacogenomic relationships primarily associated with severe toxicity rather than insufficient pharmacological efficacy [7], [8], [10]–[12].

**Phase 6. Classification by Pharmacogenomic Mechanism**

The identified interactions were subsequently classified according to their principal biological and clinical mechanisms.

Four major categories were established:

**Category I: Altered drug metabolism**

This category included variants affecting the rate at which a medication is activated or eliminated. Representative examples included CYP2D6-related opioid metabolism and CYP2C19-mediated clopidogrel activation [4], [5].

**Category II: Altered pharmacological sensitivity or dose requirement**

This group included genetic variants that modify the amount of medication required to achieve an appropriate therapeutic response, such as CYP2C9 and VKORC1 variation in warfarin therapy [9].

**Category III: Genetic susceptibility to severe adverse drug reactions**

This category included relationships associated with potentially severe or life-threatening toxicity, such as G6PD-associated hemolysis, RYR1/CACNA1S-associated malignant hyperthermia, and HLA-associated severe hypersensitivity reactions [7], [8], [10]–[12].

**Category IV: Genetic susceptibility to delayed complications capable of producing emergency presentations**

This group included associations such as SLCO1B1-related statin toxicity and TPMT/NUDT15-related thiopurine myelosuppression [13], [14].

This classification facilitated comparison of the clinical importance of different gene–drug interactions and their potential role in acute care.

**Phase 7. Assessment of Clinical Actionability**

The seventh phase examined whether the identified genomic information could produce a meaningful change in clinical management.

Each gene–drug interaction was assessed according to whether knowledge of the genotype could support:

- alternative medication selection;
- drug avoidance;
- dose modification;
- increased clinical or laboratory monitoring;
- identification of a high-risk patient;
- interpretation of unexpected treatment failure;
- prevention of recurrent adverse reactions.

Associations supported by clinical guidelines or validated implementation evidence were considered more actionable than exploratory relationships.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

This stage was essential because the existence of a statistically significant genetic association does not necessarily imply that it should modify clinical practice.

**Phase 8. Assessment of Relevance to Emergency Medicine**

Once clinical actionability had been established, each interaction was evaluated specifically within the context of emergency medicine.

Five dimensions were considered:

**Immediacy:** whether the genetic information could modify a decision made during an acute encounter.

**Severity:** whether the associated therapeutic failure or adverse reaction could result in organ dysfunction, hospitalization, critical illness, or death.

**Modifiability:** whether an alternative drug, dose adjustment, or preventive strategy was available.

**Availability:** whether pharmacogenomic results could realistically be accessible at the time of the emergency.

**Post-emergency utility:** whether identification of the interaction could modify future treatment and reduce recurrence.

This phase made it possible to distinguish between pharmacogenomic information that is scientifically relevant and information that is practically useful in an emergency setting.

**Phase 9. Analysis of Serious Adverse Drug Reactions**

The ninth phase focused specifically on pharmacogenomically influenced adverse reactions with the greatest potential clinical severity.

The analysis included acute hemolysis related to G6PD deficiency, malignant hyperthermia associated with *RYR1* and *CACNA1S*, severe cutaneous adverse reactions associated with selected HLA alleles, anticoagulant-related bleeding, opioid toxicity, severe myotoxicity, and drug-induced myelosuppression.

Each adverse reaction was evaluated according to its molecular mechanism, possible emergency presentation, preventive value of pharmacogenomic information, and potential therapeutic implications.

The objective of this phase was not only to identify adverse reactions but also to determine whether genomic information could contribute to preventing the initial event or avoiding future re-exposure.

**Phase 10. Evaluation of Preemptive Pharmacogenomic Strategies**

The tenth phase examined preemptive pharmacogenomic testing as a possible strategy for overcoming the time limitations inherent to emergency medicine.

Under this model, genetic information is generated before an acute event and stored in the patient's clinical record. If the patient subsequently requires emergency treatment, the relevant pharmacogenomic result can be accessed immediately.

This phase incorporated evidence from multigene implementation studies demonstrating that preemptive pharmacogenomic strategies can identify actionable variants and reduce clinically relevant adverse drug reactions [1], [3], [15]–[17].

Particular attention was given to the feasibility of integrating genetic information into electronic health records and clinical decision-support systems.

**Phase 11. Integration With Conventional Clinical Variables**

The eleventh phase recognized that genotype alone does not determine drug response.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Each pharmacogenomic interaction was therefore interpreted together with other variables capable of modifying pharmacological outcomes, including:

- age;
- renal function;
- hepatic function;
- comorbidities;
- drug–drug interactions;
- polypharmacy;
- inflammation;
- previous medication exposure;
- therapeutic indication;
- severity of the acute clinical condition.

This phase prevented deterministic interpretation of pharmacogenomic findings and reinforced the concept that precision medicine requires integration of genomic and non-genomic information.

The possible occurrence of phenoconversion was also considered, particularly when concomitant medications inhibit the metabolic activity of genetically functional enzymes.

**Phase 12. Analysis of Implementation Barriers**

The twelfth phase evaluated the principal factors that may limit pharmacogenomic integration into emergency practice.

The following barriers were analyzed:

- turnaround time of genetic testing;
- limited availability of preemptive results;
- differences in allele frequencies across populations;
- variability among testing platforms;
- limited clinician familiarity with pharmacogenomic interpretation;
- alert fatigue in electronic clinical decision-support systems;
- cost and healthcare-resource requirements;
- data privacy and genetic confidentiality;
- interoperability of pharmacogenomic information between institutions;
- unequal access to genomic medicine.

These limitations were evaluated alongside the potential clinical benefits to avoid overestimating the current feasibility of pharmacogenomic implementation.

**Phase 13. Comparative Synthesis of the Evidence**

The evidence obtained in previous phases was then integrated through qualitative comparative synthesis.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Gene–drug interactions were compared according to:

1. strength of evidence;
2. severity of the associated outcome;
3. availability of therapeutic recommendations;
4. degree of clinical actionability;
5. relevance to emergency medicine;
6. feasibility of implementation.

This comparative approach allowed the study to identify patterns across different pharmacological classes without reducing the analysis to a simple listing of genes or medications.

Implementation evidence was compared with pharmacogenomic guidelines to determine whether established molecular relationships were also supported by real-world clinical applications [1], [3], [15]–[19].

**Phase 14. Interpretation of Findings**

The penultimate phase consisted of interpreting the synthesized evidence in relation to the initial hypothesis and research question.

The analysis examined whether pharmacogenomic variability represented a clinically meaningful contributor to therapeutic failure and severe adverse drug reactions and whether existing evidence supported its integration into emergency care.

Particular emphasis was placed on distinguishing three levels of potential application:

**Preventive application:** identification of genetic risk before medication exposure.

**Acute application:** use of previously available genomic information during emergency pharmacological decision-making.

**Post-event application:** interpretation of an adverse reaction and prevention of future exposure.

This three-level model allowed the study to conceptualize emergency pharmacogenomics as part of a longitudinal medication-safety strategy rather than as an isolated genetic intervention.

**Phase 15. Formulation of Clinical Conclusions and Future Directions**

The final phase involved integrating the molecular, pharmacological, clinical, and implementation findings into conclusions aligned with the objectives of the study.

The conclusions were formulated according to the extent to which pharmacogenomic information may contribute to individualized treatment, medication safety, prevention of serious adverse events, and clinical decision support.

Areas requiring additional research were also identified, particularly the development of rapid testing methods, validation in diverse populations, economic evaluation, interoperability of genetic information, and prospective assessment of pharmacogenomic decision-support systems in emergency departments.

## RESULTS AND DISCUSSION

**Figure 1. Clinically relevant adverse drug reactions according to prescribing strategy**

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Figure 1 shows the frequency of clinically relevant adverse drug reactions reported in the PREPARE multicenter pharmacogenomics implementation study according to prescribing strategy. Patients whose pharmacological treatment was guided by pharmacogenetic information experienced clinically relevant adverse drug reactions in **21.0%** of cases, whereas the corresponding frequency under standard prescribing was **27.7%** [3].

The difference between the two groups was **6.7 percentage points**, with a lower observed proportion of adverse reactions in the genotype-guided group. Considering the standard-care group as the reference, the observed proportions correspond to an approximate **24.2% relative reduction** in the frequency of clinically relevant adverse drug reactions. This calculation is based directly on the reported event proportions and provides a descriptive measure of the magnitude of the difference represented in the figure [3].

These results were obtained within the PREPARE study, which evaluated a **12-gene pharmacogenetic panel** designed to support prescribing decisions across multiple medications and healthcare settings. The analysis therefore differs from studies focused on a single pharmacogenomic interaction, because the intervention incorporated several clinically actionable gene–drug relationships simultaneously [3]. This multigene approach reflects the heterogeneous nature of pharmacogenomics, in which individual patients may carry several variants capable of affecting different medications throughout their lifetime.

The difference observed in Figure 1 is particularly relevant to the structure of the present analysis because adverse drug reactions constitute one of the principal outcomes through which pharmacogenomic variability becomes clinically detectable. The result demonstrates that the group managed with pharmacogenetically informed prescribing had a lower proportion of clinically significant medication-related adverse events than the group managed through conventional prescribing criteria alone [3].

Importantly, the values represented in the figure refer to **clinically relevant adverse drug reactions**, rather than to all mild or nonspecific symptoms occurring during pharmacological treatment. Consequently, the comparison reflects events considered sufficiently relevant within the study's clinical assessment framework. This distinction is important because pharmacogenomic interventions are primarily intended to identify gene–drug combinations in which altered metabolism, pharmacological sensitivity, or predisposition to toxicity may have meaningful consequences for patient management [3], [19].

The findings also support the analytical classification used in this study, in which pharmacogenomic variability was divided into altered drug metabolism, altered pharmacological sensitivity, severe genetically mediated toxicity, and delayed complications associated with medication exposure. Different mechanisms may ultimately converge on a common measurable clinical outcome: the occurrence of an adverse drug reaction. For example, reduced metabolic capacity may increase drug exposure, altered activation of a prodrug may modify therapeutic response, and specific HLA or enzymatic variants may predispose patients to severe hypersensitivity or toxic reactions [4]–[12].

From a quantitative perspective, the absolute difference of **6.7 percentage points** indicates that the groups were not characterized by only a minimal numerical separation. At the same time, adverse reactions were not completely eliminated in the genotype-guided group, since approximately one in five patients with actionable gene–drug interactions still experienced a clinically relevant event [3]. The figure therefore also demonstrates that pharmacogenomic information captures only one component of overall variability in drug response.

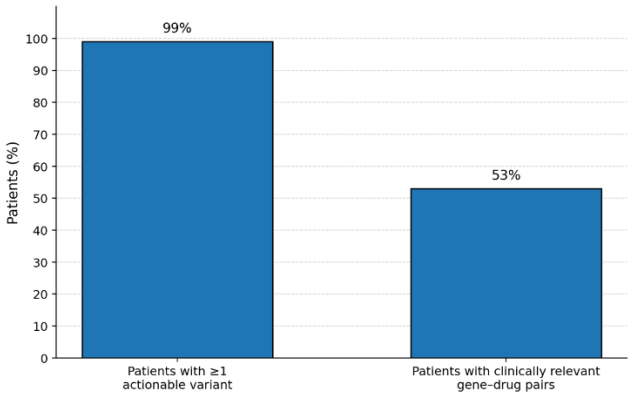
This remaining event frequency is consistent with the multifactorial nature of adverse drug reactions. Even when relevant genetic information is available, medication safety can continue to be influenced by renal and hepatic function, age, comorbidities, drug–drug interactions, polypharmacy, inflammatory conditions, treatment adherence, dose, duration of exposure, and characteristics of the underlying disease. Accordingly, the data represented in Figure 1 quantify the difference associated with the pharmacogenetic prescribing strategy without suggesting that genomic information accounts for all medication-related risk.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

**Figure 2.**

*Pharmacogenomic findings identified in an emergency department population*




.

Figure 2 summarizes the principal pharmacogenomic findings reported among **100 patients evaluated in an emergency department setting**. Actionable pharmacogenomic variants were identified in **99% of the cohort**, whereas **53%** of patients presented clinically relevant gene–drug pairs involving their current medication exposure [1]. Because the analyzed cohort consisted of 100 individuals, these percentages correspond directly to **99 patients with at least one actionable genetic finding** and **53 patients in whom genetic information coincided with an existing medication exposure capable of generating a clinically relevant pharmacogenomic interaction** [1].

The first result, represented by the 99% bar, demonstrates the extremely high frequency of potentially actionable pharmacogenomic information within the evaluated emergency population. An actionable variant refers to a genetic finding for which sufficient evidence exists to support a pharmacological interpretation or potential modification of therapy when the corresponding medication is prescribed. Therefore, the presence of an actionable variant does not indicate that 99% of patients were experiencing an adverse drug reaction at the time of evaluation. Instead, it indicates that nearly the entire cohort possessed at least one genomic characteristic that could become clinically relevant when exposed to an associated medication [1], [18], [19].

The second result provides a more immediate clinical perspective. Clinically relevant gene–drug pairs were identified in **53% of patients**, indicating that more than half of the evaluated individuals had both a pharmacogenomic finding and exposure to a medication associated with that genetic characteristic [1]. This distinction is important because genetic actionability and active gene–drug interaction represent different levels of pharmacogenomic information. A patient may carry an actionable allele throughout life without receiving the corresponding medication, whereas a gene–drug pair exists when the patient's genotype intersects with an actual pharmacological exposure.

The numerical difference between the two measurements was **46 percentage points**. Thus, although pharmacogenomic variants were nearly universal in the cohort, the proportion of patients in whom those findings coincided with relevant medication exposure was smaller. The figure therefore separates **potential pharmacogenomic actionability** from **current pharmacotherapeutic relevance**, avoiding the assumption that every actionable genetic variant necessarily requires an immediate therapeutic intervention.

The finding that 53% of emergency department patients had clinically relevant gene–drug pairs is particularly notable from a descriptive perspective because it demonstrates that pharmacogenomic information was not restricted to a small minority of individuals. More than one of every two patients in the analyzed population presented a genotype–medication combination with potential relevance to pharmacological management [1]. However, this percentage does not indicate that all such patients required a medication change, nor that all interactions produced toxicity or therapeutic

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

failure. The presence of a gene–drug pair represents an identifiable pharmacogenomic relationship whose clinical management depends on the medication, phenotype, therapeutic indication, evidence level, and corresponding prescribing guideline.

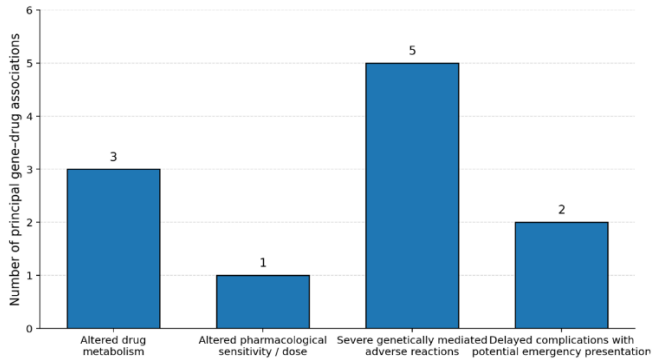
The relationship between the two bars also illustrates the longitudinal nature of pharmacogenomic information. Genetic variants remain stable throughout life, while medication exposures change over time. Consequently, the **99% prevalence of actionable variants** represents a reservoir of potentially useful information that may acquire clinical importance during future prescriptions, whereas the **53% prevalence of current gene–drug pairs** represents the subset already intersecting with pharmacotherapy at the time of assessment [1].

From the standpoint of the analytical framework established in this study, these findings also demonstrate why gene–drug interactions were selected as the principal unit of analysis rather than genetic variants alone. A genetic result becomes clinically informative when it can be linked to a specific medication and to an evidence-based pharmacological consequence. Resources such as CPIC and PharmGKB facilitate this translation by connecting genotype or predicted phenotype with recommendations concerning medication selection, dose adjustment, avoidance, or monitoring [18], [19].

Importantly, the two values displayed in Figure 2 should not be interpreted as independent groups. Patients with clinically relevant gene–drug pairs form part of the broader population in whom actionable pharmacogenomic findings were identified. The figure therefore represents two progressively more specific levels of information within the same emergency department cohort: first, identification of genetic variants with potential pharmacological actionability and, second, identification of variants that were already relevant to medications used by the patient [1].

**Figure 3.**

*Distribution of principal pharmacogenomic mechanisms identified in the analysis*




.

Figure 3 summarizes the distribution of the **11 principal gene–drug associations** selected for detailed analysis according to their predominant pharmacogenomic mechanism. The largest category corresponded to **severe genetically mediated adverse drug reactions**, with **5 of the 11 associations**, followed by **altered drug metabolism** with **3 associations**, **delayed complications with potential emergency presentation** with **2 associations**, and **altered pharmacological sensitivity or dose requirement** with **1 association** [4]–[14].

The predominance of severe genetically mediated adverse reactions reflects the strong representation of gene–drug relationships in which genomic information can identify susceptibility to clinically significant toxicity. This category included associations involving *G6PD*, *RYR1/CACNA1S*, and several *HLA* variants linked to potentially severe reactions such as hemolysis, malignant hyperthermia, and serious immune-mediated hypersensitivity syndromes [7], [8], [10]–[12]. These five associations accounted for approximately **45.5%** of the principal relationships included in the structured analysis.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The second most frequently represented mechanism was **altered drug metabolism**, comprising **3 of 11 associations**, or approximately **27.3%** of the total. This group included the pharmacogenomic relationships involving *CYP2D6* and selected opioids, *CYP2C19* and clopidogrel, and *CYP2C9* and nonsteroidal anti-inflammatory drugs [4]–[6]. In these interactions, genetic variation primarily modifies enzymatic activity and consequently alters either drug clearance or the formation of active metabolites.

This category is pharmacologically distinct from genetically mediated toxicity because the initial molecular effect occurs through variation in metabolic capacity. Depending on the medication, the clinical consequence may involve inadequate therapeutic efficacy, excessive drug exposure, delayed elimination, or increased toxicity. Thus, a single metabolic mechanism can produce different clinical manifestations depending on whether the affected medication is administered as an active compound or as a prodrug [4]–[6].

The **altered pharmacological sensitivity or dose requirement** category contained **1 principal association**, representing approximately **9.1%** of the analyzed relationships. This category was represented by the influence of *CYP2C9* and *VKORC1* variation on warfarin therapy [9]. The classification distinguishes this interaction from pure metabolic variation because warfarin response is determined not only by clearance but also by genetic variation affecting its pharmacological target and overall dose requirement.

Although this category represented the smallest proportion of the structured dataset, its lower frequency should not be interpreted as lower clinical importance. The figure represents the number of selected associations within each mechanism rather than their prevalence in the population, magnitude of effect, or severity of clinical consequences. A single gene–drug interaction may have substantial therapeutic relevance even when it constitutes only one analytical category.

The remaining **2 associations**, corresponding to approximately **18.2%**, were classified as **delayed complications with potential emergency presentation**. These included *SLCO1B1*-associated statin toxicity and *TPMT/NUDT15*-associated thiopurine toxicity [13], [14]. Their defining characteristic was that the genetically influenced adverse effect may emerge after continued medication exposure rather than immediately after administration, but can eventually result in complications requiring urgent medical attention.

In the case of statins, genetically influenced susceptibility to musculoskeletal toxicity may contribute to severe muscle injury in susceptible individuals [13]. For thiopurines, reduced activity associated with *TPMT* or *NUDT15* may increase the risk of profound myelosuppression when conventional doses are used [14]. These examples demonstrate that pharmacogenomic relevance to emergency medicine is not restricted to drugs administered during the acute encounter itself.

When considered together, the figure shows that **7 of the 11 associations, or 63.6%, were classified primarily within categories directly related to severe or delayed toxicity**. The remaining 4 associations were predominantly related to altered metabolism or pharmacological sensitivity. This distribution reflects the analytical focus of the study on both therapeutic variability and clinically important adverse drug reactions.

The classification also demonstrates that pharmacogenomics in acute care cannot be reduced to a single biological mechanism. Some associations modify enzyme activity, others alter drug targets, and others influence immune or cellular susceptibility to specific medications. Therefore, the same general concept of genotype-guided prescribing includes mechanistically distinct pathways [4]–[14].

Importantly, each association was assigned to the category representing its **predominant mechanism for the purposes of structured comparison**. Certain gene–drug relationships may involve more than one biological pathway or produce several different clinical consequences. The categories shown in Figure 3 should therefore be interpreted as an analytical organization of the selected evidence rather than as mutually exclusive biological definitions.

**Figure 4.**

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

*Clinical characteristics of the principal actionable gene–drug interactions relevant to emergency medicine*

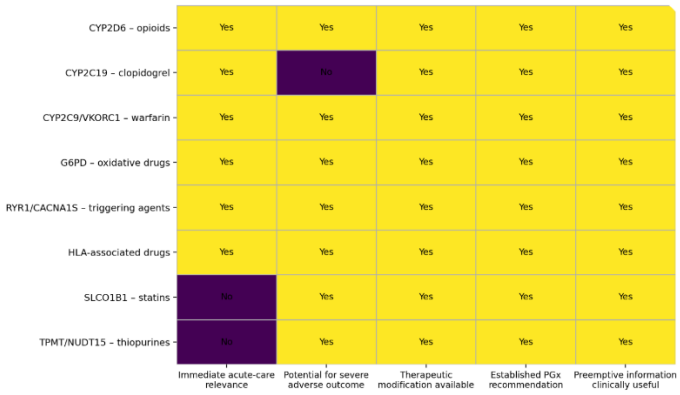



Figure 4 presents a structured comparison of the principal actionable pharmacogenomic relationships included in the analysis according to five predefined clinical characteristics: immediate relevance to acute care, potential for a severe adverse outcome, availability of a therapeutic modification, existence of an established pharmacogenomic recommendation, and usefulness of preemptively available genomic information.

The figure is intended as a **categorical clinical matrix rather than a quantitative score**. A "Yes" designation indicates that the corresponding characteristic was considered a principal feature of that gene–drug relationship on the basis of the guideline-supported and implementation evidence included in the study. Therefore, the matrix should not be interpreted as ranking one interaction above another, but as showing how different pharmacogenomic associations overlap across dimensions relevant to emergency practice.

The most consistent pattern observed was the broad availability of a therapeutic action once a clinically relevant genotype is known. All eight gene–drug groups were associated with some form of potential therapeutic modification, including selection of an alternative medication, dose adjustment, enhanced monitoring, or avoidance of a triggering drug [4]–[14]. This finding is central to the concept of clinical actionability: pharmacogenomic information is most useful when it can be translated into a concrete prescribing decision rather than remaining solely descriptive.

A similarly consistent pattern was observed for the presence of **established pharmacogenomic recommendations**. The interactions represented in the figure were selected specifically because they are supported by clinically oriented guidance or validated pharmacogenomic resources. CPIC recommendations provide therapeutic interpretation for CYP2D6 and selected opioids [4], CYP2C19 and clopidogrel [5], CYP2C9 and NSAIDs [6], RYR1/CACNA1S and malignant-hyperthermia-triggering agents [7], G6PD and selected oxidative medications [8], warfarin-related pharmacogenetics [9], HLA-associated carbamazepine and oxcarbazepine reactions [10], HLA-B*58:01 and allopurinol [11], HLA-B*57:01 and abacavir [12], statin-associated musculoskeletal toxicity [13], and TPMT/NUDT15-guided thiopurine dosing [14].

The third recurrent characteristic was the usefulness of **preemptive pharmacogenomic information**. All of the principal relationships analyzed can potentially benefit from results obtained before the acute event or before medication exposure. This is particularly important in emergency medicine because newly ordered genotyping may not return within the timeframe required for immediate treatment. When a validated result is already stored in the medical record, however, it can be accessed at the moment a relevant drug is prescribed or when an adverse reaction is being investigated [1], [3], [15]–[19].

The *CYP2D6–opioid* relationship was classified as having immediate acute-care relevance because selected opioids may be prescribed for acute pain and because CYP2D6 activity can modify both analgesic response and exposure to active metabolites [4]. The presence of a therapeutic alternative and established prescribing guidance means that previously known CYP2D6 status can potentially influence medication selection during an emergency encounter.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The *CYP2C19–clopidogrel* relationship also showed immediate relevance to acute care because clopidogrel is frequently used in cardiovascular and selected neurovascular settings where timely antiplatelet therapy may be required. However, the principal clinical concern represented in this analysis was **reduced therapeutic efficacy associated with impaired bioactivation**, rather than a genetically mediated toxic reaction. For that reason, the severe-adverse-outcome column was not designated as a primary toxicity feature for this interaction, even though inadequate antiplatelet effect can be associated with serious clinical consequences [5].

The *CYP2C9/VKORC1–warfarin* relationship was classified as relevant to acute care because genetically influenced dose sensitivity may contribute to excessive anticoagulation and bleeding risk, while genotype-guided dosing can inform subsequent management [9]. Nevertheless, emergency treatment of active hemorrhage continues to depend on conventional clinical assessment, coagulation testing, and established reversal strategies. Pharmacogenomic information is therefore complementary rather than substitutive.

The strongest overlap between immediate emergency relevance and severe toxicity was observed among the **G6PD**, **RYR1/CACNA1S**, and **HLA-associated** groups. G6PD deficiency may predispose susceptible patients to acute hemolysis after exposure to certain oxidative drugs [8]. Pathogenic variants in *RYR1* or *CACNA1S* can identify susceptibility to malignant hyperthermia after triggering anesthetic exposure [7]. Specific HLA variants are associated with serious hypersensitivity reactions to medications such as carbamazepine, oxcarbazepine, allopurinol, and abacavir [10]–[12].

These associations illustrate a different form of pharmacogenomic actionability from that observed with metabolic genes. In many such cases, the clinically relevant intervention is not simply dose adjustment but **avoidance of a medication in a genetically susceptible individual**. This is particularly important for severe immune-mediated or hypermetabolic reactions because prevention of exposure may be more clinically meaningful than attempting to manage the reaction after it has developed.

The *SLCO1B1–statin* and *TPMT/NUDT15–thiopurine* relationships showed a different pattern. Both were classified as having potential for severe adverse outcomes and as possessing established genotype-guided therapeutic recommendations [13], [14], but they were not categorized as primarily involving immediate emergency prescribing. Their major complications generally emerge after ongoing pharmacological exposure rather than within minutes of medication administration.

For statins, genetically influenced susceptibility to musculoskeletal toxicity may contribute to severe muscle injury in susceptible patients, with rhabdomyolysis representing the most clinically serious end of the spectrum [13]. For thiopurines, reduced TPMT or NUDT15 activity can substantially increase the risk of profound myelosuppression when conventional doses are used [14]. Both conditions may eventually require urgent evaluation, but the pharmacogenomic intervention is generally most effective before or during chronic therapy.

The matrix therefore distinguishes between **drugs for which genomic information may directly influence an acute prescribing decision** and medications for which the principal value of pharmacogenomics lies in preventing complications that may later result in emergency presentation. This distinction is relevant because emergency pharmacogenomics extends beyond medications physically administered in the emergency department.

Another notable finding is that the majority of the selected interactions combined at least four of the five characteristics represented in the figure. This reflects the deliberate focus of the study on gene–drug relationships with comparatively high levels of clinical translation. The results should therefore not be extrapolated to all reported pharmacogenomic associations, many of which remain investigational or lack sufficiently established therapeutic recommendations [18], [19].

**Figure 5.**

*Composition of the scientific evidence supporting the pharmacogenomic analysis*

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

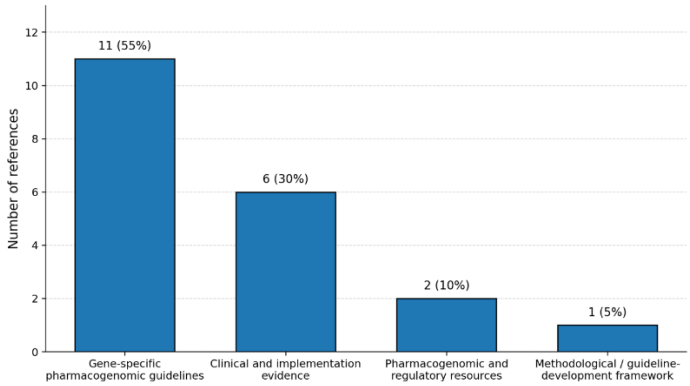



Figure 5 summarizes the composition of the **20 scientific references** used to support the pharmacogenomic analysis. The evidence base was dominated by **gene-specific pharmacogenomic guidelines**, which accounted for **11 of the 20 references (55%)**. Clinical and implementation evidence represented **6 references (30%)**, pharmacogenomic and regulatory resources accounted for **2 references (10%)**, and **1 reference (5%)** was classified as a methodological or guideline-development framework.

The predominance of gene-specific pharmacogenomic guidelines reflects the clinically oriented nature of the present study. More than half of the selected references corresponded to recommendations addressing specific gene–drug relationships, including CYP2D6 and opioids [4], CYP2C19 and clopidogrel [5], CYP2C9 and nonsteroidal anti-inflammatory drugs [6], RYR1/CACNA1S and malignant-hyperthermia-triggering agents [7], G6PD-related drug exposure [8], warfarin-associated pharmacogenetics [9], HLA-mediated reactions involving carbamazepine and oxcarbazepine [10], allopurinol [11], and abacavir [12], as well as SLCO1B1-related statin toxicity [13] and TPMT/NUDT15-guided thiopurine therapy [14].

This concentration of guideline-based evidence provided the principal foundation for determining whether the gene–drug interactions analyzed in the study could be considered clinically actionable. Rather than relying only on associations between genetic variants and pharmacological outcomes, the evidence base incorporated recommendations that translate genotype or predicted phenotype into possible therapeutic actions, such as alternative drug selection, dose modification, treatment avoidance, or enhanced monitoring [4]–[14].

The second largest category consisted of **clinical and implementation evidence**, representing **30% of the total references**. This group included studies evaluating pharmacogenomic findings in emergency department populations [1], adverse drug reactions presenting to emergency care [2], multigene genotype-guided prescribing [3], and broader implementation of preemptive pharmacogenomic testing in clinical practice [15]–[17]. These studies complemented the guideline evidence by examining how pharmacogenomic information performs outside purely theoretical or mechanistic contexts.

The combination of guidelines and implementation evidence accounted for **17 of the 20 selected references, or 85% of the evidence base**. This distribution indicates that the majority of the sources were directly related either to therapeutic decision-making or to the real-world application of pharmacogenomics. Consequently, the evidence used in the analysis was oriented primarily toward clinical translation rather than toward basic genetic association alone.

Among the implementation studies, the PREPARE trial provided one of the principal quantitative datasets because it evaluated whether a multigene pharmacogenetic strategy could modify clinically relevant adverse drug reaction rates [3]. The emergency department cohort study provided a complementary perspective by quantifying the frequency of actionable variants and existing gene–drug pairs in an acute-care population [1]. The ADRED investigation further contributed evidence concerning the relationship between pharmacogenomic profiles and adverse drug reactions presenting to emergency services [2].

The **pharmacogenomic and regulatory resource** category represented **10% of the selected evidence** and included PharmGKB and the pharmacogenetic information provided by the U.S. Food and Drug Administration [18], [20]. These resources served a different function from original clinical investigations. Rather than providing a single patient

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

cohort or intervention, they organize and contextualize gene–drug knowledge, pharmacogenomic associations, regulatory information, and levels of clinical relevance.

PharmGKB is particularly important for connecting pharmacogenomic variants with medications, clinical annotations, prescribing information, and evidence resources [18]. Regulatory information provides an additional perspective regarding gene–drug relationships recognized within medication labeling or pharmacogenetic association frameworks [20]. Their inclusion therefore strengthened the process of determining whether the associations identified in the literature had broader clinical recognition.

The smallest category, corresponding to **5% of the references**, consisted of methodological evidence related to the development and clinical implementation of pharmacogenomic guidelines [19]. Although numerically represented by only one reference, this source was relevant to understanding how pharmacogenomic recommendations are generated and how clinically actionable genetic information can be translated into prescribing guidance.

The proportions presented in Figure 5 should not be interpreted as a hierarchy of scientific quality. A larger number of references in one category does not automatically imply greater evidentiary strength than a smaller category. The figure describes the **composition of the selected evidence base**, not a formal risk-of-bias assessment or meta-analytic weighting of individual studies.

Similarly, the 55% contribution of gene-specific guidelines does not mean that 55% of the results were derived from guideline recommendations alone. The study integrated several forms of evidence for different analytical purposes. Guidelines were primarily used to characterize clinical actionability, whereas implementation studies contributed quantitative and real-world information regarding adverse drug reactions, prevalence of actionable findings, and feasibility of pharmacogenomic integration [1]–[3], [15]–[17].

This distribution also explains the structure of the preceding results. Figures 1 and 2 were derived primarily from quantitative clinical and implementation evidence [1], [3], whereas Figures 3 and 4 relied more extensively on the structured synthesis of guideline-supported gene–drug relationships [4]–[14]. Figure 5 therefore provides an overview of how the different source types contributed to the complete analytical framework.

## DISCUSSION

The present study identified pharmacogenomics as a clinically relevant component of therapeutic variability in emergency medicine, particularly in relation to adverse drug reactions, treatment failure, and the prevention of genetically mediated toxicity. The results showed that pharmacogenomic information is not limited to isolated molecular associations but can be connected to clinically actionable decisions involving drug selection, dose modification, treatment avoidance, and monitoring. The findings also demonstrated that the potential usefulness of pharmacogenomics in acute care depends not only on the biological validity of gene–drug interactions but also on the availability of genetic information at the moment when therapeutic decisions are made.

One of the most relevant findings was the lower frequency of clinically relevant adverse drug reactions observed with genotype-guided prescribing in the PREPARE study. Patients managed using pharmacogenetic information experienced adverse reactions in 21.0% of cases compared with 27.7% under standard care [3]. This difference supports the concept that pharmacogenomic-guided prescribing can influence measurable clinical outcomes rather than merely provide theoretical information about drug metabolism. Although pharmacogenomics cannot eliminate adverse reactions, the observed reduction indicates that genetic information can contribute to medication safety when it is integrated into prescribing decisions alongside conventional clinical variables.

This finding is consistent with the broader objective of precision pharmacotherapy, in which treatment is adapted according to individual biological characteristics instead of relying exclusively on population-based dosing strategies. The benefit observed in multigene pharmacogenetic implementation is particularly important because patients are rarely exposed to only one medication throughout their lives. A panel-based approach may therefore provide

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

information relevant to several future treatments rather than addressing a single gene–drug interaction at one point in time [3], [15]–[17].

The emergency department findings analyzed in this study further reinforce this perspective. Actionable pharmacogenomic variants were identified in 99% of the evaluated emergency department population, while clinically relevant gene–drug pairs were found in 53% [1]. These proportions suggest that pharmacogenomic information may be present in a substantial proportion of patients receiving acute care. However, the distinction between actionable variants and active gene–drug interactions is critical. The presence of an actionable genotype does not necessarily imply an immediate need for therapeutic modification, because its relevance depends on exposure to the corresponding medication.

This difference highlights one of the most important conceptual issues in clinical pharmacogenomics: **genetic actionability is potential, whereas gene–drug interaction is contextual**. A patient may carry a clinically meaningful variant for decades without consequence until a specific medication is prescribed. For emergency medicine, this means that the value of pharmacogenomic information increases substantially when results are already available and can be cross-referenced with current medications or proposed treatments in real time.

The distribution of pharmacogenomic mechanisms identified in the study also demonstrated that acute-care pharmacogenomics is heterogeneous. Severe genetically mediated adverse drug reactions represented the largest group of selected associations, followed by altered metabolism, delayed complications, and modified pharmacological sensitivity. This pattern is clinically meaningful because the consequences of pharmacogenomic variation differ substantially according to the underlying mechanism.

For example, CYP2D6 and CYP2C19 primarily illustrate variability in drug metabolism or activation. CYP2D6 activity can modify the response to codeine and tramadol, whereas CYP2C19 influences the bioactivation of clopidogrel [4], [5]. In these cases, the principal consequence may be inadequate therapeutic effect, excessive exposure, or altered formation of active metabolites. In contrast, pharmacogenomic relationships involving G6PD, RYR1, CACNA1S, and HLA alleles may predispose patients to potentially severe reactions such as hemolysis, malignant hyperthermia, or severe hypersensitivity [7], [8], [10]–[12].

This distinction has important implications for emergency practice. In metabolic pharmacogenomics, the clinical question often concerns whether the selected dose or medication is likely to produce the intended effect. In genetically mediated hypersensitivity or toxicity, the primary objective may instead be complete avoidance of a high-risk drug. The therapeutic consequence of a pharmacogenomic finding therefore varies from dose optimization to medication substitution or absolute avoidance.

The RYR1/CACNA1S–malignant hyperthermia relationship represents one of the clearest examples of a potentially immediate emergency application. When susceptibility is already known, exposure to triggering anesthetic agents or succinylcholine can be avoided [7]. This differs from pharmacogenomic testing performed after an acute event, because the principal value lies in prevention. Once malignant hyperthermia has developed, immediate recognition and treatment remain the clinical priority regardless of whether genetic confirmation is available.

A similar preventive principle applies to HLA-associated severe adverse reactions. Variants associated with carbamazepine, oxcarbazepine, allopurinol, and abacavir can identify individuals at increased risk of serious hypersensitivity syndromes [10]–[12]. These associations demonstrate that pharmacogenomics can provide more than dose optimization. In selected circumstances, the most appropriate genomic-guided intervention is to prevent exposure entirely.

The study also identified pharmacogenomic associations that are less likely to influence the first minutes of emergency treatment but remain highly relevant to the emergency-care continuum. SLCO1B1-associated statin toxicity and TPMT/NUDT15-associated thiopurine toxicity are examples of delayed adverse reactions that may ultimately result in rhabdomyolysis, renal injury, severe cytopenias, or infection requiring urgent evaluation [13], [14]. These findings support a broader definition of emergency pharmacogenomics that includes not only medications administered in the emergency department but also chronic therapies responsible for acute complications.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

This broader perspective is important because many medication-related emergencies originate outside the emergency department. The acute-care physician frequently encounters the consequence rather than the initial prescription. Pharmacogenomic information can therefore contribute at several points: prevention before treatment initiation, interpretation during an adverse event, and prevention of recurrence after stabilization.

The clinical matrix presented in Figure 4 showed that all selected gene–drug relationships had some form of available therapeutic modification and established pharmacogenomic guidance. This is a key finding because it separates clinically useful pharmacogenomics from genetic associations that remain primarily investigational. CPIC guidelines are particularly relevant because they are designed to answer the question of how an existing genotype should influence therapy [19].

However, clinical actionability should not be interpreted as automatic decision-making. Even when a strong gene–drug association exists, therapeutic recommendations must be integrated with renal and hepatic function, age, comorbidities, indication, drug interactions, and disease severity. For example, pharmacogenomic information concerning warfarin sensitivity may contribute to dose planning, but it does not replace measurement of anticoagulation status in a patient with active bleeding [9]. Likewise, genetic susceptibility to opioid variability does not replace respiratory assessment, pain evaluation, or consideration of concomitant sedatives [4].

This interaction between genotype and clinical context is particularly important because of **phenoconversion**, in which drug interactions or physiological conditions modify the expected metabolic phenotype. A patient genetically classified as a normal metabolizer may functionally behave as a poor metabolizer if a strong enzymatic inhibitor is present. Therefore, genotype is not equivalent to fixed pharmacological behavior. Pharmacogenomics should instead be interpreted as one component of a dynamic clinical system.

The composition of the evidence base in this study also deserves consideration. More than half of the selected references consisted of gene-specific pharmacogenomic guidelines, while approximately one-third represented clinical or implementation evidence. This combination strengthens the clinical orientation of the analysis because guideline-based actionability was evaluated alongside real-world implementation studies [1]–[3], [15]–[19]. Nevertheless, the predominance of guidelines also reflects a limitation: the number of large prospective studies performed specifically in emergency departments remains relatively small.

This limitation is particularly relevant when considering the direct applicability of pharmacogenomics in acute care. Much of the strongest evidence originates from broader clinical settings rather than emergency departments. Therefore, while existing studies support the feasibility and potential value of pharmacogenomics, additional prospective investigations are needed to determine its effect on emergency-specific outcomes such as time to appropriate therapy, medication-related admission, length of stay, intensive-care utilization, recurrent adverse reactions, and short-term morbidity.

Another important limitation is turnaround time. Emergency medicine frequently requires treatment within minutes, whereas conventional genomic testing may take considerably longer. This represents one of the strongest arguments for preemptive pharmacogenomic testing. Rather than requesting a new genetic analysis during every acute presentation, a more feasible model involves generating pharmacogenomic information in advance and storing clinically actionable results within the electronic health record [1], [15]–[17].

Under such a model, emergency clinicians would not need to interpret raw genetic data. Instead, the electronic system could identify a relevant medication order and provide a concise decision-support alert. This approach has potential advantages, but it also introduces new challenges. Excessive alerts may contribute to alert fatigue, poorly designed systems may interrupt workflow, and clinicians may distrust recommendations if the rationale is not transparent. Successful implementation therefore requires careful integration of pharmacogenomics into existing prescribing systems rather than the simple addition of more notifications.

Population diversity represents another important challenge. Allele frequencies vary across ancestry groups, and the performance of certain genotyping panels may differ depending on which variants are included. If clinically relevant variants are not represented, phenotype assignment may be incomplete or inaccurate. This is particularly important in

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

genetically diverse populations and indicates the need for validation of pharmacogenomic panels across different demographic groups.

Equity also deserves consideration. Precision medicine can improve therapeutic individualization, but unequal access to genomic testing could widen existing disparities if implementation is limited to specialized institutions or populations with greater healthcare resources. A clinically valuable pharmacogenomic system should therefore consider not only analytical accuracy but also accessibility, cost, interoperability, and long-term availability of results.

Data portability is especially important because genetic information remains relevant throughout life. A pharmacogenomic result generated in one institution may become useless during an emergency in another hospital if it cannot be accessed. Interoperability of electronic health records and standardized representation of pharmacogenomic phenotypes will therefore be essential for large-scale implementation.

Ethical considerations also remain relevant. Genetic data require confidentiality and appropriate protection, and patients should understand that pharmacogenomic testing is intended to guide medication use rather than predict all aspects of health. The presence of a risk genotype does not guarantee that an adverse event will occur, and the absence of a known variant does not eliminate pharmacological risk. Avoiding deterministic interpretation is therefore fundamental.

The present findings support the concept that pharmacogenomics may be most valuable when integrated into a **three-stage model of medication safety**. The first stage is preventive, in which actionable variants are identified before medication exposure. The second occurs during the acute encounter, when available pharmacogenomic information can support drug selection or contribute to recognition of an adverse reaction. The third occurs after stabilization, when genomic findings can guide medication reconciliation, discharge treatment, counseling, and avoidance of future re-exposure.

This model is particularly compatible with the interdisciplinary nature of emergency and internal medicine. Emergency physicians contribute acute clinical assessment, internists provide broader evaluation of chronic disease and polypharmacy, pharmacists and clinical pharmacologists interpret drug interactions, and genetic specialists contribute to complex variant interpretation. Effective implementation therefore depends on collaboration rather than on a single specialty.

The results of this study also suggest that pharmacogenomics should not be framed as a replacement for conventional medicine. Its value lies in increasing the amount of clinically relevant information available to the physician. Laboratory parameters, vital signs, organ function, medication history, disease severity, and clinical examination remain essential. Pharmacogenomics adds an additional layer capable of explaining why some patients respond differently despite apparently similar treatment conditions.

Several directions for future research emerge from these findings. Prospective emergency-department studies should evaluate whether preemptive pharmacogenomic information changes prescribing behavior and improves patient-centered outcomes. Rapid point-of-care genotyping requires further validation for scenarios in which preexisting data are unavailable. Additional work is also required to determine cost-effectiveness, optimal alert design, implementation across diverse populations, and strategies for incorporating pharmacogenomic information into interoperable electronic records.

Future investigations should also examine whether specific emergency presentations may benefit more than others. Acute coronary syndromes, severe pain, anticoagulant-associated complications, drug hypersensitivity, toxicological presentations, and peri-procedural emergencies may represent particularly relevant settings because several validated gene–drug interactions intersect with these clinical situations [4]–[12].

## CONCLUSION

Pharmacogenomics represents an increasingly relevant component of individualized pharmacotherapy in emergency and internal medicine. The evidence analyzed in this study demonstrates that inherited genetic variability can modify

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

drug metabolism, therapeutic efficacy, dose requirements, and susceptibility to severe adverse drug reactions. These effects are clinically significant because they may contribute to treatment failure, excessive pharmacological response, hypersensitivity, hemolysis, malignant hyperthermia, myotoxicity, myelosuppression, and other medication-related complications that can require urgent medical attention [4]–[14].

The results support the clinical relevance of pharmacogenomic-guided prescribing. In the PREPARE study, clinically relevant adverse drug reactions occurred in 21.0% of patients receiving genotype-guided treatment compared with 27.7% under standard prescribing conditions [3]. In addition, recent evidence from an emergency department population showed actionable pharmacogenomic variants in 99% of evaluated patients and clinically relevant gene–drug pairs in 53% [1]. Together, these findings indicate that pharmacogenomic information may be both highly prevalent and potentially useful in patients receiving acute medical care.

However, the applicability of pharmacogenomics in emergency medicine depends strongly on the timing and accessibility of genetic information. Because many emergency interventions cannot be delayed while waiting for conventional genotyping, the most feasible strategy appears to be **preemptive pharmacogenomic testing**, with clinically relevant results incorporated into electronic health records and made immediately accessible when a corresponding medication is prescribed [1], [15]–[17].

The analysis also demonstrated that pharmacogenomic actionability is heterogeneous. Some associations primarily influence drug metabolism or activation, such as *CYP2D6* with selected opioids and *CYP2C19* with clopidogrel [4], [5]. Others identify susceptibility to potentially severe toxicity, including *G6PD*-associated hemolysis, *RYR1/CACNA1S*-associated malignant hyperthermia, and HLA-associated severe hypersensitivity reactions [7], [8], [10]–[12]. Additional relationships, such as *SLCO1B1*-associated statin toxicity and *TPMT/NUDT15*-associated thiopurine toxicity, demonstrate how chronic pharmacological exposure may result in complications that ultimately present in acute-care settings [13], [14].

These findings emphasize that pharmacogenomics should not be used as an isolated decision-making system. Genetic information must be interpreted together with renal and hepatic function, age, comorbidities, concomitant medications, disease severity, laboratory findings, and conventional pharmacological principles. The genotype provides an additional layer of information but does not replace clinical assessment, therapeutic monitoring, or established emergency protocols.

The strongest potential benefit of pharmacogenomics therefore lies in its integration into a broader precision-medicine model. In this framework, genomic information can support medication selection before treatment, assist interpretation of unusual therapeutic responses during an acute event, and reduce the probability of future re-exposure after a serious adverse reaction. Its value is particularly high when evidence-based recommendations are available through resources such as CPIC and PharmGKB [18], [19].

Important limitations remain. Wider implementation requires faster and more accessible testing, validation across genetically diverse populations, appropriate clinician education, interoperable electronic records, protection of genetic data, reduction of alert fatigue, and additional prospective studies specifically focused on emergency-department outcomes. Cost-effectiveness and equitable access must also be addressed before pharmacogenomic testing can become a routine component of acute-care systems.

## REFERENCES

[1] J. L. Cole, L. Kodali, and M. Osinski, “Workflow and clinical utility of multigene preemptive pharmacogenomic testing in the emergency department: A single-center cohort study,” *J. Pharm. Technol.*, Aug. 2026, doi: 10.1177/87551225261472403.
[2] K. S. Just *et al*., “Adverse drug reactions in the emergency department: Is there a role for pharmacogenomic profiles at risk?—Results from the ADRED study,” *J. Clin. Med.*, vol. 9, no. 6, Art. no. 1801, 2020, doi: 10.3390/jcm9061801.
[3] J. J. Swen *et al*., “A 12-gene pharmacogenetic panel to prevent adverse drug reactions: An open-label, multicentre, controlled, cluster-randomised crossover implementation study,” *Lancet*, vol. 401, no. 10374, pp. 347–356, 2023, doi: 10.1016/S0140-6736(22)01841-4.

[4] K. R. Crews *et al*., "Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy," *Clin. Pharmacol. Ther.*, vol. 110, no. 4, pp. 888–896, 2021, doi: 10.1002/cpt.2149.
[5] C. R. Lee *et al*., "Clinical Pharmacogenetics Implementation Consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update," *Clin. Pharmacol. Ther.*, vol. 112, no. 5, pp. 959–967, 2022, doi: 10.1002/cpt.2526.
[6] K. N. Theken *et al*., "Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2C9 and nonsteroidal anti-inflammatory drugs," *Clin. Pharmacol. Ther.*, vol. 108, no. 2, pp. 191–200, 2020, doi: 10.1002/cpt.1830.
[7] S. G. Gonsalves *et al*., "Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of potent volatile anesthetic agents and succinylcholine in the context of RYR1 or CACNA1S genotypes," *Clin. Pharmacol. Ther.*, vol. 105, no. 6, pp. 1338–1344, 2019, doi: 10.1002/cpt.1319.
[8] R. S. Gammal *et al*., "Expanded Clinical Pharmacogenetics Implementation Consortium guideline for medication use in the context of G6PD genotype," *Clin. Pharmacol. Ther.*, vol. 113, no. 5, pp. 973–985, 2023, doi: 10.1002/cpt.2735.
[9] J. A. Johnson *et al*., "Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update," *Clin. Pharmacol. Ther.*, vol. 102, no. 3, pp. 397–404, 2017, doi: 10.1002/cpt.668.
[10] E. J. Phillips *et al*., "Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update," *Clin. Pharmacol. Ther.*, vol. 103, no. 4, pp. 574–581, 2018, doi: 10.1002/cpt.1004.
[11] Y. Saito *et al*., "Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update," *Clin. Pharmacol. Ther.*, vol. 99, no. 1, pp. 36–37, 2016, doi: 10.1002/cpt.161.
[12] M. A. Martin *et al*., "Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing: 2014 update," *Clin. Pharmacol. Ther.*, vol. 95, no. 5, pp. 499–500, 2014, doi: 10.1038/clpt.2014.38.
[13] R. M. Cooper-DeHoff *et al*., "The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms," *Clin. Pharmacol. Ther.*, vol. 111, no. 5, pp. 1007–1021, 2022, doi: 10.1002/cpt.2557.
[14] M. Maillard *et al*., "Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2025 update," *Clin. Pharmacol. Ther.*, vol. 119, no. 4, pp. 916–927, 2026, doi: 10.1002/cpt.70209.
[15] R. Tremmel *et al*., "Clinical implementation of pharmacogenomics and drug-drug interaction screening in a German academic teaching hospital and outpatient follow-up," *Clin. Pharmacol. Ther.*, vol. 119, no. 1, pp. 241–254, 2026, doi: 10.1002/cpt.70083.
[16] B. Tamraz *et al*., "Clinical implementation of preemptive pharmacogenomics testing for personalized medicine at an academic medical center," *J. Am. Med. Inform. Assoc.*, vol. 32, no. 3, pp. 566–571, 2025, doi: 10.1093/jamia/ocae293.
[17] E. Peruzzi, R. Roncato, E. De Mattia, A. Bignucolo, J. J. Swen, H.-J. Guchelaar, G. Toffoli, and E. Cecchin, "Implementation of pre-emptive testing of a pharmacogenomic panel in clinical practice: Where do we stand?," *Br. J. Clin. Pharmacol.*, vol. 91, no. 2, pp. 270–282, 2025, doi: 10.1111/bcp.15956.
[18] L. Gong, M. Whirl-Carrillo, and T. E. Klein, "PharmGKB, an integrated resource of pharmacogenomic knowledge," *Curr. Protoc.*, vol. 1, no. 8, Art. no. e226, 2021, doi: 10.1002/cpz1.226.
[19] K. E. Caudle *et al*., "Incorporation of pharmacogenomics into routine clinical practice: The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process," *Curr. Drug Metab.*, vol. 15, no. 2, pp. 209–217, 2014, doi: 10.2174/1389200215666140130124910.
[20] U.S. Food and Drug Administration, "Table of Pharmacogenetic Associations," FDA, 2026. [Online]. Accessed: Sep. 16, 2026.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal