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Warfarin Pharmacogenomics in the Era of Precision Medicine: Persistent Underrepresentation of Non-European Ancestries and Implications for Global Health Equity

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ABSTRACT

Warfarin has continued to be the leading vitamin K-dependent oral anticoagulant around the globe since its introduction in 1954. Its dosing is notoriously difficult because the medication has a very small therapeutic range and shows broad variability in dose needs across individuals, which has made it one of the most extensively investigated drugs in genotype–phenotype research. Yet, the majority of this work has focused on Asian and White cohorts, resulting in a pharmacogenomic evidence base that does not adequately represent global ancestral diversity. Since the frequencies of crucial genetic variants vary markedly between populations, findings derived from Asian/White groups may not translate reliably to groups that have historically been understudied—such as Black, Hispanic/Latino, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander communities. As a result, inequities may worsen when validated dosing algorithms improve anticoagulation outcomes primarily in Asian/White patients but underperform in others. To assess how well different racial and ethnic groups are represented in current pharmacogenomic knowledge, we summarize data on published warfarin pharmacogenomic dosing algorithms and related literature, including studies on clinical benefit, cost-effectiveness, and implementation guidance.

Keywords: Ancestry, Ethnically diverse groups, Underserved populations, Pharmacogenetics, Pharmacogenomics

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Introduction

Since its initial approval in 1954 [1], warfarin has remained the most widely used vitamin K oral anticoagulant across many countries [2]. As an example, more than seven million prescriptions for warfarin were issued in England in 2019, making it the most commonly dispensed oral anticoagulant that year [3]. The drug plays a major role in preventing and treating thromboembolic conditions, including venous thromboembolism, rheumatic heart disease, and stroke prevention in individuals with atrial fibrillation. Although it has been used for nearly 70 years, establishing the correct dose is still problematic because of its narrow margin between ineffective and excessive dosing. When a patient receives less than the minimum effective amount, their risk of thrombosis rises (reduced efficacy), while doses above the upper threshold elevate bleeding risk [4]. The close proximity of these boundaries requires particularly careful dose management. This is further complicated by substantial inter-individual and intra-individual variation in dosing needs. For instance, due to genetic and non-genetic contributors, daily doses can range from as low as 0.5 mg [5] to as high as 60 mg [6] between different patients. Within a single person, clinical features (such as age, weight, comorbid illnesses, physical activity) and environmental influences (including drug–drug or food–drug interactions) can also shift dose requirements over time [7]. These complexities contribute to frequent adverse reactions. Indeed, warfarin was the drug most often linked to emergency hospital admissions for adverse medication events among older adults in the United States from 2007

to 2009, accounting for 33% of roughly 99,628 annual admissions [8]. The necessity for ongoing monitoring also increases the burden on patients and may negatively affect quality of life, potentially leading to discontinuation of a medication that is otherwise highly effective [9]. To enhance anticoagulation quality, many investigations have focused on identifying factors affecting dose (association studies) and on constructing dose-prediction tools (clinical prediction studies). Nevertheless, as highlighted in our recent assessment of warfarin dosing algorithms [10], most of these efforts have centered on White and Asian populations.

Pharmacogenetics, a term introduced in 1959 by Friedrich Vogel, describes research aimed at explaining why individuals differ genetically in their reactions to medications [11, 12]. The broader concept of pharmacogenomics emerged in 1997 [13]. Although the two labels are often treated as equivalents, pharmacogenetics traditionally concentrates on one or several genes, whereas pharmacogenomics encompasses the full genomic landscape that might shape therapeutic responses [14, 15]. Regardless of nuance, both fields support the move toward individualized therapy by replacing empirical adjustments with strategies that match treatments to those who are most likely to benefit and least likely to be harmed [16]. Warfarin is frequently highlighted as the leading example of this paradigm [17] and remains the most intensively examined drug for links between genotype and clinical phenotype [18]. Its global use and large differences in dose needs between patients make it particularly suitable for pharmacogenomic applications [19]. More than 30 genes participate in its absorption, distribution, metabolism, and the vitamin K cycle, which together determine its pharmacokinetic and pharmacodynamic behavior **(Figure 1)**. Among these genes, CYP2C9 and VKORC1 play dominant roles: CYP2C9 metabolizes S-warfarin, the more active isomer, and VKORC1 encodes the protein targeted by the drug [20]. Warfarin blocks vitamin K epoxide reductase, thereby limiting regeneration of reduced vitamin K, which is essential for activation of coagulation factors II, VII, IX, and X. In White cohorts, CYP2C9 and VKORC1 genotypes, combined with demographic variables such as age, height, weight, and concurrent drugs, explain roughly 50% of the observed variability in daily dose requirements [4, 20]. However, the minor allele frequencies of relevant variants differ markedly across ancestries [21]. Consequently, the variants that most strongly affect warfarin dosing are not the same across populations [22]. When these differences are overlooked, dosing models may perform poorly, as demonstrated by the COAG trial [23], where a dosing algorithm predominantly derived from White participants resulted in worse anticoagulation control in African Americans: individuals in the genotype-guided group achieved a mean time in therapeutic range of 35.2% compared with 43.5% in those assigned to clinically based dosing (p = 0.01) [23].

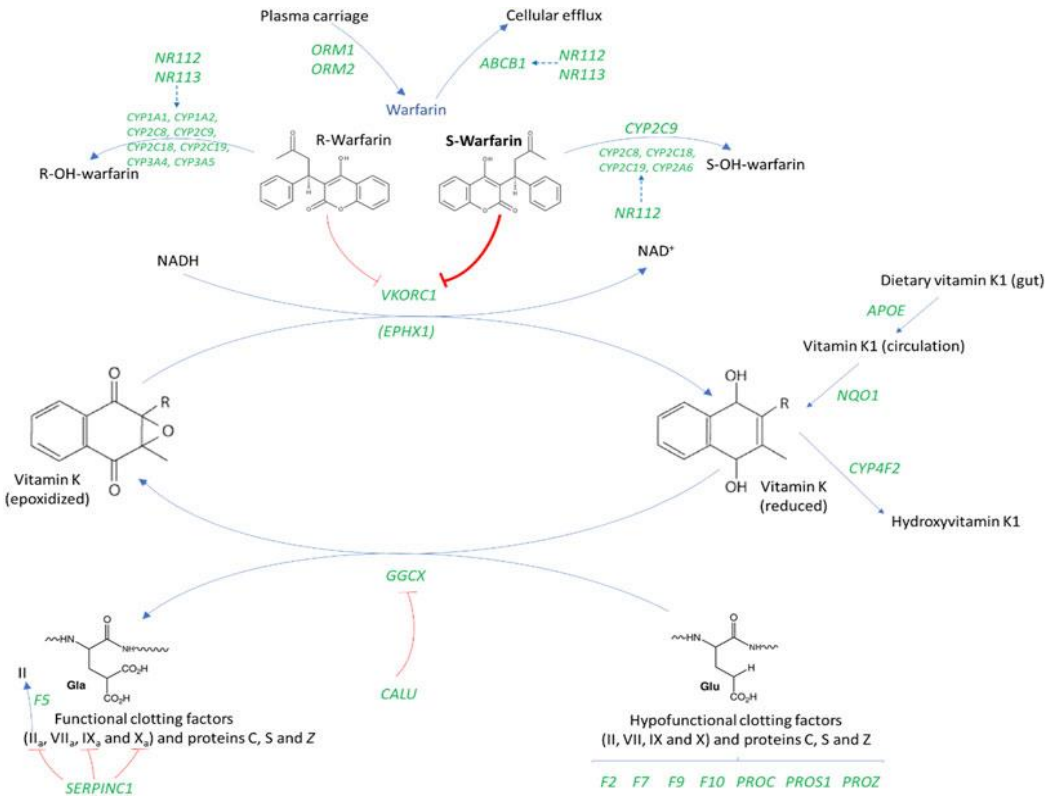


Figure 1. Summary of genes contributing to warfarin's mechanism [20, 24]. Included are ABCB1, APOE, CALU, members of the CYP family, EPHX1, GGCX, coagulation genes F2, F5, F7, F9, F10, NQO1,

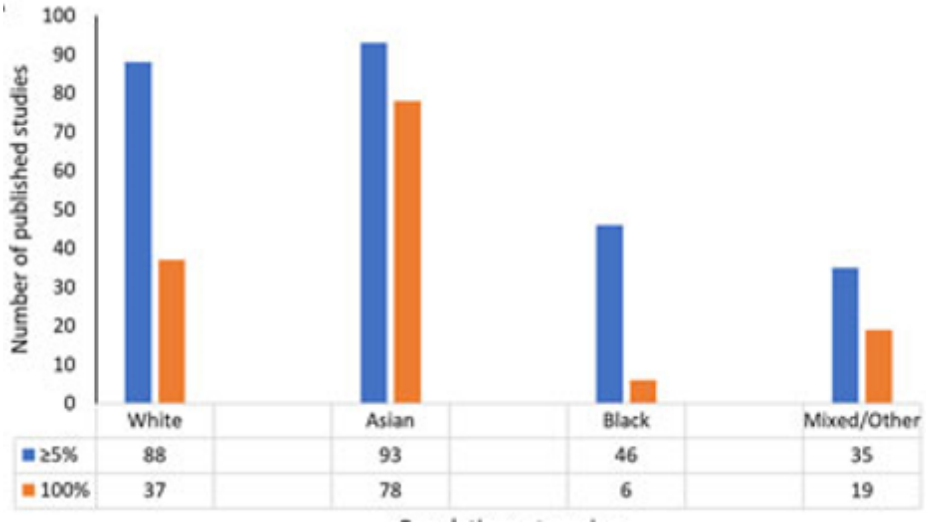
NR1I2/3, ORM, PROC, PROS1, PROZ, SERPINC1, and VKORC1. Gene symbols appear in italicized green text.

Ethnicity is a socially defined and historically fluid category with no universally accepted definition [25, 26]. It may reference ancestry, shared culture, geography, national origin, socioeconomic background, collective identity, or physical traits [25]. In the United States, the Office of Management and Budget outlines five racial groups—American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White—and two ethnic designations: Hispanic/Latino and Not Hispanic/Latino [27]. Because these categories capture sociopolitical rather than biological constructs, many researchers classify individuals instead by *genetic ancestry*, derived from statistical analyses of genomic data [28]. Although correlated, genetic ancestry and self-identified race/ethnicity measure different things and often diverge [28, 29]. As such, racial or ethnic labels should not be assumed to signify biological distinctions [27].

Despite debates over terminology, there is broad agreement that pharmacogenomic research must include diverse populations to avoid further widening existing inequities [29-31]. This concern is particularly relevant in warfarin pharmacogenomics because groups that are economically disadvantaged—who often rely on warfarin due to its low cost—are also those least represented in genomic studies [32]. This article, therefore, evaluates how different populations are represented in warfarin-related pharmacogenomic evidence. Following the categorization used by one of the field's most extensive studies [33] and our recent review [10], we adopt four broad population groups—White (including Hispanic/Latino), Asian, Black, and Mixed/Other—and use study locations to clarify finer population structure when appropriate.

Warfarin pharmacogenomic studies

Research on warfarin pharmacogenomics—including both association analyses and algorithm-development work—now numbers in the thousands [30]. Because the field is so vast, our team recently carried out a targeted systematic review limited to studies that created clinical dosing models or prediction tools [10]. This review serves as a basis for examining ethnic representation in warfarin-related pharmacogenomics. Up to 20 May 2020, 191 publications describing the creation of warfarin dosing algorithms were identified **(Figure 2a)**. Applying the criterion that a population group was considered "included" if it comprised ≥5% of the study cohort, we found that 88 (46%), 93 (49%), 46 (24%), and 35 (18%) algorithms were relevant to White, Asian, Black, and Mixed/Other groups, respectively. Stratification by race/ethnicity is essential for detecting population-specific genetic and environmental effects, but this requires that each group be adequately represented within the dataset [30]. Because a 5% threshold may not allow meaningful subgroup assessments when sample sizes are limited [34], **Figure 2** also summarizes studies where 100% of participants belonged to a single population.



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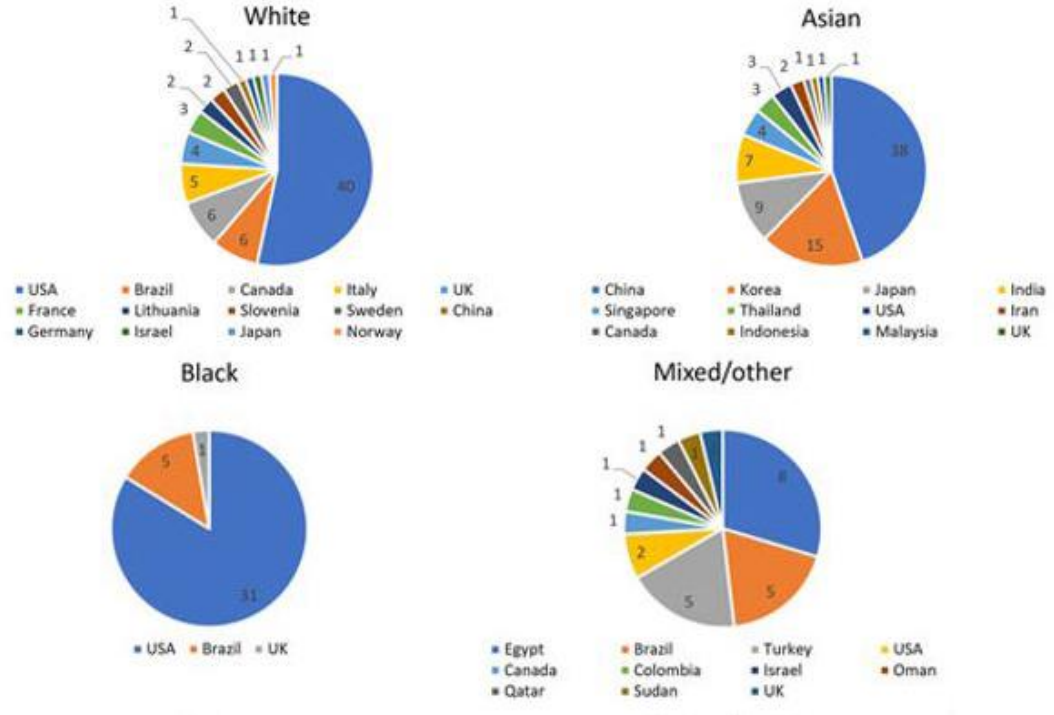

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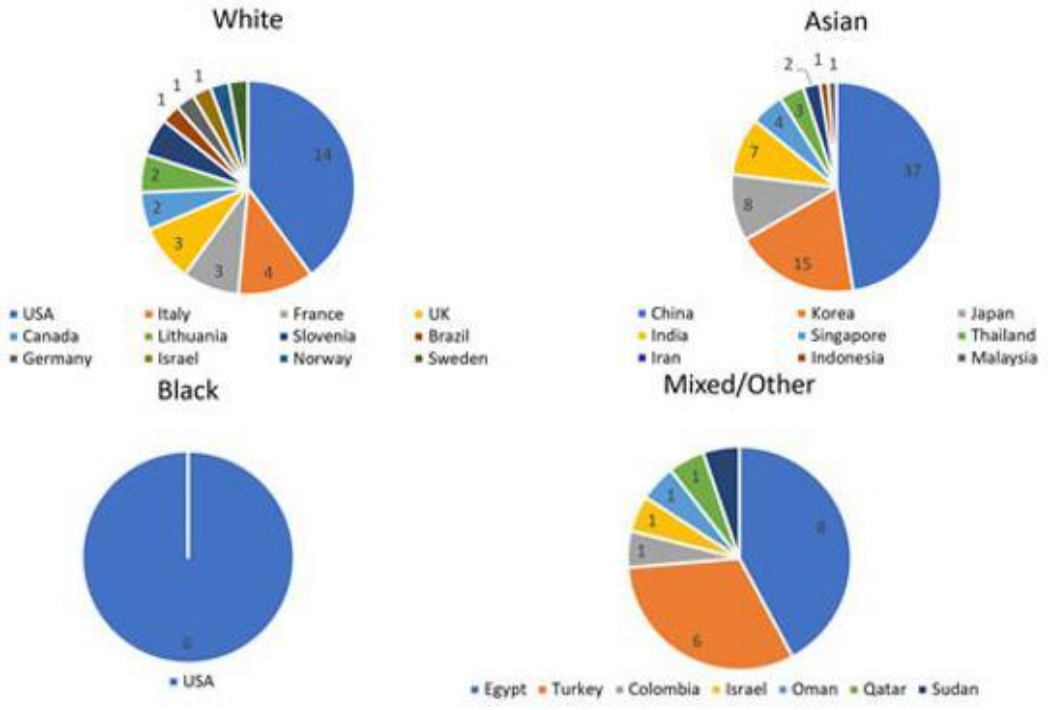


(c)

Figure 2. Counts of pharmacogenomic algorithm-development studies as of 20 May 2020. Panel (a) displays the number of studies that enrolled at least 5% or 100% of a given ancestry category. Panels (b) and (c) provide the corresponding country-level distribution, with (b) relating to the 5% cut-off and C to the 100% criterion. Because recruitment was not consistently organized by location, multi-country studies are omitted from (b) and (c).

Whites

Roughly 46% of the studies shown in **Figure 2** included at least 5% participants classified as White. Most were carried out in the United States (n = 40; five from Puerto Rico), followed by Brazil (n = 6), Canada (n = 6), and Italy (n = 5). In past reviews, this category also incorporated non-Black Hispanic groups [10]. Although often

treated as a homogeneous population, individuals of European ancestry show notable substructure: principal component analyses readily differentiate Northern Europeans (e.g., Finnish) from Southern (e.g., Italian) and Western Europeans (e.g., British), as well as Caucasian groups living outside Europe (e.g., Israelis) [35].

Hispanics/latinos

Earlier work grouped Hispanics/Latinos together with Whites unless they were identified as Black [10]. Because Hispanics/Latinos remain underrepresented in many genomic studies [22, 36], they warrant separate discussion. Following the classification used in previous literature [36], research from Brazil and Puerto Rico is commonly labeled as Latino. Using this categorization, 12 (6%) of the warfarin algorithm studies enrolled ≥5% Hispanics/Latinos: six from Brazil, five from Puerto Rico, and one from Illinois (United States) [10]. Latino groups are typically admixed; in one analysis of 642 Puerto Rican individuals typed at 93 ancestry-informative markers, the average European, African, and Native American contributions were 63.7%, 21.2%, and 15.2%, respectively [37].

Asians

Nearly half of the 191 studies (49%) included at least 5% participants of Asian ancestry. The majority were conducted in China (n = 38), followed by South Korea (n = 15), Japan (n = 9), and India (n = 7)—together representing roughly three-quarters of all Asian-focused studies. As with other global populations, Asian groups exhibit substantial substructure (expanded in the section on Genetic Variants Influencing Warfarin Response). Several Asian subpopulations remain minimally represented in the existing pharmacogenomic literature.

Blacks

Fewer than a quarter of the studies (24%) enrolled at least 5% Black participants. These were concentrated primarily in the United States (n = 31) and Brazil (n = 5). However, data based mainly on African-Americans and African-Brazilians may not reflect the full diversity across the African diaspora (further discussed later), leaving many African and Afro-descendant populations underrepresented in current datasets.

Mixed/other

The Mixed/Other category accounted for the smallest share of the evidence base, with only 18% of studies recruiting any participants in this group.

Genetic Variants Influencing Warfarin Response

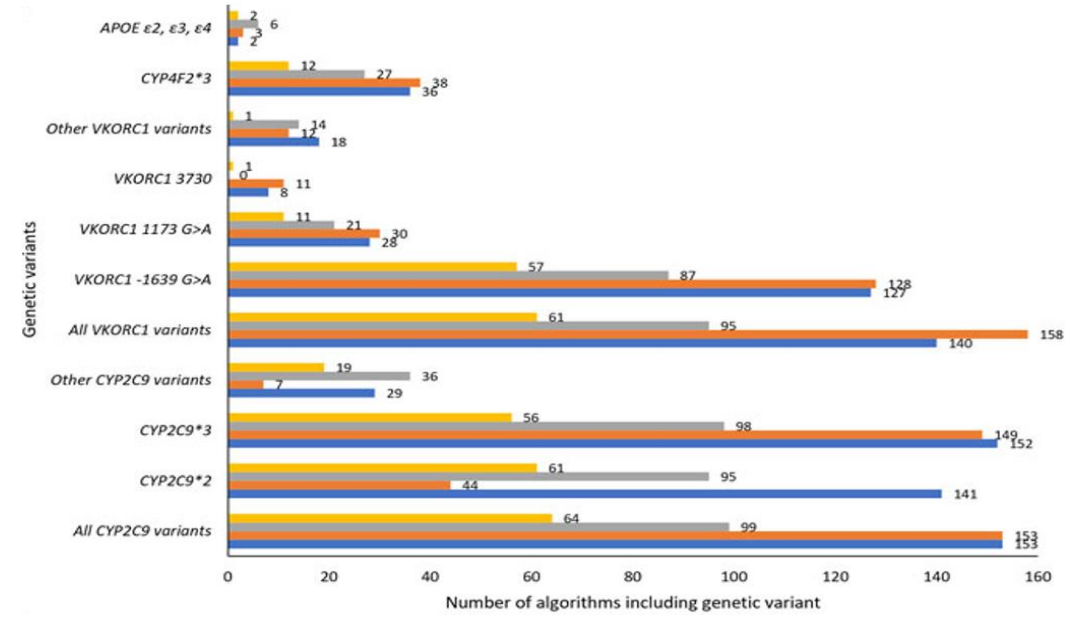
Multiple genome-wide association studies have consistently shown that the two principal genes shaping warfarin dose variability are CYP2C9 and VKORC1 [38-43]. Importantly, the relevance of specific variants differs across populations, largely because of variation in minor allele frequencies (MAFs) [22, 44]. Drawing from the data summarized in our earlier systematic review [10, 44], this section highlights the variants most commonly incorporated into warfarin dosing tools, evaluates their contribution to dose requirements across ancestral groups, and outlines key population-specific differences in MAFs.

Whites

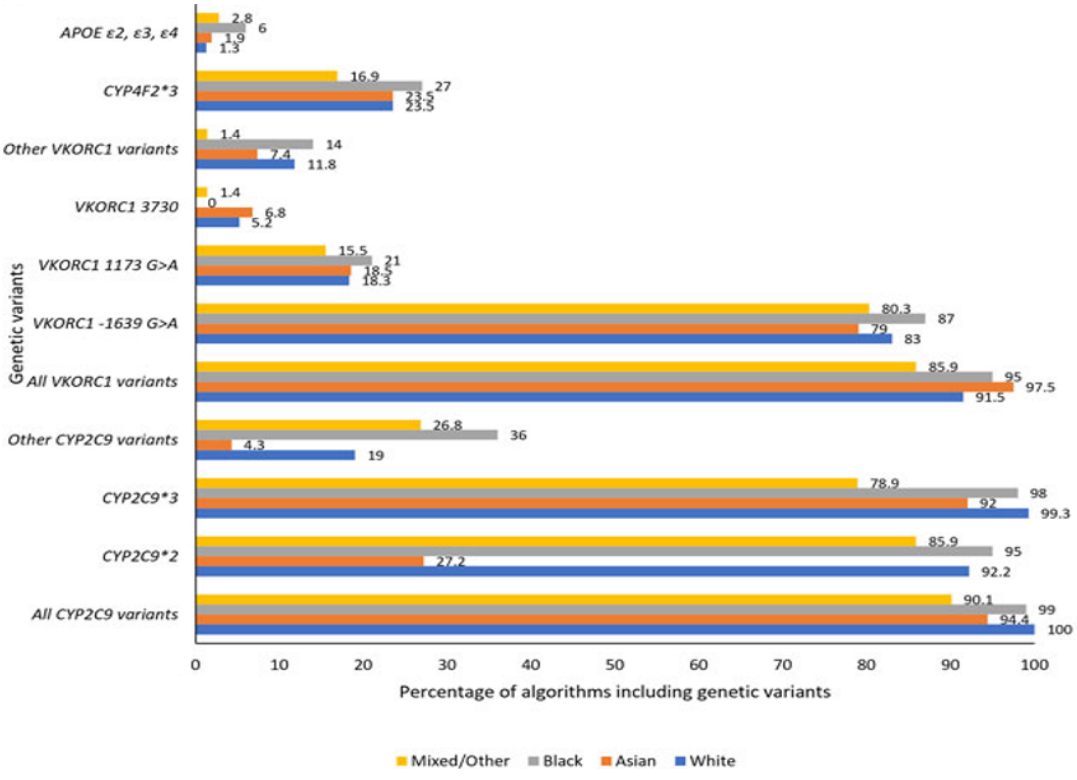
A total of 153 dosing algorithms included ≥5% individuals of White ancestry. Every one of these models incorporated at least one CYP2C9 variant, and 92% also used a VKORC1 marker **(Figure 3)**. The most frequently represented CYP2C9 alleles were CYP2C9*2 (appearing in 92% of algorithms) and CYP2C9*3 (present in 99%), whereas all remaining CYP2C9 alleles were included in only 19% of models. This low percentage is not unexpected, since variants such as CYP2C9*5, *6, *8, and *11 occur at nearly zero frequency in non-African groups, including those of European descent [1000 Genomes MAF ≈ 0.00 [21]].

The two CYP2C9 alleles that most strongly affect warfarin metabolism—CYP2C9*2 [MAF 0.12; reduces enzyme function to ~12% of wild type and lowers dose by up to 0.8 mg] and CYP2C9*3 [MAF 0.07; <5% enzyme activity and reductions up to 2.3 mg] [21, 45-47]—are therefore captured by nearly all White-applicable algorithms.

Likewise, the key VKORC1 variant (−1639G>A), associated with dose reductions of up to 3 mg/day, is reflected either directly (83% of algorithms) or indirectly through the linked VKORC1 1173C>T marker (18% of algorithms). Both variants show similar frequencies in Europeans (MAF 0.39) [21, 47]. The VKORC1 3730G>A allele, located in the 3′ UTR and linked to higher dose requirements through microRNA-related regulation [48], appeared in 5% of algorithms. The CYP4F2*3 allele—which affects vitamin K oxidation [49]—was included in 24% of algorithms, consistent with its modest contribution (1–2%) to warfarin dose variation [39].



(a)



(b)

Figure 3. Overview of genetic variables incorporated into the algorithms. Panels (a) and (b) list absolute counts and percentages for each variant. APOE = Apolipoprotein E; CYP = Cytochrome P450; VKORC1 = Vitamin K epoxide reductase complex subunit 1.

Table 1 presents the share of warfarin dose variability (R^2) explained by factors used in algorithms reporting this metric. Among 115 algorithms that enrolled at least 5% White participants, the combined genetic and clinical predictors accounted for a median of 52% of interpatient variability (range 20–82%), consistent with past summaries [4, 20]. Across algorithms reporting individual gene contributions, CYP2C9 (40 algorithms) explained a median 9% (range <1–50%) and VKORC1 (44 algorithms) explained 25% (range 1–52%). Although the 9% estimate for CYP2C9 is lower than reported elsewhere (e.g., 12% in Baker & Johnson, 2016; 15% in Pirmohamed *et al.*, 2015) [18], those earlier figures pooled multiple ancestries. Restricting the analysis only to algorithms

composed entirely of White participants increases the median gene contributions to 12% for CYP2C9 (15 algorithms; range <1–50%) and 27% for VKORC1 (16 algorithms; range 3–35%), matching previous findings [18, 50].

Table 1. Variability explained by CYP2C9 and VKORC1 [10].

Population Groups	**White**	**Asian**	**Black**	**Mixed/Other**
N	**%**	**R^2, Median (Range)**	**N**	**%**
Category	**White**	**Asian**	**Black**	**Mixed/Other**
Combined genetic + non-genetic contributors	115 / 52 / (20–82)	126 / 44 / (11–96)	72 / 46 / (22–82)	31 / 44 / (8–77)
CYP2C9-related contributors	40 / 9 / (<1–50)	48 / 7 / (<1–42)	21 / 7 / (2–17)	23 / 8 / (2–24)
VKORC1-associated contributors	44 / 25 / (1–52)	54 / 27 / (3–59)	24 / 23 / (1–52)	27 / 20 / (5–45)
Category	**White**	**Asian**	**Black**	**Mixed/Other**
Combined genetic + non-genetic contributors	61 / 51 / (20–70)	113 / 44 / (11–96)	29 / 34 / (22–66)	18 / 38 / (8–62)
CYP2C9-related contributors	15 / 12 / (<1–50)	41 / 7 / (<1–42)	1 / 9 / (—)	13 / 8 / (4–24)
VKORC1-associated contributors	16 / 27 / (3–35)	47 / 27 / (8–59)	3 / 9 / (7–10)	17 / 20 / (6–45)

CYP2C9 = cytochrome P450 2C9; VKORC1 = vitamin K epoxide reductase complex subunit 1; N = number of algorithms; R^2 = coefficient of determination.

It is essential to recognize that MAF values reflect population averages, and substantial differences may exist within subgroups. For instance, compared with the European-average MAF of 0.12, the CYP2C9*3 allele frequency shows statistically significant differences ($p < 0.05$) across Dutch (0.20), Polish (0.01), and Spanish (0.16) cohorts [51, 52].

Another analysis of 845 healthy volunteers across four Russian ethnic groups (238 Chuvash, 206 Marians, 157 Kabardians, 244 Ossetians) plus a separate group of 400 Russian atrial fibrillation patients found notable variation in CYP2C9*2 (MAF 0.06–0.12), CYP2C9*3 (MAF 0.07–0.14), and VKORC1 −1639G>A (MAF 0.38–0.50) [53, 54].

Furthermore, allele distributions do not always follow the same geographic patterns. A large cartographic study (2,197 individuals, 50 populations/ 137 ethnic or subethnic groups) demonstrated that:

- CYP2C9*2 shows a focal pattern, occurring frequently in a few groups (up to 0.23) but absent in others;
- CYP2C9*3 exhibits a nearly uniform distribution across groups (MAF 0.03–0.10);
- VKORC1 −1639G>A follows a clinal gradient, decreasing from >0.95 in the east to about 0.30 in the west [55].

Hispanics/latinos

Across Brazil and Puerto Rico, eight studies produced eleven dosing algorithms that reported partial R^2 values for CYP2C9 or VKORC1 [10]. Median partial R^2 estimates were 7% for CYP2C9 (range 2–17%) and 23% for VKORC1 (range 2–31%). The comparatively smaller influence of CYP2C9 in Hispanic/Latino groups—approximately half of that seen in Europeans—suggests that relying solely on CYP2C9*2 and *3 (present in all models) may not be optimal for these populations. Additional alleles such as **CYP2C9*5, *6, *8, and 11*, which were initially identified in individuals of Black/African ancestry, may provide better predictive value depending on the proportion of African genetic ancestry within a specific Hispanic/Latino population.

Because of their admixed origins, Hispanic/Latino allele frequencies typically fall below those observed in White populations and decrease further with increasing African ancestry. For example, in a Brazilian cohort exceeding 1,000 participants, the minor allele frequencies for CYP2C9*2, CYP2C9*3, and VKORC1-1639G>A were 0.11, 0.05, and 0.33, respectively [56]. Nevertheless, in traits shaped by differing selection pressures among ancestral populations, certain variants can display elevated frequencies in admixed groups [57].

Asians

A total of 162 pharmacogenomic algorithms included at least 5% Asian participants. Among these, 94% incorporated one or more CYP2C9 variants and 98% included at least one VKORC1 variant **(Figure 3)**. Reflecting its near-absence in some Asian subgroups [East Asian MAF ≈ 0.00; South Asian MAF 0.04 [21]], CYP2C9*2—which lowers warfarin dosage by up to 0.7 mg in Asian individuals [47]—was included in only 27% of the models. In contrast, CYP2C9*3 [East Asian MAF 0.03, South Asian MAF 0.11; effect up to 1.5 mg reduction] and VKORC1-1639G>A [East Asian MAF ≈ 0.89, South Asian MAF 0.15; also associated with dosage decreases up to 1.5 mg] were widely represented, appearing in 92% and 79% of algorithms, respectively. The related marker VKORC1 1173C>T, which is tightly linked to -1639G>A, was selected in 19% of the algorithms. Similar to findings in Europeans, CYP4F2*3, which contributes only 1–2% to dose variability in Japanese cohorts [40], appeared in 24% of models.

A subset of 113 algorithms focused exclusively on Asian populations **(Table 1)**. Within these, CYP2C9 (n = 41) and VKORC1 (n = 47) displayed median R^2 values of 7% (range <1–42%) and 27% (range 8–59%), respectively. The lower allele frequencies for CYP2C9*2 and *3 in East Asians (MAF ≈ 0.00 and 0.03) compared with South Asians (MAF 0.04 and 0.11) corresponded with reduced partial R^2 values. Specifically, among 32 East Asian algorithms (China n=18; South Korea n=12; Japan n=2), CYP2C9 accounted for a median of 6% of variability (range 1–33%). In contrast, the two South Asian datasets (both Indian) showed substantially higher contributions, with a median partial R^2 of 27% (range 12–42%).

Despite the much higher VKORC1 -1639G>A MAF in East Asians (0.89) compared with South Asians (0.15), the variance explained was comparable between regions: East Asian median 27% (range 8–49%, 39 algorithms: China n=22; South Korea n=12; Japan n=5) versus South Asian median 28% (range 23–32%, two Indian algorithms). This similarity follows from the fact that alleles with frequencies p and q = 1–p generate similar variability when effect sizes are equal—thus an East Asian MAF of 0.89 is effectively comparable to a South Asian frequency near 0.11.

Most existing pharmacogenomic algorithms originate from East Asian regions (China, South Korea, Japan), leaving Southern, Southeast, Western, and other Asian populations underrepresented. Within China, the majority of research involves Han Chinese, although minority groups such as Tu, Tujia, and Xibo—which can show CYP2C9*3 frequencies exceeding 0.10—remain insufficiently characterized [58]. Increasing levels of urbanization and interethnic admixture further complicate the genetic landscape.

For South Asia, most studies focus on India, a country with considerable genetic structure arising from contributions of ancestral North Indians, South Indians, Tibeto-Burmans, and Austro-Asiatics [59, 60]. In one analysis, CYP2C9*2 MAF reached 0.09 among 803 North Indians (peaking at 0.14 in 375 individuals from Lucknow, Uttar Pradesh) and 0.04 among 481 South Indians (dropping to 0.02 in 120 participants from Kerala) [61]. Another study evaluating 2,680 individuals across 24 Indian subpopulations found highly variable VKORC1-1639G>A frequencies, ranging from below 0.07 in one out-group population to above 0.70 in Tibeto-Burman groups [62].

Blacks

Among the 100 dosing algorithms containing at least 5% Black participants, 99% incorporated one or more CYP2C9 variants, and 95% included a VKORC1 marker **(Figure 3)**. Despite their very low population frequencies—CYP2C9*2 MAF 0.01 and CYP2C9*3 MAF ≈ 0.00 [21]—these alleles appeared in 95% and 98% of the algorithms, respectively. Their inclusion remains critical for individualized therapy: earlier evidence shows that Black-African carriers heterozygous for *2 or *3 require weekly warfarin reductions of 6.8 mg and 12.5 mg, respectively [63], values comparable to those reported in Whites (3.9 mg and 12.5 mg decreases) [47]. Ensuring these variants are represented in algorithms helps prevent under- or overdosing [64].

Beyond *2 and *3, additional CYP2C9 alleles—**CYP2C9*5, *6, *8, and *11—are now recognized as clinically relevant for Black-African groups [22, 63]. Yet only 36% of the algorithms included at least one of these other star alleles, indicating that most models omitted key contributors. Limited statistical power is one reason, although combining these lower-frequency alleles into a unified "CYP2C9 star variant" category can help [65]. Another important marker, rs12777823 within the CYP2C cluster (African MAF 0.25), can lead to dose reductions up to 12.7 mg/week in Black-African patients [63]; however, it appeared in only 19 algorithms from six studies. Notably, this SNP influences dosing only in Africans [41], despite being found in other ancestries [21].

Two VKORC1 variants—-1639G>A and 1173C>T—which are strongly linked and lower weekly warfarin requirements by as much as 18.1 mg and 21.6 mg [63], were widely represented, appearing in 87% and 21% of

algorithms. (Totals exceed 100% because 13 algorithms treated the two SNPs as interchangeable or cited both.) Conversely, VKORC1 3730G>A, which raises the weekly dose by up to 6.9 mg [63] and occurs with a MAF of 0.45 in Black-Africans [21], was absent from every Black-focused model. CYP4F2*3 was present in 27% of algorithms, even though no dose association was identified in a previous review [63]. Given its modest impact—only 1–2% of dose variability in Caucasians (MAF 0.29) [39] and East Asians (MAF 0.21) [40]—its influence is expected to be even smaller in Africans (MAF 0.08).

Although combined genetic and clinical covariates explain over half of warfarin dose variation in White patients, the 29 algorithms restricted to Black populations accounted for a median of only 34% (range 22–66%) of variability **(Table 1)**. Merely one algorithm reported a CYP2C9 partial R^2 (9%) and three reported VKORC1 values (median 9%, range 7–10%), all from U.S. cohorts. These modest contributions reflect the low allele frequencies. In the study providing CYP2C9 effect estimates [65], the included star alleles were CYP2C9*2 (MAF 0.02), *3 (0.01), *5 (0.01), *8 (0.06), and *11 (*0.04*), totaling 0.14 or less (considering individuals may carry two alleles). These contributed 5.6% univariable and 7.7% partial R^2. By comparison, in White populations, CYP2C92 (MAF 0.12) and *3 (MAF 0.07) alone account for ~12% of variability. If only *2 and *3 had been analyzed in the Perera dataset, the CYP2C9 contribution would have been even lower—highlighting the need to include all relevant variants. In the same analysis, VKORC1 1173 (study MAF 0.12) produced a partial R^2 of 7.4% (univariable 9.9%), far below the ~27% contribution seen in Whites (MAF 0.39).

Prior work [63] noted that much of the available evidence for Black populations originates from African Americans and Black Brazilians—groups of predominantly West African descent with substantial European and Amerindian admixture [66]. Consequently, these findings may not fully apply to other Black-African groups, including those throughout sub-Saharan Africa. In a Brazilian dataset of 109 individuals self-identifying as Black, mean ancestries were 51% African (95% CI 45–57%), 42% European (95% CI 36–48%), and 7% Amerindian (95% CI 6–9%) [67]. In the United States, some people who identify as African American may have almost no African genetic ancestry [68]. This helps explain why the VKORC1 -1639G>A MAF of 0.05 in the African super-population is 2–5 times higher in African Americans (0.15) than in various sub-Saharan groups: Yoruba (0.03), Mende (0.05), Luhya (0.04), Gambian (0.07), and Esan (0.03) [21]. Additionally, the internal diversity within sub-Saharan Africa is considerable, sometimes surpassing that seen between non-African groups [69, 70]. Some regions, such as South Africa, also have admixed communities [71] with distinct genetic patterns despite self-identifying as Black.

Mixed/other

This category includes individuals labeled as “mixed,” “other,” or “unknown” in the original studies, as well as studies that did not fit within the three main ancestry groupings (“White,” “Asian,” “Black”). Among the 71 dosing algorithms that incorporated at least 5% Mixed/Other participants, 90% included one or more CYP2C9 variants, 86% incorporated a VKORC1 variant, and 17% accounted for CYP4F2*3 **(Figure 3)**. A total of 18 algorithms were developed entirely from Mixed/Other populations **(Table 1)**; of these, 13 and 17 algorithms reported CYP2C9 and VKORC1 effects, with median R^2 values of 8% (range 4–24%) and 20% (range 6–45%), respectively. These studies were conducted in Egypt (9), Turkey (6), and Colombia, Oman, and Sudan (1 each).

Egypt

Although situated in North Africa, Egypt was not grouped with the Black category because genome-wide analyses indicate that North African populations share more genetic similarity with Near Eastern groups than with sub-Saharan Africans [72]. Because Egypt is geographically in Africa but not typically classified as Asian [73], it was placed in the Mixed/Other category.

Across six algorithms reporting CYP2C9 partial R^2 values, the median contribution was 8% (range 5–16%), similar to findings in Black populations. This is notable given that Egyptian CYP2C9 allele frequencies resemble European patterns more closely than African ones. In one example [74], MAFs for CYP2C9*2, *3, *4, *5, and *8 were 0.12, 0.09, <0.01, 0.01, and <0.01, respectively, yet the partial R^2 was only 5%, a result that warrants additional scrutiny.

For eight Egyptian algorithms that reported VKORC1 partial R^2, the median was 14% (range 7–32%), roughly half the ~27% seen in Whites. This pattern is unexpected because Shahin *et al*. reported a VKORC1-1639G>A MAF of 0.46, higher than the 0.39 typically observed in Europeans. A pharmacogenetic systematic review, largely comprising Egyptian studies (10 of 14), identified VKORC1-1639G>A and several CYP2C9 alleles (*2, *3, *5, *8, *11) as significant contributors to dose variation [75].

Turkey

Turkish populations contain a blend of European and Asian ancestries [76, 77]. In four Turkish studies, CYP2C9 partial R^2 had a median of 16% (range 8–24%), while VKORC1 partial R^2 across six studies had a median of 22% (range 6–34%).

A CYP2C9 median contribution of 16%, slightly above the 12% typically reported in Whites, corresponds with higher CYP2C9*3 frequencies in Turkey (reported as 0.10 and 0.15 in two studies). VKORC1 -1639G>A frequencies were 0.50 and 0.40, similar to or exceeding the European MAF of 0.39. Despite this, VKORC1 partial R^2 (22%) remained slightly below the White estimate (27%), illustrating the variability of such estimates.

Colombia

Colombian populations, similar to Puerto Ricans and Brazilians, are genetically admixed. Approximate ancestry proportions are 49% Mestizo, 37% European, 10% African, and 3.4% Amerindian [78]. One Colombian algorithm reported CYP2C9 and VKORC1 partial R^2 values of 4% and 26%, respectively, which aligned with allele frequencies: CYP2C9*2 (*0.07*), CYP2C9*3 (0.03), and VKORC1 -1639G>A (0.44) [79].

Oman

Omani populations reflect mixtures of Caucasian, African, and Asian ancestries [80]. In one study, CYP2C9 and VKORC1 partial R^2 values were reported as 17% and 45%, with corresponding allele frequencies of CYP2C9*2 (*0.08*), CYP2C9*3 (0.06), CYP2C9*8 (<0.01), and VKORC1 -1639G>A (0.38). Interestingly, these R^2 values exceed those commonly reported for Whites despite having similar MAFs, though the finding is based on a single dataset.

Sudan

Sudanese populations include Nilotic groups in the south and Arab-African groups in the north [81]. Due to notable Arab admixture, Sudan was grouped similarly to Egypt. The Shrif *et al*. study found CYP2C9 (*2, *5, *6, *11) and VKORC1 (1542G>C, 3730G>A, rs7199949) partial R^2 values of* 5% *and* 27%, *respectively. Reported MAFs were: CYP2C9*3 (0.00), *5 (0.01), *6 (0.02), and *11 (*0.05*), comparable to Black-African and African American values, whereas CYP2C9*2 (0.05) fell between West/Southern African and North African/European ranges. The VKORC1-1639G>A MAF (0.37) closely resembled European estimates, although this variant was not included in the dosing model.

Clinical Utility Studies

Before any dosing algorithm is put forward for routine clinical use, its practical value must be demonstrated, ideally through randomized controlled trials (RCTs), which remain the strongest methodological standard. In this setting, clinical utility [82] refers to demonstrable gains in anticoagulation management—typically the duration patients maintain therapeutic INR values—or improved clinical outcomes such as reduced bleeding complications. This section summarizes which RCTs have been carried out in different demographic groups to determine which dosing tools are sufficiently validated for clinical rollout.

By 20 May 2020, investigators had published 23 RCTs examining genotype-based warfarin dosing, involving 8,487 treated individuals [10]. A more recent evidence review [83] added additional studies, bringing the total to 10,046 randomized participants who received either genotype-informed therapy or a control regimen **(Table 2)**. **Table 2** highlights population coverage; detailed interpretations of the study outcomes and study rigor can be found in prior syntheses [83, 84].

Table 2. RCTsa evaluating clinical usefulness as of July 2021 [10, 83].

Clinical Utility Study	Nation	Total Sample	Randomized (Total)	White (Hispanic)	Asian	Black	Mixed/Other	Primary PGx Algorithm Used
Hillman *et al*. (2005) [85]	USA	38	38	—	—	—	—	Hillman model [86]
Anderson *et al*. (2007) [87]	USA	200	200	189	—	—	11	Carlquist model [88]
Huang *et al*. (2009) [89]	China	142	—	—	142	—	—	Huang model [89]

Burmester *et al*. (2011) [90]	USA	230	230 (ethnicity not provided)	—	—	—	—	Caldwell model [49]
Korneva *et al*. (2011) [91]	Russia	61	61[b]	—	—	—	—	Not reported (abstract only)
Borgman *et al*. (2012) [92]	USA	26[c]	24	—	—	—	2	PerMIT system [93]
Radhakrishnan *et al*. (2012) [94]	USA	56	—	—	—	—	—	Not reported (abstract only)
Wang *et al*. (2012) [95]	China	106	—	—	106	—	—	Huang model [89]
Jonas *et al*. (2013) [96]	USA	109	79	—	—	30	—	WarfarinDosing.org [97]
Kimmel *et al*. (2013) [23]	USA	1,015	740 (65)	—	—	275	—	WarfarinDosing.org [97]
Li *et al*. (2013) [98]	China	220	—	—	220	—	—	Not described (English abstract)
Pirmohamed *et al*. (2013) [99]	UK & Sweden	455	447	2	5	1	—	Modified IWPC model (IWPC, 2009)
Pengo *et al*. (2015) [100]	Italy	200	200	—	—	—	—	Zambon model [101]
Duan *et al*. (2016) [102]	China	55	—	—	55	—	—	Not reported (abstract only)
Jiang *et al*. (2016) [103]	China	60	—	—	60	—	—	Jiang model [103]
Pavani *et al*. (2016) [104]	India	207	—	—	207	—	—	Neural-network dosing model [104]
Gage *et al*. (2017) [105]	USA	1,650	1,502 (42)	29	106	13	—	WarfarinDosing.org [97]
Jin *et al*. (2017) [106]	China	238	—	—	238	—	—	WarfarinDosing.org [97]
Wen *et al*. (2017) [107]	Taiwan (China)	318	—	—	318	—	—	Wen model [108] + IWPC equation (IWPC, 2009)
Jiang *et al*. (2018) [109]	China	87	—	—	87	—	—	Lou model [109]
Makar-Ausperger *et al*. (2018) [110]	Croatia	205	205[b]	—	—	—	—	WarfarinDosing.org [97]
Syn *et al*. (2018) [111]	Singapore & Malaysia	322	—	—	322	—	—	Tham model [112]
Xu *et al*. (2018) [113]	China	201	—	—	201	—	—	Cen model [114]
Al-Metwali *et al*. (2019)[d] [115]	UK	26[c]	20	4	—	2	—	Differential-equation framework [116]
Hao *et al*. (2019) [117]	China	2,264	—	—	2,264	—	—	IWPC equation (IWPC, 2009)

Guo *et al*. (2020) [118]	China	660	—	—	660	—	—	Updated IWPC-based equation
Lee *et al*. (2020) [119]	South Korea	125	—	—	125	—	—	Lee model [120]
Panchenko *et al*. (2020) [121]	Russia	263	263	—	—	—	—	WarfarinDosing.org [97]
Zhu *et al*. (2020b) [122]	China	507	—	—	507	—	—	Zambon model [101]

a A few reports labeled as randomized lacked enough methodological detail to confirm randomization.
b Race/ethnicity unspecified; recruitment occurred in predominantly White nations.
c Based on the analyzed participants (34 randomized; race/ethnicity unreported).
d Pediatric cohort.
e Based on the analyzed participants (29 randomized; race/ethnicity unreported).
IWPC = international warfarin pharmacogenetics consortium; PerMIT = personalized medicine interface tool; UK = United Kingdom; USA = United States of America.

Whites

Roughly 40% of all individuals enrolled in genotype-guided warfarin RCTs identified as White. Three major investigations contributed most of these data: the U.S.-based GIFT study [105], the COAG trial [23], and the EU-PACT study conducted in the UK and Sweden [99].

COAG and EU-PACT were both released in 2013, but they arrived at incompatible conclusions. EU-PACT (n = 427) showed that incorporating genetic information improved percent time in therapeutic range (PTTR), hastened achievement of a stable dose, and lowered the frequency of INR values >4. COAG (n = 955) did not observe benefits in PTTR, stabilization time, or extreme INR values (>4 or <2). Numerous factors likely contributed to the discrepancy, including fundamental differences in dosing approach (loading in EU-PACT vs. maintenance in COAG), the near-homogeneous 99% Caucasian composition of EU-PACT compared with COAG's ethnically mixed cohort—27% of whom were African-American—as well as variation in the control strategies used (fixed vs. clinically adjusted dosing) [18].

Across all COAG participants (n = 955), genotype-based dosing altered mean PTTR by −0.2 (95% CI −3.4 to 3.1, p = 0.91). When Black participants were removed (n = 700 remained), the estimate shifted to an increase of 2.8 (95% CI −1.0 to 6.6, p = 0.15), though still not reaching statistical significance.

GIFT produced clearer evidence. Among older adults (≥65 years) starting warfarin for elective hip or knee surgery, those in the genotype-guided arm (n = 803) achieved a higher PTTR over 4 weeks than the clinically guided group (n = 785)—mean difference 3.4 (95% CI 1.1 to 5.8, p = 0.004). The effect was slightly stronger in non-Black individuals (751 vs. 735 participants; mean difference 3.7, 95% CI 1.2 to 6.1, p = 0.003). The genotyped group also experienced a lower combined incidence of major bleeding, INR ≥4, venous thromboembolism, or death—an absolute reduction of 3.9% (95% CI 0.7%–7.2%; relative rate 0.73, 95% CI 0.56 to 0.95, p = 0.02).

Hispanics/latinos

Three studies [23, 90, 105] included Hispanic or Latino participants, though one [90] did not specify how many were "White Hispanics." From the other two reports, at least 107 Hispanic individuals were represented, just 1% of the total 10,046 enrolled.

Asians

Individuals of Asian ancestry made up approximately 55% of the 10,046 participants in pharmacogenomic-guided warfarin RCTs. While this seems substantial, it still falls slightly below their approximate 60% share of the global population [123]. A single large Chinese RCT [117] accounted for 2,264 participants—41% of all Asian subjects. In that study of patients undergoing heart valve replacement, genotype-directed dosing shortened the time to reach therapeutic INR (3.8 ± 2 vs. 4.4 ± 2 days, p < 0.001), though major bleeding and thrombotic events were unchanged.

Two additional sizeable Chinese trials, with sample sizes of 660 and 507, reported meaningful improvements in PTTR with genetic dosing [mean differences 5.6 (95% CI 1.1 to 10.2, p = 0.01) and 17.4 (95% CI 11.8 to 22.9, p < 0.01)] [118, 122]. Together with several other Chinese investigations, these accounted for 4,858 participants—88% of all Asian enrollment—highlighting the limited representation of non-Chinese Asian groups. Additional

recruitment came from Singapore/Malaysia (n = 322, 6%), India (n = 207, 4%), South Korea (n = 125, 2%), and the UK/USA (n = 35, <1%).

Blacks
Only 416 individuals (4% of the 10,046) were identified as Black, indicating very limited representation in clinical-utility research. Of these, 411 (99% of all Black participants) were enrolled in U.S.-based studies, most notably the COAG [23] and GIFT [105] trials. In both studies, genotype-guided treatment did not outperform standard clinical dosing. In COAG, the mean PTTR difference was −8.3 (95% CI −15.0 to −2.0, p = 0.01; n = 255), while GIFT reported a mean difference of 0.2 (95% CI −8.9 to 9.4, p = 0.96; n = 102). These outcomes have largely been attributed to dosing tools that were not designed to incorporate genetic variants commonly found in individuals of African ancestry. Notably, no randomized trial evaluating pharmacogenomic dosing has yet included participants from sub-Saharan Africa or Latin America.

Mixed/other
Five studies conducted in Sweden, the United Kingdom, and the United States together enrolled 29 participants (representing 0.3% of the 10,046). These individuals were categorized as mixed, other, or unknown ancestry, highlighting the absence of clinical-utility evidence for groups outside the standard "White," "Asian," or "Black" classifications.

Cost-effectiveness studies
A recent systematic review by Zhu and colleagues examined the economic value of pharmacogenomic strategies in cardiovascular care, identifying 16 relevant warfarin studies [124]. Fourteen of these reported their study locations: United States/Canada (n = 8, 57%), United Kingdom/Europe (n = 4, 29%), and Asia (n = 2, 14%). The two studies without explicit geographic reporting [125, 126] were likely conducted in the United States or Canada, based on later publications by the same group [127, 128].
Among the primary economic evaluations, 11 studies incorporated specific dosing algorithms. These included the IWPC model [33], used alone or alongside other formulas (n = 5); the Anderson/Carlquist approach [88] (n = 3); and one study each using the Caraco [129], Gage [130], and Kim [131] algorithms. Apart from the Kim model—developed in an Asian cohort and integrating additional CYP2C9 variants (13 and 14)—most algorithms were created primarily in White populations and relied on **CYP2C92* and CYP2C9*3. Consequently, existing cost-effectiveness data predominantly apply to White populations.

Clinical implementation guidelines
Implementation guidelines serve as a bridge between pharmacogenomic evidence and practical clinical use [132]. Early observational findings and preliminary RCTs [85] led the U.S. FDA to revise the warfarin label in August 2007, adding information on how genetic variation affects dose requirements [133]. However, major professional societies—including the American College of Medical Genetics and the American College of Chest Physicians—called for more robust clinical research before formal recommendations could be issued [133].
After further data accumulated, the FDA updated the label again in 2010, this time including explicit guidance on how genotype should be used to estimate individualized dosing [134]. One year later, the Clinical Pharmacogenetics Implementation Consortium (CPIC) released practice recommendations for dosing based on VKORC1 and CYP2C9 genotypes [135].
As of 19 June 2020, there are four established guideline systems for pharmacogenomic warfarin dosing [132]:

- The Dutch Pharmacogenetics Working Group (DPWG),
- The Clinical Pharmacogenetics Implementation Consortium (CPIC),
- The Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and
- The French RNPGx network.

These are described in **Table 3**, with the discussion again emphasizing ancestry-related considerations.

Table 3. Clinical implementation guidelines [123].

Guideline Source	Genetic Markers[a]	Recommended Algorithms	Evidence Level[b]

CPIC [44]	Non-African populations: CYP2C9*2*, *CYP2C9*3, VKORC1 −1639G>A	Gage model and IWPC model [33, 97]	Strong
	African populations: CYP2C9*2*, *CYP2C9*3, VKORC1 −1639G>A	—	Moderate
	African individuals carrying CYP2C9*5, *6, *8, or *11	Recommended dose adjustment: reduce predicted dose by 15–30% (or 20–40% if homozygous for the variant)	Moderate
	African individuals with CYP2C rs12777823 A allele	Suggested dose reduction: 10–25%	Moderate
CPNDS [136]	CYP2C9*2*, *CYP2C9*3, VKORC1 −1639G>A	www.warfarindosing.org[c]	++++, Moderate
DPWG [137]	CYP2C9*2*, *CYP2C9*3, VKORC1 −1639G>A	EU-PACT approaches (IWPC equation as primary model)	4A–D
RNPGx [138]	CYP2C9*2*, *CYP2C9*3, VKORC1 −1639G>A	Dosing recommendations per dosing chart	Advisable

[a] CPIC optional variants, such as CYP4F2*3, are not included.
[b] CPIC provides three recommendation strengths (strong, moderate, optional); CPNDS uses a four-level evidence scale (+ to ++++) and three tiers for genotype-based advice; DPWG uses five evidence ratings (0–4) and eight levels of clinical relevance (AA–F); RNPGx classifies recommendations as essential, advisable, or possibly useful.
[c] The principal algorithm is Gage 2008 [97], although multiple other studies [33, 139-141] contributed to the models available at the same site. Consequently, warfarindosing.org also supports CYP4F2*3, GGCX, rs11676382, and additional CYP2C9 alleles (CYP2C9*5, CYP2C9*6). The IWPC algorithm is also hosted as a secondary option.
CPIC = Clinical Pharmacogenetics Implementation Consortium;
CPNDS = Canadian Pharmacogenomics Network for Drug Safety;
DPWG = Dutch Pharmacogenetics Working Group;
EU-PACT = European Pharmacogenetics of Anticoagulant Therapy;
IWPC = International Warfarin Pharmacogenetics Consortium;
RNPGx = French National Pharmacogenetics Network.

From **Table 3**, the two principal dosing models that yield closely aligned dose predictions [44] are the Gage and IWPC formulas, both of which were derived from sizeable datasets composed largely of individuals of White ancestry [33, 97]. The Gage model was generated using records from 1,015 warfarin users (83% White, 15% Black, 2% Mixed/Other), whereas the IWPC tool was built from 4,043 subjects (55% White, 30% Asian, 9% Black, 6% Mixed/Other) drawn from nine nations across four continents. In our earlier review, these models had the greatest volume of external validation studies (Gage: 46; IWPC: 72) and were the most frequently assessed in clinical settings (Gage: eight clinical utility evaluations; IWPC: seven), which was a major factor in our recommendation of them [10]. From **Table 2**, among 10,046 randomized participants, at least 7,177 (71%) were included in ten RCTs that tested one of these two tools, reaffirming their extensive adoption. Yet, within these 7,177 participants, the majority were White (n = 4,236; 45%) or Asian (n = 7,511; 49%), while only 416 (6%) were Black (primarily African American) and 14 (0.2%) identified as Mixed/Other. When Hispanic individuals are classified separately, they total just 107 (<2%).
Between the two models, only the Gage algorithm (warfarindosing.org) incorporates variants beyond CYP2C92, CYP2C93, and VKORC1-1639G > A **(Table 3)**. However, it still omits variants such as CYP2C98, CYP2C911, and CYP2C rs12777823, which are particularly relevant for Black patients and certain Hispanic groups. Consequently, the CPIC guideline advises additional dose reductions for African patients who carry these alleles, although these adjustments stem mostly from evidence in African Americans, who are predominantly of West African descent. For African Americans genotyped only for CYP2C92 and CYP2C93, gene-guided dosing is not recommended. CPIC also offers pediatric dosing advice, but these recommendations (with a "moderate" evidence grade) apply only to children of European ancestry [44].

Future directions in warfarin pharmacogenomic research

Accounting for race/ethnicity in warfarin pharmacogenomic research

When constructing pharmacogenomic dosing tools, racial and ethnic groups can be incorporated either through adjustment or through stratified analyses, with existing work indicating that stratification often produces more

accurate dose predictions [142]. Beyond ensuring that diverse racial/ethnic groups are adequately represented in study populations [30], both approaches require precise and consistent definitions of race/ethnicity, particularly when comparing data across studies. Advanced statistical methods can now estimate genetic ancestry reliably, but ancestry estimates should not replace race/ethnicity classifications because the latter still capture important non-genetic contributors to health disparities, including those not fully explained by socioeconomic variables [29]. Although institutions such as the United States National Institutes of Health have established racial/ethnic categories for research, these groupings are broad and may overlook within-group diversity and admixture, potentially contributing to misclassification and overly generalized conclusions that could hinder clinical translation [143]. To reflect the multidimensional nature of race/ethnicity—including social determinants of health and biological/genetic contributors to drug response—improved methods for characterizing racial/ethnic identity and evidence-based guidance on using self-reported race/ethnicity are necessary [29, 143].

Identifying novel genetic variants in underrepresented populations

While multifactor pharmacogenomic models (those combining genetic and clinical variables) account for roughly half of the variance in warfarin dose among Whites **(Table 1)**, they explain only about one-third among Black individuals. This indicates that Black patients and other underrepresented groups would significantly benefit from additional research aimed at discovering new, relevant variants. Although most earlier investigations relied on candidate-gene strategies, several genome-wide association studies (GWASs) have been conducted [38-43], scanning the genome for novel contributors. Notably, one study [41] identified CYP2C rs12777823, a variant that independently affects warfarin dose beyond CYP2C92, CYP2C93, and VKORC1-1639G > A. Its impact is specific to individuals of African ancestry, meaning it likely would not have been detected without an African-centered study. Furthermore, because African populations exhibit high haplotype diversity and lower linkage disequilibrium, research in these groups can aid the identification of causal variants that also benefit more genetically homogeneous populations, such as Europeans or Asians, through finer mapping [144]. Achieving such fine-scale mapping requires that causal variants be captured during genotyping or imputation, implying that genotyping arrays and reference panels must be tailored to these populations.

GWASs are relatively uncomplicated in genetically uniform populations but become considerably more challenging in admixed groups such as African Americans and Hispanics/Latinos. Studies that include admixed individuals must account for correlations among genetic markers that arise at both a fine scale (SNP-level linkage disequilibrium inherited from the ancestral source populations) and a broader scale (admixture LD caused by chromosomal tracts derived from different ancestries) [145]. Newer analytical approaches, including Tractor, are able to model both SNP-based and admixture-driven LD patterns in admixed populations, thereby improving power and refining the localization of GWAS-associated variants [145, 146].

Any newly discovered genetic variants require functional evaluation to confirm their relevance to drug response. These experiments should be supplemented by replication of the same phenotype across multiple populations, and when functional data are lacking, cross-population studies may help exclude causal relationships, as shown for CYP2C rs12777823 [41].

Finally, it should be acknowledged that warfarin response in some groups may follow a polygenic architecture—where numerous variants of small effect collectively influence therapy—rather than being governed by a few variants with major impact [147]. In settings where influential single loci cannot be identified, polygenic scores or polygenic-informed dosing strategies may be warranted.

Improving clinical utility through ethnic diversity

Insufficient inclusion of diverse ethnic groups in pharmacogenomic dosing tools may partly explain why some trials have reported limited clinical benefit. For instance, the COAG study [23] found no improvement in PTTR when using genotype-guided dosing compared to clinical dosing alone (mean PTTR fell by 0.2, $p = 0.91$, $n = 955$). This result may reflect the relatively high proportion of African American participants (27%) who did not benefit from a model lacking African-specific genetic predictors [mean PTTR decreased by 8.3; $p = 0.01$]. Among non-Black participants in the same trial, the treatment effect shifted direction (mean TTR increased by 2.8%), although this change was not statistically significant ($p = 0.15$), possibly due to the reduced sample size ($n = 700$). In contrast, the later GIFT trial, which enrolled more individuals ($n = 1,588$) and included fewer Black participants (6%), showed that genotype-based dosing significantly increased the mean PTTR by 3.4 ($p = 0.004$) [105]. Moving ahead, ensuring that algorithms account for all racial/ethnic groups should reduce inconsistencies in RCT findings, and with declining genotyping costs, promote more cost-effectiveness analyses supporting genotype-

guided dosing. This body of evidence should help shape clinical guidelines that better serve multiple populations and facilitate broader acceptance among patients, clinicians, and healthcare systems.

Reducing healthcare disparities through ethnic diversity

As illustrated by the COAG trial [23], using pharmacogenomic models that omit ancestry-specific genetic contributors can lead to suboptimal anticoagulation for those populations, potentially worsening existing health inequities [148]. For example, in our earlier studies conducted in South Africa and Uganda, fixed-dose initiation produced a median TTR of 41% [149], far below that reported in a European cohort from Sweden and the United Kingdom (mean TTR 60%) [99]. In that European cohort, applying a pharmacogenomic algorithm increased the mean TTR to 67% [99], thereby widening the quality gap further since no validated pharmacogenomic dosing tool currently exists for sub-Saharan Africa [150]. Additionally, wealthier regions such as Europe can use newer direct oral anticoagulants (DOACs), while most countries in sub-Saharan Africa continue to rely on the less expensive warfarin [151]. Because optimal anticoagulation is essential for all groups—warfarin performs as effectively and safely as DOACs when patients maintain an INR TTR ≥66% [152]—we are developing a pharmacogenomic algorithm for two sub-Saharan countries and testing a point-of-care panel incorporating Africa-specific variants (War-PATH; http://warpath.info/). We encourage additional research in other underrepresented communities. Editors and reviewers should also appreciate the value of pharmacogenomic research in minority populations and avoid undervaluing such studies simply because comparable work has already been carried out in European or Asian cohorts [153].

Impact of DOACs on warfarin pharmacogenomic research

Direct oral anticoagulants are increasingly replacing vitamin K antagonists like warfarin. For instance, although warfarin remained the most commonly prescribed single oral anticoagulant in England in 2019 (38% of prescriptions), DOAC use (apixaban, dabigatran, edoxaban, rivaroxaban) grew dramatically, rising from 16% of prescriptions in 2015 to 62% in 2019 [3]. Because DOACs have demonstrated non-inferior or superior outcomes in patients with non-valvular atrial fibrillation, many guidelines now recommend them, and the World Health Organization's inclusion of DOACs in its 21st Model List of Essential Medicines is expected to expand their availability in low-resource settings [154]. Nevertheless, even with the approval of less costly generics (e.g., apixaban in the United States in 2019 and rivaroxaban in Europe in 2020), DOACs will likely remain more expensive than generic warfarin and may not reach low-income regions—including those in sub-Saharan Africa—for some time [155, 156]. Therefore, warfarin pharmacogenomic research will continue to be especially relevant for underrepresented groups who depend on warfarin because it is more accessible and affordable.

Although many major DOAC trials enrolled patients from multiple regions worldwide [157], the data that inform current preferences for DOAC therapy over warfarin still come primarily from White participants [30]. A clear example is the ROCKET AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), which enrolled 13,997 individuals across 1,178 sites in 45 countries. Despite this broad geographic spread, 83% of the cohort was White, with the remainder consisting of 13% Asian, 1% Black, and 3% other groups [157, 158]. Consequently, the extent to which these findings apply to communities with limited representation remains uncertain. In sub-Saharan Africa, for instance, rivaroxaban may not demonstrate superior safety compared with warfarin because many patients receive tuberculosis and HIV therapies that influence P-glycoprotein and CYP3A4 activity, potentially reducing rivaroxaban's bleeding-related advantage [156, 159]. For these reasons, DOAC performance needs to be properly evaluated in underrepresented groups before recommending that warfarin be replaced. This is especially important given that DOAC exposure varies markedly between individuals due to genetic factors (variants affecting CES1, ABCB1, CYP3A4, and CYP3A5) and clinical factors such as renal status and concomitant medications—variability that can contribute to bleeding or clotting events. Yet, the current evidence based on this topic is limited, and further research is required [160, 161].

Only a small number of investigations have compared DOAC outcomes with warfarin prescribed according to genotype, and this gap matters because the comparative benefit of DOACs may shift in certain genetic subgroups. In the ENGAGE AF-TIMI 48 study (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48), among 4,833 individuals receiving clinically dosed warfarin, 1,711 (34%) and 140 (3%) were classified as sensitive and highly sensitive responders on the basis of their CYP2C9 and VKORC1 genotypes [162]. During the first 90 days, edoxaban reduced bleeding more effectively in these genetically sensitive categories than in normal responders (60 mg edoxaban P-interaction =

0.0066; 30 mg edoxaban P-interaction = 0.0036), indicating that the safety benefit of edoxaban may be greatest in these groups. Genotype-guided warfarin dosing itself reduces bleeding [83, 84], particularly for sensitive responders, which leaves open the question of whether DOACs would still outperform genotype-tailored warfarin on both safety and efficacy. Addressing this uncertainty would require a large randomized trial that is improbable to conduct because of expense and limited funding prospects.

Because DOACs depend partly on renal excretion, reduced kidney function can lead to drug accumulation and higher bleeding risk [163]. As a result, DOACs are typically avoided when the estimated glomerular filtration rate (eGFR) falls below 30 ml/min, especially for DOACs cleared extensively through the kidneys. Even in mild or moderate impairment, careful monitoring is required since renal function can decline abruptly, making regular eGFR checks essential [163]. In comparison with White patients, individuals in underrepresented groups such as Black patients may face higher risks when using DOACs in the context of renal impairment: they have increased rates of progression to end-stage kidney disease—where DOACs are contraindicated—and commonly experience less accurate eGFR estimation [164]. Apart from advanced kidney disease, warfarin remains necessary for patients with mechanical heart valves, children, and individuals taking interacting medications [165]. Additional limitations—including the absence of a robust laboratory marker to monitor DOAC effect, twice-daily dosing requirements for some agents such as apixaban and dabigatran, and the high cost of reversal agents like idarucizumab and andexanet alfa [165, 166]—mean that warfarin is likely to continue as the main anticoagulant in many underserved settings, reinforcing the importance of further pharmacogenomic research in these populations.

Ethnic diversity and pharmacogenomics: warfarin as a pathfinder drug

Warfarin has long been viewed as one of the flagship examples of pharmacogenomics in action [17], shaping both methodological directions and clinical expectations in the field. Accordingly, the pharmacogenomic literature for other vitamin K antagonists is far smaller. Only five acenocoumarol and two phenprocoumon algorithms have been reported, compared with 32 developed for warfarin [167]. All seven acenocoumarol and phenprocoumon algorithms were created using cohorts from European nations (Germany, Greece, the Netherlands, Spain) or India, meaning they also fail to encompass global ethnic diversity. Beyond anticoagulation, clopidogrel and statins represent two additional cardiovascular drug classes regarded as ready for pharmacogenomic use [168], and these agents are addressed in the following sections.

Clopidogrel is a thienopyridine precursor drug that undergoes hepatic conversion into an active compound responsible for suppressing platelet aggregation [138, 169]. Its major biotransformation pathway involves the Cytochrome P450 enzyme CYP2C19, encoded by the CYP2C19 gene. Loss-of-function variants such as CYP2C192 (rs4244285, a splice-site defect producing a stop codon) and CYP2C193 (rs4986893, a premature stop codon) result in reduced metabolic capacity, leading to diminished production of the active metabolite and therefore weaker clopidogrel response. Conversely, the CYP2C1917 allele (rs12248560, located in the promoter region) enhances transcription and elevates protein levels, which may cause greater platelet inhibition and raise bleeding risk in users who carry this variant [138, 169]. The clinical relevance of these alleles varies among populations due to differences in their reported MAFs—CYP2C192: African 0.17, American 0.11, East Asian 0.31, European 0.15, South Asian 0.36; CYP2C193: East Asian 0.06, South Asian 0.01, others ~0.00; CYP2C1917: African 0.24, American 0.12, East Asian 0.02, European 0.22, South Asian 0.14 [21]. As a result, findings in one ancestral group may not generalize to another. Nevertheless, most work examining CYP2C19 in relation to antiplatelet therapy—primarily clopidogrel—has focused on White cohorts [30], limiting applicability to diverse groups and potentially introducing clinical repercussions. One example is the legal action against the clopidogrel manufacturer for failing to warn Hawaiian patients about decreased drug effectiveness related to higher rates of CYP2C192 and CYP2C193 in Hawaii, compared with the largely White CAPRIE trial population (95% of 19,185 participants) that supported U.S. approval [170].

Statins, including atorvastatin and simvastatin, act by blocking 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thereby preventing the conversion of HMG-CoA to mevalonate, a central step in cholesterol production [138]. Statin disposition is strongly influenced by the transporter gene SLCO1B1, which encodes OATP1B1, a hepatic uptake protein essential for statin clearance through the hepatobiliary route. The SLCO1B15 allele (rs4149056, a missense variant) reduces transporter efficiency, slowing statin removal and elevating plasma concentrations. This increases the likelihood of statin-related muscle injury—ranging from mild myalgia to severe rhabdomyolysis—and risk differs by genotype (heterozygotes versus homozygotes), dosage, and the specific statin, with simvastatin showing the highest association [138, 171]. MAFs for SLCO1B15 also vary across groups:

Africans 0.01, Americans 0.13, East Asians 0.12, Europeans 0.16, South Asians 0.04 [21]. Compared with warfarin and clopidogrel, genetic studies of statins are limited [168] and remain heavily centered on White populations. For instance, in a recent statin pharmacogenomic RCT, 86% of the 408 participants were White [172], and two major GWAS investigations comprising more than 20,000 individuals included only European ancestry participants [173, 174].

Increasing ethnic representation in warfarin pharmacogenomic studies may encourage similar expansion across other drug classes, as warfarin has served as a prototype medication in this research field.

Conclusion

Overall, contemporary warfarin pharmacogenomic evidence—especially trials assessing clinical utility—mainly reflects data from White and Han-Chinese groups. Many other populations, including several non-Chinese Asian communities, Black individuals, Hispanics/Latinos, American Indians/Alaska Natives, and Native Hawaiians/Pacific Islanders, are insufficiently represented or missing entirely. Because MAFs for key variants affecting warfarin sensitivity differ markedly among populations, dosing algorithms optimized in one group can perform suboptimally in others. Although dosing guidelines now exist, they are predominantly informed by studies carried out in White cohorts. Consequently, current evidence does not adequately represent genetic diversity and may worsen disparities in health outcomes. Expanded research focused on populations that have historically been understudied is necessary to ensure equitable benefits from warfarin pharmacogenomics and to help reduce health inequities.

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