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Review

Clinical Application of Pharmacogenomics in Stroke Management: Current Evidence and Future Directions

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Pharmacogenomic variations may significantly influence responses to commonly prescribed stroke medications. Despite accumulating evidence, genetic testing has not yet been widely integrated into stroke care. This review summarizes current evidence and provides practical guidance for clinical implementation. Pharmacogenomic studies and clinical guidelines related to antiplatelet agents, anticoagulants, and statins were reviewed, with particular emphasis on East Asian populations. Substantial evidence supports genotype-guided use of clopidogrel (*CYP2C19*), warfarin (*CYP2C9*, *VKORC1*, *CYP4F2*), and statins (*SLCO1B1*, *ABCG2*). For aspirin, *PTGS1/2* and *PEAR1* variants have been investigated; however, current data remain insufficient for clinical application. Regarding direct oral anticoagulants (DOACs), candidate genes such as *ABCB1* and *CES1* demonstrate pharmacokinetic associations, though robust clinical outcome data are lacking. Distinct allele frequencies in East Asians—such as higher prevalence of *CYP2C19* and *ABCG2* variants—underscore the need for population-specific strategies. Beyond single-gene approaches, polygenic risk scores, pharmacogenomic panels, and integration with multi-omics data and artificial intelligence represent promising directions for personalized therapy. Pharmacogenomic testing can enhance stroke

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pharmacotherapy, particularly in populations with high frequencies of actionable variants. Broader implementation requires rapid testing platforms, clinician education, tailored clinical guidelines, and real-world validation of aspirin, DOACs, and multi-gene approaches. Future research should expand population-specific studies and integrate pharmacogenomics within the broader framework of precision medicine to ensure equitable clinical benefit.

Keywords Pharmacogenomics; Stroke; Antiplatelet agents; Anticoagulants; Statins; Precision medicine

Introduction

Stroke remains a leading cause of mortality and disability worldwide, with treatment outcomes significantly influenced by interindividual variability in drug response.[1,2] Advances in genomic medicine have underscored the importance of genetic factors in modulating both the efficacy and safety of pharmacologic therapies used in stroke care.[3]

Pharmacogenomics (PGx) offers an opportunity to tailor drug therapy according to a patient's genetic profile, thereby improving treatment outcomes through personalized medicine.[4] Although clinical adoption has progressed in oncology and cardiology, its implementation in stroke management has lagged despite growing evidence of its clinical relevance.[3,5]

The complexity of stroke pharmacotherapy—encompassing both acute interventions and long-term secondary prevention—presents opportunities as well as challenges for pharmacogenomic application.[2] Key medication classes, including antiplatelet agents, anticoagulants, and statins, exhibit pharmacogenetic variability with significant implications for therapeutic decision-making.[6-8] Among these, the impact of cytochrome (CYP) P450 2C19 (*CYP2C19*) genetic variants on clopidogrel metabolism is well established and particularly relevant to East Asian populations, in which loss-of-function (LOF) alleles are highly prevalent.

This review summarizes current evidence supporting pharmacogenomic testing in stroke care, with an emphasis on drugs with established genetic associations. It also explores population-specific considerations, implementation strategies, and future directions to facilitate the integration of PGx into precision stroke medicine.

Current status of pharmacogenomic evidence

Evidence base and guidelines

Several established resources provide evidence-based guidance for implementing pharmacogenomic testing in stroke care. The Clinical Pharmacogenetics Implementation Consortium (CPIC) serves as a leading authority, publishing regularly updated guidelines that translate genetic test results into actionable prescribing recommendations.[9]

The Pharmacogenomics Knowledge Base (PharmGKB) complements CPIC by grading the strength of gene–drug associations from Level 1A (highest) to Level 4 (lowest), thereby enabling clinicians to assess the robustness of available evidence efficiently.[10,11] Currently, Level 1A evidence supports testing for three drug classes highly relevant to stroke management: clopidogrel, warfarin, and statins. CPIC's genotype-based prescribing recommendations for antiplatelet and anticoagulant therapy, emphasizing efficacy, are summarized in Table 1, and recommendations for statin therapy and statin-associated muscle symptoms (SAMS) are provided in Table 2.

Recently, CPIC and PharmGKB were integrated into a unified platform, ClinPGx (https://www.clinpgx.org/), to streamline access and harmonize pharmacogenomic guidance. While CPIC guidelines primarily focus on pharmacokinetics—especially drug metabolism pathways (the "M" in Absorption, Distribution, Metabolism, Excretion [ADME])—PharmGKB has traditionally cataloged a broader range of evidence, including pharmacodynamic associations and genetic determinants of adverse drug reactions. This distinction highlights the complementary value of these resources: CPIC provides explicit prescribing recommendations for well-validated pharmacokinetic variants, whereas PharmGKB includes pharmacodynamic and safety-related variants that may be highly relevant to stroke medications but are not yet incorporated into formal guidelines.

In addition, the Dutch Pharmacogenetics Working Group (DPWG) issues prescribing recommendations that sometimes differ from those of CPIC, thereby offering alternative perspectives that may assist clinical decision-making.[12] For example, therapeutic recommendations synthesized in CPIC guidelines are largely based on expert consensus, whereas DPWG relies more heavily on quantitative pharmacokinetic data from studies of good or moderate quality.[13] Taken together, these international

Table 1. Clinical Pharmacogenetics Implementation Consortium recommendations for pharmacogenomic testing on antithrombotic medication used for stroke prevention

A. Clopidogrel – CYP2C19 genotype interpretation and dosing guidance				
Drug	Gene	Phenotype	Genotype or key variants	Clinical recommendations
Clopidogrel[6]	*CYP2C19*	Ultrarapid metabolizer	Two increased function alleles (**17/*17*)	Use standard dose.
		Rapid metabolizer	One normal + one increased function allele (**1/*17*)	Use standard dose.
		Normal metabolizer	Two normal function alleles (**1/*1*)	Use standard dose.
		Intermediate metabolizer	One normal + one no function allele (**1/*2*, **1/*3*)	Consider alternative P2Y12 inhibitors.
		Poor metabolizer	Two no function alleles (**2/*2*, **2/*3*, **3/*3*)	Avoid clopidogrel; use alternative P2Y12 inhibitors.
B. Warfarin – Dosing-relevant genes				
Warfarin[7]	*CYP2C9*	-	**2*, **3*	Recommend using validated dosing algorithms (e.g., IWPC and Gage).
	VKORC1	-	c.-1639G>A (rs9923231)	
	CYP4F2	-	c.1297G>A (rs2108622)	

-, not applicable; IWPC, International Warfarin Pharmacogenetics Consortium.

frameworks provide a coherent foundation for integrating pharmacogenomics into clinical practice and reinforce the growing consensus regarding its clinical significance.

Landmark clinical trial evidence

The Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial marked a milestone in stroke PGx, providing the first large-scale validation of genotype-guided antiplatelet therapy in acute stroke.[14] In this trial, 6,412 patients with minor ischemic stroke or high-risk transient ischemic attack (TIA) in China were randomized to receive ticagrelor or clopidogrel based on their *CYP2C19* LOF carrier status.

Among LOF carriers, ticagrelor reduced the risk of recurrent stroke by 34% (risk ratio 0.66; 95% confidence interval [CI], 0.48–0.99; *P*=0.009), confirming the clinical benefit of genotype-guided therapy. These findings strengthened the rationale for *CYP2C19* testing in antiplatelet selection and directly informed updates to regional stroke guidelines in East Asia.[15]

Importantly, the CHANCE-2 trial demonstrated how pharmacogenomic information can be integrated into time-sensitive clinical workflows, indicating that genetic testing can be both actionable and feasible at the point of care. This trial therefore, serves as a model for future research evaluating PGx in acute stroke management, although its genetic testing platform has not yet been widely implemented outside China.

Methodology and evidence selection criteria

To synthesize current knowledge, a systematic literature review was conducted focusing on pharmacogenomic studies relevant to medications commonly used in stroke care. Priority was given to high-quality evidence incorporated into CPIC guidelines or classified as Level 1 or 2 in PharmGKB, with particular emphasis on studies conducted in East Asian populations.

This review concentrated on three major drug classes—antiplatelet agents (particularly clopidogrel), anticoagulants (primarily warfarin), and statins—for which substantial pharmacogenomic evidence supports clinical utility. Additional stroke-related medications, including aspirin and direct oral anticoagulants (DOACs), were also evaluated, although robust pharmacogenomic evidence for these agents remains limited despite their central role in current stroke management.

Of note, substantial knowledge gaps remain in other drug classes, such as antihypertensive and antidiabetic agents, despite their widespread use in stroke prevention. For example, only metoprolol demonstrates modest pharmacogenomic associations through *CYP2D6* variants.[16] This paucity of evidence is particularly concerning given recent findings from the NIH All of Us Research Program, which identified racial differences in drug responses to commonly used antihypertensives.[17] These gaps are particularly pronounced among East Asian populations, including Koreans, highlighting the need for population-specific pharmacogenomic studies to inform clinical practice in this regional context.

To address this issue, allele frequency data from Korean populations were incorporated using the ongoing GENomic Exploration in Stroke and pharmacogenomic Innovation Study–Korea (GENESIS-K) cohort, highlighting areas where population-tailored pharmacogenomic guidance is urgently required. This approach aimed to contextualize global evidence within the East Asian clinical framework.

PGx of antiplatelets

Clopidogrel

Clopidogrel is a widely used antiplatelet agent in stroke pre-

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vention, but its effectiveness varies considerably due to genetic variations that influence its metabolism. As a prodrug, clopidogrel requires two-step hepatic bioactivation—primarily mediated by *CYP2C19*—to be converted into its active metabolite.[18] This metabolite irreversibly inhibits the platelet P2Y12 receptor, thereby reducing platelet aggregation.

Genetic polymorphisms in *CYP2C19* are strongly associated with clopidogrel's therapeutic efficacy.[6] The most clinically relevant variants include the LOF alleles (*2, *3) and the gain-of-function (GOF) allele (*17). Approximately 30% of the general population carries at least one LOF allele, whereas the prevalence is considerably higher in East Asians, reaching up to 60%, compared with a lower prevalence in other ethnic groups (11%–19% in Europeans and 11%–17% in Africans) (Table 3).[19]

The LOF alleles reduce the formation of the active metabolite by 25%–40%, resulting in diminished platelet inhibition and an increased risk of recurrent vascular events.[20] Meta-analyses have shown that carriers of *2/*2 or *2/*3 genotypes have a 1.5- to 3.5-fold higher risk of stroke or other cardiovascular events compared with non-carriers.[21] In contrast, carriers of the *17 GOF allele exhibit enhanced response to clopidogrel but face a higher risk of bleeding.[22] Consistent with these findings, a Korean multicenter prospective study reported a higher incidence of composite vascular outcomes among LOF carriers (2.7% vs. 1.6%).[23]

The CHANCE-2 trial provided definitive evidence supporting genotype-guided antiplatelet therapy.[14] In this randomized trial involving 6,412 Chinese patients with minor ischemic stroke or TIA, ticagrelor was superior to clopidogrel among *CYP2C19* LOF allele carriers, resulting in a 34% reduction in stroke recurrence. These findings informed updates to East Asian stroke guidelines, including those of the Chinese Stroke Association, which now recommend genotype-guided therapy for selected patients.[15]

Beyond *CYP2C19*, several other genes have been investigated for their potential influence on clopidogrel pharmacokinetics and pharmacodynamics, although their clinical relevance remains less well established:

Table 2. Clinical Pharmacogenetics Implementation Consortium recommendations for pharmacogenomic testing on statins

C. Statins – SLCO1B1 & ABCG2 variants and SAMS risk				
Drug	Gene	Phenotype	Genotype or key variants	Clinical recommendations
Statins[8]	*SLCO1B1*	Increased function	Two increased function alleles (**14/*14*)	Prescribe desired starting dose.
		Normal function	Two normal function alleles OR one normal + one increased function allele (**1/*1*, **1/*14*)	Prescribe desired starting dose.
		Decreased function	One normal or increased + one no function allele (**1/*5*, **1/*15*)	Avoid statins with high SAMS risk*; use with caution for statins with moderate SAMS risk†.
		Poor function	Two no function alleles (**5/*5*, **5/*15*, **15/*15*)	Avoid statins with high SAMS risk‡; use with caution for statins with moderate SAMS risk§.
Rosuvastatin[8]	*ABCG2*	Normal function	c.421 C/C	Prescribe desired starting dose.
		Decreased function	c.421 C/A	Prescribe desired starting dose.
		Poor function	c.421 A/A	Prescribe ≤20 mg as a starting dose. If >20 mg needed, consider alternative statin or combination with non-statin drug.
	SLCO1B1 × *ABCG2*	*SLCO1B1* decreased or poor function AND *ABCG2* poor function	-	Prescribe ≤10 mg as a starting dose. If >10 mg needed, consider an alternative statin or combination with non-statin drug.
Fluvastatin[8]	*CYP2C9*	Normal metabolizer	Two normal function alleles (**1/*1*)	Prescribe desired starting dose.
		Intermediate metabolizer	One normal + one decreased function allele OR two decreased functional alleles (**1/*2*, **1/*3*, **2/*2*)	Prescribe ≤40 mg as a starting dose. If >40 mg needed, consider an alternative statin or combination with non-statin drug.
		Poor metabolizer	One no function + one decreased function allele OR two no function alleles (**2/*3*, **3/*3*)	Prescribe ≤20 mg as a starting dose. If >20 mg needed, consider an alternative statin or combination with non-statin drug.
	SLCO1B1 × *CYP2C9*	*SLCO1B1* decreased or poor function AND *CYP2C9* poor metabolizer	-	Prescribe an alternative statin.

SAMS, statin-associated muscle symptoms; -, not applicable.
*Atorvastatin 80 mg, lovastatin 40–80 mg, pitavastatin 4 mg, simvastatin 20–40 mg; †Atorvastatin 40 mg, rosuvastatin 40 mg, fluvastatin 80 mg, pitavastatin 2 mg, pravastatin 80 mg, lovastatin 20 mg, simvastatin 10 mg; ‡Atorvastatin 40–80 mg, rosuvastatin 40 mg, lovastatin 20–80 mg, pitavastatin 2–4 mg, simvastatin 10–40 mg; §Fluvastatin 80 mg, pravastatin 80 mg.

- *ABCB1*: Affects drug absorption and distribution.[24]
- *CES1*: Participates in hydrolysis of the prodrug.[25]
- *PON1*: May contribute to clopidogrel activation.[26]
- *P2Y12*: Modifies target receptor function.[27]
- *CYP2B6*/*CYP2C9*: May influence alternative metabolic pathways.[20]

Currently, only *CYP2C19* has sufficient evidence for clinical actionability and is recommended by CPIC and PharmGKB for genotype-guided therapy (Table 1). Other candidate genes remain under investigation.

Aspirin

Aspirin remains a cornerstone of both primary and secondary stroke prevention. It irreversibly inhibits cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which are encoded by the *PTGS1* and *PTGS2* genes, thereby reducing thromboxane A2–mediated platelet aggregation.[28] Although generally effective, substantial interindividual variability in aspirin response has been observed, and genetic factors may partially account for this variation.[29]

Variants in *PTGS1* and *PTGS2* may alter the antiplatelet efficacy of aspirin. For instance, the *PTGS1* -842A>G polymorphism has been associated with reduced *COX-1* expression and increased cardiovascular risk (hazard ratio 2.57; 95% CI, 1.87–3.54).[30] Similarly, the *PTGS2* -765G>C variant may influence *COX-2* activity and has been linked to an attenuated antiplatelet response.[31] *The PEAR1* rs12041331 A allele, which encodes platelet endothelial aggregation receptor 1,[32] has also been associated with increased cardiovascular risk, although findings are inconsistent and have not yet been validated in stroke-specific cohorts.[33]

Genetic factors may also influence aspirin safety. *HLA-DPB1*

Table 3. Actionable pharmacogenomic variants in stroke medications: ethnic differences between Korean and other populations

Drug	Gene/variant (allele)	Carrier frequency among Korean stroke patients (GENESIS-K, n=3,840)	Carrier frequency across ethnic groups in the general population (UKBB)	Clinical implications
Clopidogrel	*CYP2C19* *2, *3	*2: 1,861 (48.5%) *3: 749 (19.5%)	*2: 26.0% in Europeans, 27.2% in Africans, 44.7% in East Asians, and 50.8% in South Asians. *3: 0.0% in Europeans, 0.3% in Africans, 9.4% in East Asians, and 0.2% in South Asians.	CHANCE-2 trial (Chinese patients): genotype-guided therapy effective. Reduced clopidogrel activation; recommend ticagrelor for intermediate/poor metabolizers.
Warfarin	*VKORC1* -1639G>A (rs9923231)	3,825 (99.6%)	60.8% in Europeans, 15.5% in Africans, 98.2% in East Asians, and 32.4% in South Asians.	Increased warfarin sensitivity; lower initial dose required.
	CYP2C9 *2, *3	*2: 1 (0.03%) *3: 337 (8.8%)	*2: 23.9% in Europeans, 1.8% in Africans, and 0.0% in East Asians, and 10.4% in South Asians. *3: 12.3% in Europeans, 1.1% in Africans, 8.2% in East Asians, and 20.5% in South Asians.	Reduced warfarin metabolism; contributes to higher bleeding risk; consider dose reduction.
	CYP4F2 V433M (rs2108622)	2,080 (54.2%)	51.2% in Europeans, 17.2% in Africans, 39.4% in East Asians, and 60.7% in South Asians.	May require slightly higher warfarin dose due to altered vitamin K metabolism.
Statins	*SLCO1B1* *5, *15	*5: 4 (0.1%) *15: 1,024 (26.7%)	*5: 6.1% in Europeans, 0.3% in Africans, 0.8% in East Asians, and 1.1% in South Asians. *15: 16.9% in Europeans, 3.0% in Africans, 21.6% in East Asians, and 7.2% in South Asians.	Associated with higher risk of SAMS, avoid statin with high SAMS risk.
	ABCG2 c.421C>A (rs2231142)	1,837 (47.8%)	21.3% in Europeans, 3.4% in Africans, 52.2% in East Asians, and 18.3% in South Asians.	Increases rosuvastatin plasma levels, recommended starting with ≤20 mg/day.
	CYP2C9 *2, *3	*2: 1 (0.03%) *3: 337 (8.8%)	*2: 23.9% in Europeans, 1.8% in Africans, and 0.0% in East Asians, and 10.4% in South Asians. *3: 12.3% in Europeans, 1.1% in Africans, 8.2% in East Asians, and 20.5% in South Asians.	Increased fluvastatin plasma levels, associated with SAMS.

GENESIS-K, GENomic Exploration in Stroke and pharmacogenomic Innovation Study–Korea; UKBB, UK Biobank; CHANCE-2, Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II; SAMS, statin-associated muscle symptoms.

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variants have been associated with aspirin-induced asthma, with *HLA-DPB1*03:01* increasing susceptibility and *HLA-DPB1*04:01* conferring protection.[34,35] Additionally, *UGT1A6 AA* polymorphisms have been linked to altered aspirin metabolism and differential long-term colorectal cancer risk reduction.[31]

Despite these associations, no genetic markers related to aspirin currently have sufficient evidence for clinical implementation. According to CPIC and PharmGKB classifications, routine pharmacogenomic-guided aspirin use is not recommended.

PGx of anticoagulants

Warfarin

Warfarin remains an important agent for stroke prevention in patients at risk of cardioembolic stroke, including those with atrial fibrillation—particularly in settings where DOACs are contraindicated or unavailable.[36] However, warfarin therapy exhibits substantial interindividual variability in dose requirements and bleeding risk, much of which can be attributed to genetic variation.[37]

The three principal pharmacogenes associated with warfarin response are *CYP2C9*, *VKORC1*, and *CYP4F2*.[38] The *CYP2C9* gene encodes the primary enzyme responsible for warfarin metabolism. The most common variants, *CYP2C9*2* and *CYP2C9*3* alleles, reduce enzymatic activity, resulting in slower warfarin clearance and an elevated risk of bleeding.[39] Carriers of these variants typically require lower maintenance doses and longer periods to achieve a stable international normalized ratio (INR).[39]

The *VKORC1* gene encodes the warfarin target enzyme, which catalyzes the reduction of vitamin K epoxide to its active form.[40] The common -1639G>A variant (*VKORC1 A allele*) decreases gene expression and increases warfarin sensitivity.[40] Homozygous carriers (AA genotype) generally require approximately 50% lower doses compared with wild-type individuals.[40] Population-based studies have identified significant ethnic differences in *VKORC1* allele frequencies, partially explaining interethnic variability in warfarin dose requirements across populations (Table 3).[41]

CYP4F2 variants, particularly c.1297G>A (rs2108622), affect vitamin K metabolism, with carriers typically requiring higher warfarin doses.[42] The combined effects of variants in these three genes, along with clinical factors, can lead to as much as a 20-fold difference in warfarin dose requirements among individuals.[38]

Warfarin dosing algorithms that integrate *CYP2C9* and *VKORC1* genotypes, along with clinical factors such as age, body size, and concomitant medications, have been developed and validated. The International Warfarin Pharmacogenetics Consortium[43] and Gage algorithms[44] are among the most widely used. Several clinical trials—Clarification of Optimal Anticoagulation through Genetics (COAG), European Pharmacogenetics of Anticoagulant Therapy (EU-PACT), and Genetic Informatics Trial (GIFT)—have evaluated genotype-guided dosing.[45-47] Although results have been mixed, the GIFT trial demonstrated reduced bleeding and thromboembolic events in the genotype-guided group, supporting its clinical utility in selected populations.[46] Similarly, in the EU-PACT trial, pharmacogenetic-guided dosing was associated with a greater percentage of time within the therapeutic INR range and significantly fewer episodes of excessive anticoagulation (INR ≥4.0) compared with standard dosing.[47] Accordingly, CPIC guidelines recommend incorporating CYP2C9 and VKORC1 genotypes into initial dosing whenever available (Table 1).[7]

However, several challenges persist in translating these findings into clinical practice, particularly for Asian populations. First, most dosing algorithms have been derived from predominantly European cohorts and may overestimate warfarin dose requirements in East Asians. Second, East Asians, including Koreans, have a substantially higher frequency of the *VKORC1-1639A* allele and *CYP2C9 *3/*3* genotypes, which are associated with markedly reduced warfarin dose needs (often <2 mg/day).[48] Third, minor alleles in other genes, such as *CYP4F2* and *GGCX*, although less influential, may further modulate dosing requirements in specific populations.[7,49] Finally, the risk of warfarin-associated intracranial hemorrhage is significantly higher among Asians, emphasizing the importance of precise dosing and vigilant INR monitoring.[50]

Only a limited number of studies have evaluated genotype-guided warfarin dosing in Korean populations, demonstrating that existing algorithms frequently overestimate dose requirements and do not adequately account for the high prevalence of ultra-sensitive genotypes.[51] These findings underscore the necessity for validated, population-specific dosing models that integrate Korean-specific allele frequencies and clinical outcomes (Table 3).

DOACs

DOACs have become a cornerstone of thromboembolic event prevention in patients with atrial fibrillation and other high-risk conditions.[52,53] In Korea, the prescription rate of DOACs for patients with acute ischemic stroke and atrial fibrillation increased from 4.6% in 2013 to 73.9% in 2019.[54] Unlike warfarin, DOACs exhibit more predictable pharmacokinetic profiles and generally do not require routine coagulation monitoring. Their mechanisms of action include direct thrombin inhibition by dabigatran[55] and factor Xa inhibition by apixaban, edoxaban, and rivaroxaban.[56-58]

Dabigatran is administered as a prodrug (dabigatran etexi-

late mesylate) and is converted to its active form by intestinal and hepatic carboxylesterases (*CES1*). In contrast, apixaban, edoxaban, and rivaroxaban are administered in their active forms. All DOACs are substrates of the efflux transporter P-glycoprotein, and their plasma concentrations can be influenced by P-glycoprotein inhibitors, which may alter both anticoagulant efficacy and bleeding risk.[55-58]

Genetic variations may contribute to interindividual variability in DOAC pharmacokinetics and pharmacodynamics, although their clinical significance remains under investigation. Key genes implicated include *ABCB1*, which encodes P-glycoprotein; *CES1*, responsible for dabigatran activation; and *CYP3A4/5*, involved in the metabolism of factor Xa inhibitors, especially apixaban and rivaroxaban.[59-65]

Polymorphisms in *ABCB1*, such as rs4148738 and rs1045642, have been associated with increased peak plasma concentrations of dabigatran, apixaban, and rivaroxaban, and in some studies, with an elevated bleeding risk.[59,60] However, associations with clinical outcomes, including thromboembolism and major bleeding, remain inconclusive. Similarly, *CYP3A5*3*, a LOF variant, has been linked to higher plasma levels of apixaban, although findings have been inconsistent across studies.[61,62]

For dabigatran, the *CES1* rs2244613 variant has been associated with lower plasma concentrations and a reduced bleeding risk.[60] Other *CES1* variants, including rs8192935 and rs71647871, have demonstrated similar associations; however, their clinical utility has not yet been clearly established.[63-65]

To date, no pharmacogenomic markers associated with DOACs have been incorporated into clinical guidelines, including those from the CPIC or the DPWG, owing to limited and inconsistent evidence. Future research should prioritize validating candidate variants in large, ethnically diverse cohorts and evaluating their additive or synergistic effects through polygenic modeling approaches.

PGx of statins

Statins represent the cornerstone of lipid-lowering therapy for stroke prevention; however, interindividual variability in both therapeutic efficacy and adverse effect risk—particularly SAMS—limits their clinical utility, as reflected in the CPIC guidelines.[66-69] Pharmacogenomic studies have identified key genetic variants that influence statin metabolism, transport, and toxicity.[70,71]

The most well-established pharmacogenomic association involves the *SLCO1B1* gene, which encodes the hepatic uptake transporter *OATP1B1*. Reduced-function alleles, such as *5 and *15, result in elevated plasma statin concentrations and an increased risk of SAMS. This risk is particularly pronounced with simvastatin, for which homozygous carriers of the *5 allele may experience up to a 17-fold greater risk of myopathy.[8,72,73] These findings have led to *SLCO1B1*-guided prescribing recommendations in the CPIC guidelines, particularly for simvastatin therapy (Table 2).[8,72,73]

Variants in *ABCG2*, particularly rs2231142 (c.421C>A), affect the efflux of rosuvastatin and other statins.[74] Carriers of this variant exhibit increased systemic exposure, especially in East Asian populations, where the allele frequency is relatively high.[75] Accordingly, the CPIC recommends initiating rosuvastatin at a reduced dose (≤20 mg/day) in individuals with poor function (Table 2).[8]

CYP enzymes also play a critical role in statin metabolism. The *CYP3A4*22* (rs35599367) variant reduces enzymatic activity, resulting in approximately 50% higher plasma exposure to statins such as simvastatin and atorvastatin.[76] In contrast, hydrophilic statins, including rosuvastatin and pravastatin, are less affected by *CYP3A4* activity. Fluvastatin metabolism is influenced by *CYP2C9*2* and *3* alleles, and the CPIC guidelines recommend dose reduction in intermediate or poor metabolizers to mitigate toxicity risk (Table 2).[8]

Population-specific differences in allele frequencies add another important dimension to statin PGx.[77,78] For instance, the *SLCO1B1 5* variant is present in fewer than 1% of Koreans but in approximately 6% of Europeans. Similarly, nearly half of Korean stroke patients carry the *ABCG2* rs2231142 A allele (Table 3). These variations underscore the need for ethnicity-informed prescribing strategies to optimize safety and efficacy.

Clinical implementation of statin PGx involves genetic risk–based stratification, dose adjustment, or selection of alternative statins. In genetically susceptible individuals, clinicians may consider hydrophilic statins, lower starting doses, or combination regimens with non-statin lipid-lowering agents.[8] Clinical decision support systems (CDSS) have demonstrated utility in interpreting genetic test results and generating patient-specific recommendations at the point of care.[79,80]

Looking ahead, future research should aim to broaden the range of validated pharmacogenomic markers, particularly those associated with efficacy and non–muscle-related adverse effects. Emerging evidence indicates that variants implicated in muscle metabolism and inflammatory pathways may also contribute to SAMS risk, although additional validation is required to confirm their clinical relevance.[81]

Given the widespread use of statins across diverse populations, expanding the clinical application of pharmacogenomic strategies is particularly justified. Efforts to address current barriers—such as enhancing provider education, incorporating testing into clinical workflows, and promoting equitable access—will be crucial for translating existing evidence into routine

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clinical practice.

Clinical implementation and future directions

Considerations in translating genetic evidence to clinical practice

While pharmacogenomic associations are well established for several stroke medications, clinicians should remain mindful of key limitations in translating genetic findings into clinical outcomes. First, genetic variants explain only part of the interindividual variability in treatment response: *CYP2C19* polymorphisms account for approximately 12% of clopidogrel response variability,[82] whereas *VKORC1* and *CYP2C9* variants together explain about 30%–50% of warfarin dose requirements.[7,38] Second, the pathway from genotype to clinical benefit involves several sequential steps—altered drug metabolism (pharmacokinetics), modified drug effects (pharmacodynamics), intermediate outcomes (e.g., platelet inhibition or INR control), and clinical endpoints (e.g., stroke recurrence or bleeding)—with differing levels of evidence supporting each stage.[83] For the *CYP2C19*–clopidogrel association, this full causal pathway has been validated in randomized clinical trials, most notably CHANCE-2, which demonstrated improved outcomes with genotype-guided therapy.[14] However, for aspirin and DOACs, current evidence remains limited to pharmacokinetic or pharmacodynamic associations, without robust outcome data confirming clinical benefit. Third, functional assays that assess drug effects in real time can complement pharmacogenomic testing. Platelet function testing may assist in evaluating antiplatelet response, particularly in intermediate metabolizers where the clinical implications of genetic results remain uncertain.[84] For warfarin, genotype-guided initial dosing should always be used alongside INR monitoring rather than as a replacement.[7] In the case of DOACs, plasma concentrations or anti–factor Xa activity may provide supplementary information in select high-risk scenarios, although routine laboratory monitoring is not currently recommended.[85] Clinicians should interpret pharmacogenomic results with an understanding that genetic data represent one important dimension of personalized therapy, not a sole determinant of drug response.

An additional challenge arises when pharmacogenomic evidence and conventional clinical trial data do not align perfectly. Although *CYP2C19* LOF alleles clearly predict reduced clopidogrel responsiveness, alternative P2Y12 inhibitors such as ticagrelor and prasugrel have been evaluated primarily in non–genotype-selected cohorts, often with higher bleeding risk.[86-88] The CHANCE-2 trial confirmed the clinical benefit of ticagrelor in carriers of LOF alleles; however, clinicians must balance this benefit against individual bleeding risk and comorbid conditions.[14] Patients with high thrombotic risk and low bleeding risk are likely to benefit most from genotype-guided selection of alternative antiplatelet therapy, whereas those with a history of bleeding may remain better candidates for clopidogrel, even when harboring LOF alleles.[89] This scenario illustrates a broader principle: pharmacogenomic data should inform, not replace, clinical judgment, emphasizing the need for integration with conventional risk assessment and individualized patient characteristics.

Integration of PGx into stroke care and healthcare systems

The integration of pharmacogenomic testing into stroke care presents both substantial opportunities and notable challenges. To achieve successful clinical implementation, several interdependent components must be addressed, including cost-effectiveness, testing logistics, clinician education, and healthcare infrastructure development.

Cost-effectiveness remains a key determinant, particularly within resource-limited healthcare systems. Although some studies have demonstrated the economic value of pharmacogenomic testing—such as *CYP2C19* genotyping to guide antiplatelet therapy in high-risk patients[90]—the overall evidence remains heterogeneous across healthcare settings.[91] However, a growing body of research suggests that *CYP2C19* genotype–guided therapy for clopidogrel is cost-effective and, in some analyses, represents a dominant strategy (both less costly and more effective).[92] Evidence indicates that the expenses associated with pharmacogenomic testing may be offset by reductions in downstream healthcare costs through the prevention of adverse cardiovascular events such as stroke, myocardial infarction, and stent thrombosis among poor metabolizers.[93,94]

Timeliness of testing is another key factor, especially in acute stroke management where therapeutic decisions must be made rapidly. Conventional genotyping, which often requires several days to weeks for results, is incompatible with real-time clinical decision-making. Point-of-care (POC) genotyping platforms have emerged as a potential solution, enabling same-day results that can guide clopidogrel selection. However, their widespread adoption necessitates integration into clinical workflows, structured staff training, and rigorous quality control procedures.[95,96] Despite these advantages, the clinical accessibility of such platforms remains substantially limited. Currently, laboratory-based *CYP2C19* genotyping is commercially available from multiple vendors with turnaround times ranging from 1 to 7 days. In contrast, POC systems validated in research contexts—such as the GMEX platform used in the CHANCE-2 trial[95,96]—have yet to achieve broad commercial distribution due to regulatory, logis-

tical, and market-related constraints. Reimbursement policies further restrict implementation. In the United States, Medicare provides coverage for *CYP2C19* testing in patients undergoing percutaneous coronary intervention; however, coverage for stroke-related indications varies across regional contractors and private insurers.[97] In Korea, the National Health Insurance reimburses *CYP2C19* testing for patients with acute coronary syndrome or stroke requiring antiplatelet therapy, although specific eligibility criteria apply.[98] While pharmacogenomic testing for warfarin (*VKORC1*, *CYP2C9*) is reimbursed in some healthcare systems, its clinical relevance has declined with the increasing preference for DOACs.[54,98] Conversely, statin testing targeting *SLCO1B1* variants has yet to be incorporated into reimbursement frameworks, despite CPIC recommendations supporting its clinical utility.[99] The persistent discrepancy between favorable cost-effectiveness data—particularly for *CYP2C19* testing in populations with high frequencies of LOF alleles—and limited reimbursement policies represents a major implementation barrier that will require coordinated policy reform in parallel with technological progress.

Workforce education remains essential.[100,101] Clinicians must be adequately trained to interpret pharmacogenomic results and apply them appropriately, which underscores the importance of integrating PGx into medical education and continuing professional development programs.

Effective integration also requires adaptation of electronic health record systems to store and retrieve pharmacogenomic data and to link this information with CDSS.[102] These tools must provide clear, actionable recommendations while minimizing alert fatigue to ensure clinical usability.[103] Standardized reporting formats and transparent, interpretable algorithms will be essential to maintain consistency and scalability across institutions.

Equally important, shared decision-making between clinicians and patients is critical when implementing pharmacogenomic testing—especially in situations where genetic associations are well established but clinical outcome evidence remains limited.[104,105] Patients should be informed of the potential benefits and limitations of genotype-guided therapy, alternative treatment options, and associated costs to ensure that decisions align with individual values and preferences.

Quality assurance frameworks are also vital. Institutions should establish standardized protocols for assay validation, specimen handling, and result interpretation.[106,107] Continuous evaluation of testing accuracy, clinical outcomes, and adverse drug reactions will facilitate ongoing improvement in PGx-guided care.[108,109]

Despite technological and guideline advancements, real-world adoption in stroke care remains modest. Barriers include fragmented infrastructure, variable reimbursement, and limited clinician familiarity. A stepwise implementation strategy—starting with high-yield use cases such as *CYP2C19* testing—may represent the most practical path forward. Strong institutional leadership, sustainable funding mechanisms, and interdisciplinary collaboration will be critical to transitioning PGx from pilot programs into routine clinical care.

Role of pharmacogenomic polygenic risk scores

Polygenic risk scores (PRS) are emerging as promising tools in precision medicine, and their extension to PGx-PRS has garnered increasing attention.[110,111] Unlike single-gene approaches, PGx-PRS combine multiple variants across pharmacokinetic, pharmacodynamic, and target-response pathways, thereby enhancing the prediction of interindividual variability in both drug efficacy and toxicity.

In the context of stroke care, PGx-PRS may be particularly useful for therapies where drug response is multifactorial and cannot be fully explained by individual genetic variants. For instance, in antiplatelet therapy, integrating variants in *CYP2C19*, *ABCB1*, and *PON1* into a composite score may improve the prediction of clopidogrel resistance compared with *CYP2C19* genotyping alone.[112,113] Preliminary analyses from CHANCE and CHANCE-2 indicate that PGx-PRS can stratify clopidogrel response more effectively than single-gene testing.

Similarly, PGx-PRS could refine warfarin dosing algorithms by accounting for cumulative genetic contributions from *CYP2C9*, *VKORC1*, *CYP4F2*, and additional loci involved in vitamin K metabolism and coagulation. Although current dosing models incorporate some of these genes, PRS-based frameworks may further improve dose accuracy by capturing gene–gene interactions and subtle additive effects.[43,44,114]

However, the development of clinically robust PGx-PRS remains constrained by methodological and translational challenges.[110,111,115] Large-scale, multiethnic genome-wide studies are required to identify predictive variants, optimize score calibration, and validate models across diverse populations, considering significant interethnic differences in allele frequencies and linkage disequilibrium structures. Incorporating deep learning approaches may further enhance PGx-PRS by uncovering nonlinear genetic interactions and complex multi-locus effects.[116-118]

A major limitation is the absence of reliable biomarkers for drug response in certain therapeutic classes. For example, while low-density lipoprotein cholesterol levels or blood pressure can serve as pharmacodynamic markers for statins and antihypertensive agents, antiplatelet response lacks standardized and clinically validated surrogate endpoints. Platelet function assays—such as *P2Y12* reaction units—are available but not universally accepted, which complicates the development and calibration

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of PGx-PRS models.[119] In such cases, validation based directly on clinical outcomes may be required to ensure clinical relevance.

In summary, PGx-PRS represent a scalable and promising framework for advancing personalized pharmacotherapy in stroke. Although the field remains in its early stages, ongoing research and emerging analytic technologies are likely to broaden their applicability across multiple drug classes. Crucially, validation in underrepresented populations remains indispensable. Large-scale East Asian cohorts—such as the GENESIS-K study in Korea—can play a pivotal role in developing and validating population-specific PRS, thereby ensuring both regional applicability and equity in precision stroke medicine.

Future directions: population-specific considerations

Population-specific genetic variation plays a pivotal role in PGx and must be incorporated into the implementation of precision stroke therapy. The frequency and functional consequences of pharmacogenomic variants differ markedly across ancestral groups (Table 3),[120,121] and neglecting these differences may result in suboptimal therapeutic efficacy or increased risk of adverse drug reactions.

A prominent example is the high prevalence of *CYP2C19* LOF alleles among East Asian populations, which underpins the demonstrated benefit of genotype-guided antiplatelet therapy in the CHANCE-2 trial. These findings prompted updates to regional clinical guidelines—such as those issued by the Chinese Stroke Association—recommending CYP2C19 genotyping to guide clopidogrel use in appropriately selected patients.[15] In contrast, such genotype-based strategies have not been widely adopted in Western populations, where LOF allele frequencies are lower and ethnicity-specific evidence remains limited.

Beyond antiplatelet therapy, population-tailored pharmacogenomic data remain sparse for other stroke-related drug classes. For instance, warfarin dosing algorithms specifically optimized for patients of African ancestry have been developed,[7] yet comparable ethnicity-specific frameworks are lacking for statins, aspirin, and DOACs, despite clear interethnic differences in allele frequencies and pharmacologic response patterns.

This paucity of population-representative data reflects a broader inequity in pharmacogenomic research participation. Recent analyses reveal that over 60% of participants in PharmGKB-referenced studies are of European ancestry, compared with only 28% of East Asian ancestry, and an even smaller proportion of African, South Asian, or Indigenous descent.[122] Such underrepresentation undermines the generalizability of existing evidence and risks reinforcing disparities in precision medicine implementation across global populations.

To address this imbalance, future pharmacogenomic research must prioritize underrepresented populations.[110,111,123] Research efforts should emphasize allele frequency mapping, clinical validation of gene–drug associations, and the development of population-specific prescribing guidelines. Large-scale biobanks—such as the GENESIS-K cohort in Korea—are essential for generating regionally relevant evidence and informing locally appropriate implementation strategies. GENESIS-K is a government-funded, nationwide, multicenter prospective registry designed to enroll ≥10,000 patients with acute ischemic stroke. It includes comprehensive genomic profiling through genome-wide genotyping arrays supplemented with pharmacogene variants supported by CPIC guidelines or high-level PharmGKB evidence. The registry integrates clinical, radiologic, genomic, and long-term outcome data to enable the validation of established pharmacogenomic associations in Korean populations, the identification of population-specific variants, the development of Korean-tailored dosing algorithms, and the exploration of polygenic risk scores for stroke prognosis and medication response. Genomic results for key pharmacogenes (e.g., *CYP2C19*, *SLCO1B1*, *VKORC1*, *CYP2C9*) are reported to participating physicians, accompanied by structured education programs to support clinical implementation. As shown in Table 3, preliminary data from GENESIS-K participants have already provided population-specific allele frequency information that informs genotype-guided therapeutic strategies for Korean stroke patients, serving as a model for similar initiatives in other underrepresented populations worldwide.

Ultimately, equitable precision medicine depends on the deliberate inclusion of diverse populations in both discovery and translational research. Without such inclusion, the clinical benefits of PGx risk remaining inaccessible to substantial segments of the global population.

Future directions: next candidates for pharmacogenomic implementation

Beyond *CYP2C19*-guided clopidogrel therapy, several additional candidates represent the next frontier for pharmacogenomic integration into stroke care, albeit with differing levels of supporting evidence and clinical feasibility. Statin PGx—particularly involving *SLCO1B1* and *ABCG2* variants—appears to be among the most promising targets for implementation. This promise is supported by strong recommendations from both CPIC and DPWG guidelines, the widespread prescription of statins in stroke populations for both primary and secondary prevention, and the high frequency of *ABCG2* variants in East Asians (approximately 50% in Koreans) (Table 3).[8,124] However, the clinical utility of statin pharmacogenomic testing is currently constrained by its primary focus on adverse event risk rather than therapeutic efficacy.

Because SAMS can often be effectively managed through dose adjustments or statin switching, payers have demonstrated limited interest in reimbursement, despite robust scientific evidence supporting genetic risk stratification.[99] Warfarin PGx represents one of the most mature fields in this domain, supported by well-validated dosing algorithms and clinical trials demonstrating improved anticoagulation control through genotype-guided therapy. Nonetheless, its practical relevance has diminished markedly with the growing preference for DOACs as first-line agents for stroke prevention in atrial fibrillation.[7,54]

Cilostazol represents a particularly important candidate for pharmacogenomic research in Asian populations. The Lacunar Intervention Trial-2 (LACI-2) trial demonstrated cilostazol's superiority over aspirin in preventing recurrent stroke among patients with lacunar infarction, thereby establishing its clinical efficacy in secondary prevention.[125] Given its widespread use in Korea, Japan, and China, cilostazol offers a significant opportunity for pharmacogenomic application.[126] Genetic polymorphisms in *CYP2C19* and *CYP3A5* have been shown to significantly influence plasma concentrations of cilostazol and its active metabolites.[127,128] Moreover, studies have reported associations between *CYP* genotypes and platelet responsiveness to cilostazol in patients with cerebral infarction.[129] However, robust clinical outcome data linking these genotypes to stroke recurrence or major adverse cardiovascular events remain limited. Considering cilostazol's established benefit in secondary prevention of lacunar stroke and its prevalent use in Asian populations, targeted pharmacogenomic research in this domain represents a key future priority. Such efforts could follow a developmental trajectory analogous to that of the clopidogrel–*CYP2C19* model, progressing from pharmacokinetic and pharmacodynamic validation to genotype-guided clinical application.

Future directions: integration with precision medicine

Pharmacogenomics constitutes a central pillar of the broader precision medicine paradigm, which aims to individualize therapy based on each patient's genetic, clinical, and environmental characteristics.[130,131] As testing technologies advance and sequencing costs continue to decline, the integration of pharmacogenomics with complementary omics platforms—such as transcriptomics, proteomics, and metabolomics—holds considerable promise for generating more comprehensive and clinically actionable insights.

Panel-based genetic testing, enabling the simultaneous analysis of multiple pharmacogenes, is becoming increasingly feasible in clinical settings. Compared with single-gene assays, multigene panel approaches improve cost-effectiveness and provide information applicable to a wider range of medications. Commercially available and institution-specific panels are already established in cardiology and oncology, and their extension to stroke pharmacotherapy represents a logical next step.[132,133]

In addition, advanced bioinformatics pipelines and artificial intelligence (AI)–driven methods, including machine learning and deep learning, are enhancing the interpretive power of pharmacogenomic data. These approaches facilitate the identification of complex gene–drug interactions, uncover novel associations, and support clinical decision-making through predictive modeling and real-time alert systems.[134,135] Notably, AI now enables the integration of pharmacogenomic data with high-dimensional clinical information, encompassing EHRs, neuroimaging, laboratory findings, and multi-omics profiles.[136] This multimodal integration, illustrated in Figure 1, offers a robust framework for developing individualized, context-specific prediction models that may elucidate previously unrecognized gene–environment and gene–phenotype interactions in stroke management.

Real-world implementation programs are essential to translate recent pharmacogenomic advances into routine clinical practice. Large-scale initiatives enable the evaluation of feasibility, optimization of workflows, and generation of evidence on clinical outcomes, safety, and cost-effectiveness across diverse healthcare systems.[137] Ultimately, the successful integration of pharmacogenomics into precision stroke medicine will depend on the establishment of robust data infrastructure, sustained interdisciplinary collaboration, comprehensive workforce education, and supportive health policy. Efforts to harmonize pharmacogenomic data with EHRs, standardize testing and reporting protocols, and engage key stakeholders—including patients—will be crucial for long-term sustainability.

Recent national initiatives exemplify this trajectory. The Estonian Biobank, for instance, integrates genomic data with EHRs, multi-omics datasets, and digital health information for more than 200,000 participants.[138] This population-based model demonstrates that pharmacogenomics can be implemented not only in disease-specific contexts such as cardiovascular or stroke medicine, but also as a component of broader preventive and public health strategies.

Conclusion

Pharmacogenomics offers a powerful framework for personalizing pharmacotherapy in stroke management. The strongest evidence currently supports genotype-guided strategies for clopidogrel, warfarin, and statins, which should be prioritized for clinical integration. In contrast, although genetic associations have been reported for aspirin and DOACs, the evidence remains insuffi-

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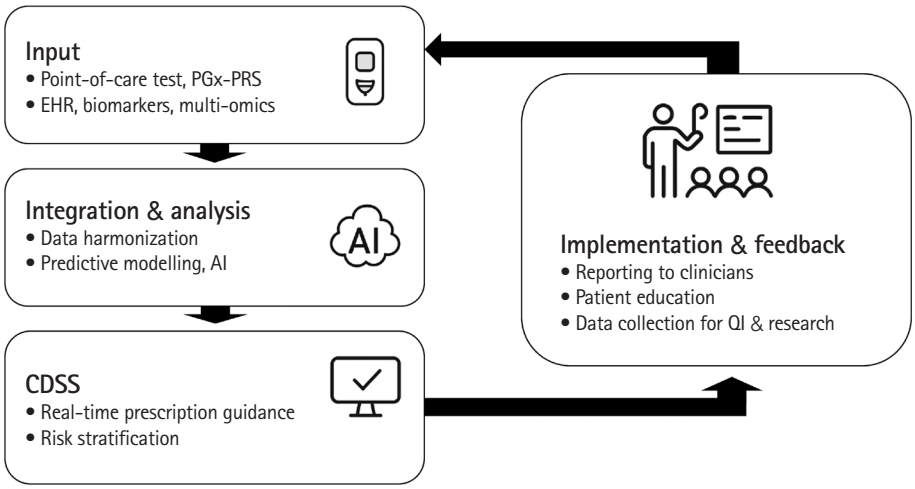

Figure 1. Integrated framework for precision stroke medicine using PGx. This figure illustrates a systems-based framework for implementing PGx within stroke care. The process begins with genetic testing conducted through point-of-care assays or multigene panel–based platforms, which generate pharmacogenomic data on clinically relevant drug–gene interactions. These data are subsequently integrated with EHRs, neuroimaging findings, laboratory results, and multi-omics profiles to form a high-dimensional, multimodal dataset. AI and machine learning techniques serve a central function in synthesizing and analyzing these heterogeneous data streams, facilitating the development of predictive models for drug response, adverse reactions, and clinical outcomes. Model outputs are incorporated into CDSS embedded within EHRs, enabling real-time, genotype-informed prescribing recommendations. The framework is reinforced through structured clinician education and feedback mechanisms, alongside continuous data collection for QI and translational research. This integrative model supports the scalable and sustainable implementation of individualized pharmacotherapy in stroke management. PGx, pharmacogenomics; PRS, polygenic risk scores; EHR, electronic health record; AI, artificial intelligence; CDSS, clinical decision support system; QI, quality improvement.

cient to justify routine clinical testing, emphasizing the need for further validation through large-scale, outcome-based studies.

Population-specific allele frequencies—particularly among East Asian patients—underscore the importance of developing regional implementation strategies grounded in locally derived evidence. In Korea, advancing pharmacogenomics requires a dual approach: establishing comprehensive, population-based genomic data through initiatives such as GENESIS-K and building practical infrastructures that include POC testing platforms, CDSS, and structured clinician education programs.

Importantly, this review is not intended merely as a reiteration of existing CPIC or FDA drug-label recommendations. Rather, by synthesizing pharmacogenomic evidence across major stroke-related medications, it aims to delineate areas where current guidance aligns with clinical practice, identify persisting evidence gaps, and contextualize these gaps within East Asian populations characterized by distinct genotype distributions (e.g., *CYP2C19*, *ABCG2*). Furthermore, while certain variants listed in CPIC guidelines may have limited or uncertain clinical impact in stroke settings, others demonstrate stronger associations in real-world East Asian cohorts—highlighting the necessity for population-tailored interpretation and implementation.

Looking ahead, the advancement of stroke pharmacogenomics must extend beyond the consolidation of existing guidelines toward the generation of population-specific evidence and its incorporation into clinical practice frameworks. This dual focus—on evidence synthesis and real-world applicability–will enable the transition of pharmacogenomics from theoretical concept to practical precision stroke medicine. The integration of polygenic risk scores, multigene testing panels, and multi-omics data with AI–driven analytics offers considerable potential to refine therapeutic strategies across a wider spectrum of pharmacologic agents. However, successful implementation will require not only robust scientific evidence but also coordinated, system-level strategies that bridge the gap between research and clinical application. Ultimately, ensuring global participation and equitable access will be essential to translate pharmacogenomic innovations into measurable improvements in outcomes for patients with stroke worldwide.

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Conflicts of interest

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