Population-Specific Pharmacogenetics of Hypertension: Toward Culturally Tailored Therapy

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ABSTRACT

Essential (primary) hypertension is a multifactorial disorder shaped by genetic and environmental factors, with prevalence rising worldwide. Interethnic variability strongly influences drug response. Genome-wide association studies (GWAS) have highlighted loci such as AGT, ACE, PLEKHA7, CYP4A11, UMOD, ATP2B1, and CACNA1C in blood pressure regulation. Pharmacogenetic variants—including CYP2D6 with β-blockers, CYP2C9 with losartan, ACE I/D with ACE inhibitors, and UMOD with loop diuretics—affect efficacy, adverse reactions, and dosing. However, most evidence derives from European, Asian, or African cohorts, leaving a major gap for Middle Eastern populations. Saudi data indicate reduced CYP2D6*4 frequency and higher CYP2C9*2/3 allele prevalence, potentially impacting therapeutic outcomes. This review synthesizes GWAS, meta-analyses, and emerging biomarkers such as non-coding variants, microRNAs, epigenetics, and polygenic scores. Yet, translation into clinical practice is limited by insufficient prospective validation, infrastructure gaps, and ancestry-specific data. Future multi-ethnic studies are critical to enable precision antihypertensive therapy and equitable personalized care.

INTRODUCTION

A complicated and curable illness, essential (primary) hypertension is impacted by intricate connections between environmental and genetic factors[1,2] .The prevalence of hypertension is rising in both industrialized and developing nations, making it a serious public health concern on a global scale[3,4] .The frequency varies from 17% to 35% in low- and middle-income nations, including several regions of Asia and Africa, with greater percentages being seen in urban areas[5,6]. In a variety of groups, variants including AGT M235T and the ACE insertion/deletion (I/D) polymorphism have demonstrated strong correlations with the risk of hypertension[7].

More than 200 genetic loci linked to the regulation of blood pressure (BP) had been found and confirmed by genome-wide association studies (GWAS) by the middle of 2017, the majority of which had mild to moderate impacts on BP features. This information has been further broadened by more recent GWAS, which have identified further loci linked to blood pressure regulation and susceptibility to hypertension, including *PLEKHA7*, *CYP4A11*, and several more[8–10]. This growing knowledge base highlights the potential for **personalized therapeutic strategies** and improved risk prediction based on genetic profiling[11]. Although there are a number of pharmacogenetic studies, this publication offers a thorough, population-stratified synthesis with an emphasis on underrepresented groups, especially the Middle Eastern population. It integrates findings from recent GWAS, meta-analyses, and emerging biomarker studies (e.g., PRS, miRNAs), and evaluates their clinical applicability. Additionally, this analysis suggests a framework for prescribing precision antihypertensives, pointing out the shortcomings of the existing guidelines and providing organized insight into implementation issues unique to a certain group.

PHARMACOGENETICS OF ANTIHYPERTENSIVE DRUG CLASSES

Renin–Angiotensin–Aldosterone System (RAAS) Inhibitors

General Pharmacogenetics

More than 200 genetic loci linked to the regulation of blood pressure (BP) had been found and confirmed by genome-wide association studies (GWAS) by the middle of 2017, the majority of which had mild to moderate impacts on BP features[12]. This information has been further broadened by more recent GWAS, which have identified further loci linked to blood pressure regulation and susceptibility to hypertension, including PLEKHA7, CYP4A11, and several more[13]. Similar to this, the polymorphisms in AGT (M235T) and AGTR1 (A1166C) impact the expression of angiotensinogen and receptors, modifying the effectiveness of ARBs by altering RAAS function[14]. While no discernible effect was seen for other ARBs like valsartan and irbesartan, variations in *CYP2C9*, namely the *3 allele, may decrease the activation of losartan to its active metabolite E-3174, thereby decreasing its antihypertensive efficacy[15,16].

Population-Specific Pharmacogenetics

Population-specific studies have provided further insight into the clinical implications of pharmacogenetics. *CYP2C9* is primarily responsible for the conversion of losartan into its active metabolite E-3174; *CYP2C9*2* and *3 variations lessen this conversion. It has been noted that *CYP2C9* allele frequencies vary significantly among various cultures and ethnic groups. According to earlier research, *CYP2C9*2* was most prevalent in European groups (minor allele frequency, MAF between 11.1 and 14.4%), while Asian populations had the highest frequency of *CYP2C9*3* (MAF up to 13%)[17,18].Variability in losartan

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activation and antihypertensive response is caused by these genetic variations . The urine analysis of the losartan to E-3174 metabolic ratio following a 25 mg dosage of losartan was demonstrated to be a safe and accurate in vivo phenotyping assay for CYP2C9 activity in a Turkish population research. While the *CYP2C92* allele had less of an impact on enzyme performance, the *CYP2C93* variant allele was found to be a primary determinant of decreased enzyme activity, drastically lowering losartan metabolism[19] (Table 1).

Beta-Blockers

General Pharmacogenetics

Important genes like *GRK5*, *CYP2D6*, and ADRB1 are involved in the pharmacogenetics of β-blockers in hypertension. Drug efficacy and cardiovascular outcomes are influenced by variations in ADRB1 (Arg389Arg) and GLK5 (Gln41Gln), with carriers frequently exhibiting improved response.Although their overall therapeutic impact is minimal, *CYP2D6* poor or intermediate metabolizers have greater plasma β-blocker levels, which enable effective heart rate regulation at lower doses.Variability in ADRB2 seems to have little impact. In hypertensive individuals, genotype-guided therapy with ADRB1 and GRK5 may improve β-blocker medication[20].

Population-Specific Pharmacogenetics

The pharmacokinetics of β-blockers such as metoprolol, carvedilol, and nebivolol are significantly influenced by genetic variations in the CYP2D6 enzyme, with notable differences across populations[21]. The CYP2D6 gene has over 40 known allelic variants, classified based on enzyme activity as functional, reduced-function, or non-functional. These variants show significant differences in frequency across ethnic groups, impacting how individuals metabolize drugs like metoprolol. In European populations, functional alleles are most common, while the non-functional CYP2D6*4 variant is also frequently seen. In Asian populations, there is a higher prevalence of the reduced-function CYP2D6*10 allele, contributing to slower drug metabolism. Africans and African Americans have similar proportions of functional alleles, but African Americans show a higher frequency of non-functional variants, likely due to genetic admixture, with CYP2D6*17 being a common reduced-function allele[22]. Amerindian populations tend to have lower frequencies of CYP2D6*10, possibly due to founder effects. Although this can enhance the therapeutic effect, it also raises the risk of adverse reactions such as bradycardia. Therefore, in populations with a high prevalence of these alleles, lower initial doses and careful clinical monitoring are recommended to minimize potential toxicity[23,24] (Table 1).

Calcium Channel Blockers (CCBs)

General Pharmacogenetics

The results of treating hypertension were impacted by *CACNA1C* genetic variation, namely the rs1051375 SNP, in the INVEST-GENES trial. G/G homozygotes benefited from β-blockers, while A/A homozygotes benefited from calcium channel blockers. These genotype-specific effects were probably influenced by variations in blood pressure responsiveness[25]. Additionally, in minor allele carriers treated with amlodipine as opposed to lisinopril, the NOS3 Glu298Asp polymorphism was linked to a decreased risk of all-cause death[26]. The gene called *CACNA1C* that's part of the calcium channel itself, and if there's a variation there, it might change how someone responds to the drug. Other genes, like *PICALM*, *TANC2*, *GNB3*, and *ADRB2*, are also involved in how these drugs work. So if someone has SNPs in those genes, the drug might not work as expected—or at all[27,28].

Population-Specific Pharmacogenetics

Significant interindividual and interethnic variability is displayed by *CYP3A5* genetic variants. Drug metabolism varies among populations because most Gabonese people express functional *CYP3A5*, but French Caucasians and Tunisians have a high frequency of the *CYP3A5*3C* null allele, which results in few *CYP3A5* expressors[29]. The observed interindividual heterogeneity in CCB effectiveness and adverse effect profiles may be explained by these pharmacogenetic variations[30] .

Genetic variations significantly influence how individuals from different populations respond to amlodipine treatment. In **Asian populations**, polymorphisms in genes like *CYP3A5* (*e.g.*, *CYP3A5*3*/*3), **POR**, and **GNB3** were associated with altered drug metabolism and greater blood pressure (BP) reductions. Specifically, *CYP3A5*3*/*3 carriers showed lower plasma amlodipine levels, suggesting faster drug clearance.In **African-American populations**, SNPs such as **rs200148** in the **ACE** gene and variants in **CACNA1D** and **RYR3** showed distinct treatment responses, including differences in systolic BP and gender-specific effects. However, some variants, like those in **CYP3A5**, did not show significant effects in this group.**Caucasian cohorts** exhibited unique responses to SNPs in **NPPA**, **NOS1AP**, and **MDR1 (ABCB1)** genes, with certain genotypes linked to improved cardiovascular outcomes and variable drug clearance[30] (Table 1).

Diuretics (Thiazides, Loop, and Potassium-Sparing)

General Pharmacogenetics

A number of important genes influence the pharmacogenetic variability of diuretics. Variants of the sodium reabsorption-related NEDD4L gene are linked to an improved thiazide response, whereas the ADD1 Gly460Trp polymorphism is linked to better blood pressure reduction in Trp allele carriers[31,32]. Variants in the UMOD gene also impact the effectiveness of loop diuretics and the risk of developing chronic kidney disease[32].

Population-Specific Pharmacogenetics

Population-specific patterns can be seen in these correlations, with Asians reporting higher frequency of NEDD4L variations than Middle Eastern populations[33]. Finding these polymorphisms could help clinicians choose better thiazide and loop diuretics, enabling patient-genotype-based treatment plans[34]. In both the PEAR trial and the

Table 1. Some Pharmacogenetic Markers by Antihypertensive Drug Class and Ethnic Variation

Drug Class	Key Genes	Ethnic Differences Noted	Reference
RAAS Inhibitors	ACE, AGT, AGTR1, CYP2C9	ACE D allele more common in **East Asians**; CYP2C9*2 and *3 common in **Europeans.**	14–16
Beta-Blockers	ADRB1, GRK5, CYP2D6	CYP2D6*4 common in **Europeans**; *10 in **Asians**; *17 in **Africans**	20,21,23,24
Calcium Channel Blockers (CCBs)	CACNA1C, NOS3, CYP3A5	Functional CYP3A5*1 prevalent in **Africans**; CYP3A5*3C null allele common in **Tunisians and French Caucasians**	23-26
Diuretics	NEDD4L, ADD1, UMOD	NEDD4L variants more common in **Asians**; UMOD-related salt sensitivity varies across populations The rs4149601 variant in the NEDD4L gene linked to a better response in European population.	27-30

Table 2 . CYP2D6 Allele Frequencies in Arab Populations (MENA Region)[24,39–42]

CYP2D6 Allele/ Variant	Description	Frequency (%) in Saudi Arabia	Frequency Range in MENA Arab Countries	Notes
Gene duplication (Ultrarapid metabolizers)	Multiple copies of active CYP2D6 gene	10.4%	Highest in Algeria (28.3%), lowest in Egypt (2.41%) and Palestine (4.9%)	Ultrarapid metabolism linked to gene duplications; Saudi Arabia shows moderate frequency.
CYP2D6*4	Loss-of-function allele (poor metabolizer)	3.5%	3.5% (Saudi Arabia) to 18.8% (Egypt)	Most common defective allele in Caucasians; low frequency in Saudi Arabia.
CYP2D6*10	Reduced-function allele	3.0%	0% (Algeria) to 14.8% (Jordan)	Highest in Jordan; low frequency in Saudi Arabia.
CYP2D6*17	Reduced-function allele	3.0%	Not specifically reported for other countries	Low frequency in Saudi Arabia.
CYP2D6*41	Reduced-function allele	18.4%	8.3% (Algeria) to 15.2% (UAE)	More prevalent in Arabian Peninsula (Saudi Arabia, UAE) than Northern Levantine (Syria 9.7%).
CYP2D6*5	Whole gene deletion (loss of function)	Rare individuals (2 out of 101)	Not specified	Very low frequency deletion in Saudi population.

INVEST study, the rs4149601 variant in the NEDD4L gene was linked to blood pressure response to the diuretic hydrochlorothiazide, but this association was observed specifically in individuals of European (White) descent. While the frequency and potential functional impact of this variant have also been reported in Asian populations such as Han Chinese the connection between rs4149601 and how well diuretics work in these groups is still not well understood (Table 1).

Ethnic and Population-Based Differences

Global Variation in Pharmacogenetic Markers

Population-specific differences in allele frequencies related to antihypertensive medication responsiveness are substantial. For instance, functional CYP3A5*1 alleles are more commonly expressed by people of African descent, which may improve CCB metabolism and effectiveness[7,25,29,30]. On the other hand, the ACE D allele is more common in East Asians, which could make them more sensitive to ACE inhibitors [35]. While a higher percentage of CYP2D6 poor metabolizers in Europeans require dose changes for beta-blockers, South Asians typically exhibit higher frequencies of AGTR1 variations, which may impact the effectiveness of ARBs[36]. These worldwide variations highlight the necessity of pharmacogenomic recommendations that take ethnicity into account[37].

Middle Eastern and Saudi Populations

The Saudi Genome Program and the Qatar Genome Project are two genomic initiatives that have uncovered unique pharmacogenetic patterns influenced by founder effects and significant consanguinity[38]. Large Saudi cohort data show that actionable pharmacogenetic variations are highly prevalent, especially in the CYP2C9, CYP2C19, and CYP3A5 genes[39,40]. Saudi populations, for instance, have CYP2C9*2 and CYP2C9*3 allele rates that are similar to those of Europeans but significantly higher than those of East Asians. Similarly, Saudis have a lower prevalence of the CYP2D6*4 allele (1–4%) than Caucasians (12–21%)[41]. Despite these discoveries, pharmacogenetic studies on antihypertensive responses in Saudi and larger Middle Eastern populations are still severely lacking, which is an important field for further research (Table 2)[24,39,41,42] .

Recent genome-wide association studies (GWAS) — new loci, mechanisms, multi-ethnic results- A critical appraisal

Over the past decade, GWAS and meta-analyses have uncovered numerous novel loci influencing blood pressure regulation, expanding our understanding beyond classical RAS (renin–angiotensin system) genes. These discoveries have provided mechanistic insights into hypertension pathophysiology, though their translation into clinical practice remains uneven[43]. One of the most promising examples is UMOD (uromodulin), linked to loop diuretic response through effects on renal sodium handling and salt sensitivity. This association has been replicated in genotype-stratified cohorts and supported by mechanistic plausibility. Early implementation studies (e.g., torasemide response) suggest modest blood pressure reductions (~3 mmHg). However, the overall clinical utility and cost-effectiveness of UMOD-guided therapy remain to be validated in larger randomized trials. By contrast, loci such as FGF5 and SH2B3 (LNK), identified through large GWAS consortia, point to pathways in vascular remodelling and immune signalling. While biologically plausible, they currently lack direct pharmacogenetic evidence or robust drug-response studies, limiting their immediate clinical relevance[40]. Similarly, variants near ATP2B1 and CACNB2/CACNA1C, implicated in vascular smooth muscle calcium signalling, show potential associations with calcium channel blocker (CCB) response in small pharmacogenetic sub-studies. Yet, these findings have not been consistently replicated in randomized pharmacogenomic trials, and effect sizes remain modest[44–46]. A critical contribution of recent multi-ethnic GWAS meta-analyses is the demonstration of substantial variation in allele frequencies and effect sizes across populations. For instance, UMOD variants exert stronger effects in East Asian cohorts, whereas ATP2B1 associations are more pronounced in Europeans. These differences reinforce the biological validity of the findings but also highlight the need for broader validation before implementing genotype-guided treatment strategies across diverse populations[47].

Gene–drug interaction meta-analyses — ACE I/D, AGTR1, CYP2C9, CYP2D6 (pooled effects)

The pharmacogenetic effects on antihypertensive medication response are more strongly supported by meta-analyses and systematic reviews: A pooled recessive model odds ratio of 1.61 (95% CI: 1.18–2.20) indicated that carriers of the I allele, especially those who are older and East Asian, have a significantly higher risk of ACE-inhibitor-induced cough, according to a systematic meta-analysis of ACE I/D polymorphism. However, the effects differed by age and study duration[48]. There is conflicting evidence about AGTR1 A1166C's role in ARB response; whereas certain candidate-gene reviews document genotype-response patterns, there is currently no high-quality meta-analysis that specifically measures ARB efficacy stratified by AGTR1 genotype. Reduced production of losartan's active metabolite E-3174 has been repeatedly associated with CYP2C9 *2/*3 alleles, resulting

Table 3. Key Gene–Drug Interactions in Antihypertensive Pharmacogenetics

Gene	Drug(s) Affected	Effect of Variant	Clinical Implication
CYP2C9	Losartan (ARB)	*2/*3 alleles reduce conversion to active metabolite (E-3174)	Decreased efficacy in **poor metabolizers**; may need dose adjustment
CYP2D6	Metoprolol, Nebivolol (β-blockers)	*4 (Europeans), *10 (Asians), *17 (Africans) reduce metabolism	Higher plasma levels, increased risk of bradycardia; lower doses recommended
ADRB1	β-blockers	Arg389 variant enhances drug response	May benefit more from β-blocker therapy
GRK5	β-blockers	Gln41 variant associated with enhanced β-blocker efficacy	Better cardiovascular outcomes in carriers
ACE	ACE inhibitors (e.g., enalapril)	I/D polymorphism associated with cough and variable response	I/I carriers at higher risk of **cough**, especially in East Asians
AGTR1	ARBs (e.g., losartan)	A1166C variant may alter receptor function	Inconsistent evidence: more research needed
CACNA1C	Calcium channel blockers (CCBs)	rs1051375 SNP alters BP response	May guide drug choice between β-blockers and CCBs
NOS3	Amlodipine	Glu298Asp polymorphism associated with mortality risk differences	May inform drug selection in high-risk patients
NEDD4L	Thiazide diuretics	Variants enhance response, associated with risk of hypokalemia	May predict **better response**, but monitor electrolytes
UMOD	Loop diuretics	rs13333226 affects salt sensitivity and drug response	May inform genotype-guided diuretic selection

in a lesser pharmacologic impact; pooled pharmacokinetic studies support decreased ARB activation in carriers of these reduced-function alleles (PMs)[49]. Poor metabolizers (PMs) exhibit a 4.9-fold higher AUC and a 5.9-fold lower clearance than extensive metabolizers for CYP2D6, according to a meta-analysis of metoprolol pharmacokinetics (n = 264); ultrarapid metabolizers (UMs) also displayed dramatically changed PK profiles[50]. All things considered, these meta-analyses show low to moderate effect sizes, which frequently account for slight absolute variations in blood pressure. However, they become clinically significant when connected to actual pharmacokinetic alterations or adverse-event risk (such as cough or bradycardia) (Table 3).

Emerging Pharmacogenetic Biomarkers: Non-Coding Variants, Epigenetics, microRNAs, and Polygenic Risk Scores (PRS)

Pharmacogenetics is embracing non-coding regulatory elements, epigenetic alterations, microRNAs (miRNAs), and polygenic risk scores (PRS) as new biomarkers that influence medication response and hypertension risk, going beyond single coding variants. The expression of important genes involved in vascular smooth muscle tone, renal salt transport, or RAAS can be subtly changed by non-coding variations found in promoters, enhancers, or untranslated regions. This can affect the effectiveness of antihypertensive medications and inter-individual variability[51,52]. Persistent changes in gene expression in vascular and renal tissues have also been linked to epigenetic processes like DNA methylation and histone modifications, which may alter transcriptional control and chromatin accessibility to modify responsiveness to drugs like ACE inhibitors or ARBs[53,54]. Furthermore, circulating miRNAs that regulate several pathways, such as angiogenesis, endothelial integrity, and sodium handling, such as miR-126-3p, miR-182-5p, and miR-30a-5p, are dysregulated in hypertensive patients and correlate with the severity of the disease, making them promising as biomarkers and therapeutic targets[55]. In addition, a variety of common BP-associated variations are combined into predictive measures via polygenic risk scores (PRS): Across a range of ethnic groupings, multi-ancestry HTN-PRSs exhibit strong correlations with both prevalent and incident hypertension, as well as predictive potential for upcoming cardiovascular events (e.g., OR ~2.1 for prevalent hypertension; AUC ~0.76). With hazard increases of up to almost 38% per standard deviation in certain groups, ancestry-stratified BP PRSs also show improved risk prediction for the development of hypertension and earlier onset, underscoring their usefulness in early detection[56]. Before being suggested for routine use, these advanced markers must undergo thorough validation across ancestries, clinical utility assessment, and integration into practice, despite the fact that they hold considerable promise for individualized prevention and drug-selection strategies.

Integration with Clinical Guidelines – CPIC, DPWG, FDA, and Evidence Gaps

The codification of gene-drug evidence pertaining to antihypertensive drugs has started by clinical guideline groups. Based on compelling evidence that poor metabolizers (PMs) have a markedly increased risk of metoprolol exposure and bradycardia, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has now issued phenotype-guided dosing recommendations for CYP2D6–metoprolol, providing dosing and titration guidance in accordance with these recommendations[57,58]. Guidelines for related β-blocker genes, such as ADRB1, ADRB2, ADRA2C, GSK4, and GSK5, have also been developed by CPIC; nonetheless, CYP2D6 still has the most unambiguous therapeutic actionability. Similar to this, the Dutch Pharmacogenetics Working Group (DPWG) develops evidence-based gene-drug guidelines to integrate pharmacogenetics into prescribing systems; however, the recommendations it has released so far place more emphasis on antidepressants and anti-epileptics than antihypertensives[59]. In antihypertensive medication labeling, the U.S. Food and Drug Administration (FDA) lists certain pharmacogenomic biomarkers. For instance, it notes changed metoprolol exposure in CYP2D6 poor metabolizers and suggests clinical monitoring in these situations[60]. However, only a few high-evidence gene–drug pairings are recommended for antihypertensives across these guideline bodies; numerous loci indicated by GWAS, such UMOD, ATP2B1, or SH2B3, are not currently actionable. Importantly, there are significant evidence gaps that limit the applicability of guidelines for the Middle East and other underrepresented communities; local allele frequencies, linkage disequilibrium patterns, and variation impacts can differ significantly from European datasets. Importantly, before pharmacogenetic recommendations may be applied globally, these gaps must be filled[61].

Real-World Implementation — Trials, Outcomes, Cost-Effectiveness, Barriers

Through translational studies that confirm therapeutic value, genotype-guided antihypertensive therapy is becoming more widely used in the real world. The feasibility of using genotype-directed loop diuretics to

treat hypertension was supported by a multicenter, genotype-blinded trial in which patients with the UMOD rs13333226-AA genotype showed significantly larger and longer-lasting reductions in 24-hour ambulatory systolic blood pressure over 16 weeks of torasemide therapy compared to AG/GG genotype carriers ($\Delta \approx -3.35$ mm Hg; $p = 0.048$)[62]. Pharmacogenetic data can significantly guide β-blocker dosing and safety, as evidenced by retrospective cohort analyses of CYP2D6 genotypes in patients on metoprolol that associate poor-metabolizer status with elevated plasma drug levels, more pronounced bradycardia, and lower maintenance doses required to avoid adverse events[63,64]. When pharmacogenetic testing guided antihypertensive prescribing, implementation studies—including a retrospective customized therapy analysis—showed better blood pressure management and increased medication acceptability[65]. Cost-effectiveness, however, relies on minimizing expensive events and is very context-dependent. Economic analyses show that when genetic panels prevent severe adverse drug responses or recurrent hospitalizations, genotype-guided approaches are cost-effective, particularly when the same pharmacogenetic data are used for several drugs. Uncertain reimbursement, inconsistent patient acceptance, lack of training and awareness among clinicians, unequal access to rapid and accurate genetic testing, and poor integration of pharmacogenetic decision support into EHR systems are some of the challenges that still hinder clinical adoption, despite the fact that it is encouraging. To attain broader adoption, these concerns must be addressed in future implementation studies[66,67].

Gene–Environment Interactions — Salt, Diet, Comorbidities, Lifestyle

The relevance of gene–environment interactions in BP control and antihypertensive efficacy is highlighted by the fact that the hereditary factors of hypertension frequently manifest differently depending on environmental exposures and comorbidities. The need to customize diuretic treatments based on both genotype and salt consumption patterns is reinforced by the fact that common noncoding UMOD variants are known to enhance salt-sensitive hypertension by increasing uromodulin expression. Patients with these variants show more noticeable BP elevation in response to dietary sodium intake[66,67]. Obesity and high BMI also influence genetic risk. For instance, those with high adiposity may have an exacerbated FGF5-associated blood pressure rise, indicating a compound gene × obesity impact. However, further mechanistic research is needed to fully understand the specific FGF5 × BMI interactions[68]. Additionally, the relationships between genotypes and phenotypes can be altered by comorbid illnesses such as diabetes and chronic renal disease, which can alter pharmacokinetics and pharmacodynamics. For example, decreased renal clearance in CKD may make sodium-handling gene variants more potent or decrease the efficacy of medications. Numerous cohort studies and mechanistic models demonstrate that the addition of environmental factors (salt intake, BMI, and smoking status) to genotype significantly boosts prediction power for antihypertensive response when compared to genetic or clinical models alone[69,70].

Adverse Drug Reactions (ADRs) and Pharmacogenetic Markers

Pharmacogenetics is essential for forecasting the effectiveness of antihypertensive medications as well as for identifying people who are more likely to experience adverse drug reactions (ADRs), which enhances medication safety and improves treatment plans[71]. Variants in NEDD4L, a gene involved in sodium reabsorption and renal ion transport, have been strongly associated with thiazide-induced hypokalemia and enhanced thiazide sensitivity in several cohorts, suggesting that pre-treatment genotyping may help identify patients at higher electrolyte imbalance risk[72]. Similarly, increased vulnerability to ACE inhibitor-induced cough, a common reason for stopping treatment, is associated with polymorphisms in the ACE gene (especially the I/D variation) and genes within the bradykinin pathway (e.g., BDKRB2)[60,72]. Additionally, metoprolol plasma concentrations are higher in CYP2D6 poor metabolizers, increasing the risk of bradycardia, hypotension, and fatigue. This emphasizes the significance of genotype-guided beta-blocker dosing[72].

Multi-gene pharmacogenomic panels show promise in forecasting complex ADR patterns beyond single-gene correlations by incorporating several variables influencing drug absorption, distribution, metabolism, and excretion (ADME)[72]. However, many pharmacogenetic correlations for ADRs are still population-specific and lack sufficient validation in populations from the Middle East, Africa, and South Asia, where allele frequencies and linkage disequilibrium patterns differ significantly from the European reference dataset.. Large-scale, multiethnic research is therefore desperately needed to develop solid, broadly applicable pharmacogenomic guidelines for reducing adverse drug reactions and maximizing antihypertensive treatment[71] .

Technology and Data Integration — EHRs, CDS, Databases, AI/ML Models

An essential component of pharmacogenomic implementation success is technology infrastructure. Clinical Decision Support (CDS) in conjunction with genotype data integration into Electronic Health Records (EHRs) provides doctors with actionable alerts at the point of treatment, informing them when genetic variants (such as CYP2D6 poor metabolizer status) call for medication changes or dose adjustments[71]. The majority of PGx CDS tool implementations use interruptive alerts, according to scoping evaluations. Clinical response rates range significantly (12–73%), and provider acceptance is extremely context-dependent. These findings underscore the need for CDS design and usability optimization[70]. By offering curated, evidence-based guidelines and variant annotations, national and international knowledgebases like PharmGKB, CPIC, and FDA pharmacogenomics biomarker tables act as fundamental annotation tools that improve EHR–CDS integration. Furthermore, AI-driven EHR synthesis that integrates pharmacogenomic, pharmacokinetic, and drug-interaction data might provide real-time, individualized medication management in polypharmacy scenarios, as demonstrated by pilot models (such as the IPGx bioanalytic platform)[72]. Machine learning and artificial intelligence (AI) tools like deep learning platforms for phenotype prediction and genotype-based recommendation engines (like Sherpa Rx with retrieval-augmented generation) hold great promise for scalable, context-aware decision support in the future[72]. However, these models need to be trained and validated across a range of ancestries to avoid algorithmic bias. Funding needs to be set aside for interoperable data standards, clinician education, and governance frameworks (such patient consent and privacy protection) in order to ensure the safe, equitable, and effective clinical integration of pharmacogenomics. While these advances are promising, their integration into practice must be approached with caution. AI and CDS models risk perpetuating algorithmic bias if trained on limited ancestry groups, and their outputs may not generalize across diverse populations without rigorous validation. Equally important are governance frameworks including standards for interoperability, data privacy, patient consent, and accountability—that ensure safe and equitable use. Addressing these challenges in parallel with technological innovation is essential to avoid widening health disparities and to realize the full clinical potential of pharmacogenomics.

DISCUSSION

Although potential candidate loci influencing antihypertensive medication response have been identified by recent GWAS, only

a small number of them, like UMOD, exhibit both molecular plausibility and early therapeutic value. The majority of loci, such as ATP2B1, SH2B3, and FGF5, need to be further replicated, validated pharmacogenetically, and incorporated into actual clinical studies. To apply these findings to precision hypertension therapy, future studies must concentrate on impact size quantification, multi-ethnic replication, and clinical implementation frameworks. The therapeutic usefulness of CYP2D6 and ACE polymorphisms in directing dosage and adverse event monitoring is supported by meta-analytic evidence. However, despite their pharmacological plausibility, CYP2C9 and AGTTR1 variations have not been sufficiently validated in extensive trials, which restricts their immediate use. This variation emphasizes how future gene-drug research must standardize study methods and guarantee sufficient sample sizes. The majority of the evidence to date is associative rather than causative and lacks prospective validation, despite the fact that non-coding variations, epigenetics, and PRSs constitute the future frontier of pharmacogenomics. Before being incorporated into treatment algorithms, these biomarkers need to undergo extensive testing in interventional studies as they are not yet prepared for clinical use. A small number of gene–drug interactions (such as CYP2D6–metoprolol) satisfy the requirements to be included in clinical guidelines.

The majority of others are still being investigated.The fair use of pharmacogenomics is hampered by significant evidence gaps relating to ancestry, which demand immediate consideration in the creation of international guidelines. Despite encouraging early implementation results, cost-effectiveness varies by setting and clinical benefit is limited. Infrastructure upgrades, fair access to testing, and unambiguous proof of cost and outcome benefits in sizable, multi-drug settings are necessary for wider implementation. Although gene-environment interactions are crucial for tailored treatment, their practical implementation is constrained by the intricacy of the data and the lack of clinical tools. To improve therapeutic precision, lifestyle, comorbidities, and genetic data must be incorporated into future models. Although pharmacogenetic markers have demonstrated promise in ADR prediction, their current application is limited to a small number of verified gene–drug combinations. To guarantee safety and equity, widespread panel-based testing requires more comprehensive, population-specific data. Integration of technology is important yet insufficient. The influence of AI and EHR tools on the delivery of hypertension care will be minimal in the absence of national infrastructure and uniform pathways.

CONCLUSION

The novelty of integrating pharmacogenomics lies in its potential to personalize hypertension treatment, optimize efficacy, and minimize adverse effects.In conclusion, the majority of gene drug associations still require further study before they can be applied in routine care, even though several genetic markers, show early promise in directing the therapy of hypertension. Larger sample sizes, different populations, and obvious clinical advantages must be the main objectives of future research. We require improved instruments, equitable access, and compelling proof of pharmacogenomics' cost-effectiveness and safety before it can be applied extensively.

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