PHARMACOGENOMICS OF WARFARIN: RECENT ADVANCES

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Abstract:
Genotype-guided warfarin dosing algorithms offer a rational method to optimize warfarin dosing and possibly lower adverse medication effects. Compared to people of European ancestry, diverse communities, such as African Americans and Asian population, have higher rates of warfarin-related adverse events and larger dose variability, which suggests that these groups could stand to gain more from improved warfarin dose estimate. However, data from prospective randomised studies, which make up a large portion of the literature on genotype-guided warfarin dose, are from individuals with European ancestry. The majority of the research in different groups assesses variations that are most prevalent in populations of European ancestry, despite differences in the frequencies and consequences of variants by race/ethnicity. Algorithms are unlikely to help a wide range of populations if they do not take into account variations that are significant across racial/ethnic groups. The development of race-specific or admixture-based algorithms may enable genotype-guided warfarin dosing algorithms that are superior to those seen in people with European ancestry in particular racial/ethnic groups. The evaluation of current research assessing the therapeutic usefulness of genotype-guided warfarin dose should take these observations into account. For the practical use of warfarin pharmacogenomics to be successful, careful consideration of race and ethnicity as well as more research aimed at refining warfarin dosing algorithms across race and ethnic groups will be required. The results of the warfarin pharmacogenomics have important implications for Pharmacogenomic testing, underscoring the significance of considering race and ethnicity when identifying gene-drug interactions and developing therapeutic recommendations for pharmacogenetic testing.

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1. Introduction:

Approximately 34 million warfarin prescriptions are filled annually in the United States to reduce the morbidity and mortality associated with various hypercoagulable states [1]. Even after more direct oral anticoagulants (DOACs) were approved, warfarin remained a key component of the treatment and prevention of thromboembolic events.Warfarin, however, has a limited therapeutic index and continues to be a major contributor to drug-related adverse events resulting in hospitalization[2].Incorrect dosage greatly raises the risk of thromboembolism, bleeding, hospitalization, and death [3,4]. This risk is greatest in the early stages of warfarin therapy, and adequate therapeutic anticoagulation may lead to safer and more efficient dose of warfarin [5]. Due to the restricted therapeutic index and dose variability of warfarin, dose prediction algorithms have been created to assist patients in achieving optimal anticoagulation.Age, weight, race/ethnicity, drug interactions, and the desired International Normalised Ratio (INR) are all taken into account by these dose prediction algorithms.Genetic variations affecting warfarin dose have been incorporated into these algorithms to improve them. This has resulted in the FDA-approved warfarin labeling for the drug being updated as well [6,7].For warfarin and other coumarin anticoagulants, more than 30 genotype-guided warfarin dosing algorithms have been made available [8].However, there are few clinical guidelines that support the use of pharmacogenetic testing, and its incorporation into clinical practise has been gradual[9]. The daily dose of warfarin needed to achieve a stable therapeutic INR is estimated to be 5.1 mg in people of European ancestry, 5.7 mg in people of African ancestry, 4.4 mg in people of Latino ancestry, 3.4 mg in people of Asian ancestry, and 4.5 mg in people who are American Indian or Alaska Native (AI/AN) [10,11,12].Warfarin dose variability appears to be greatest in populations without European ancestry [13]. Additionally, Latinos and AAs are more likely than Europeans to experience poor outcomes as a result of inadequate warfarin therapy, including an increased risk for cerebral haemorrhage [14,15].

In this article, we review the available data for polymorphisms that impact the dosag e required for warfarin and the effectivene ss of genotypeguided dosing algorithms.To summarize the inclusion of racial/ethnic groups, the prevalence of genetic variants, and the effectiveness of genotype-guided dosage algorithms by racial/ethnicity, we give comprehensive data from research in diverse populations, concentrating on significant minority communities.

Warfarin Pharmacogenetic Variants

Warfarin dose requirements have been linked to single nucleotide polymorphisms (SNPs) in genes encoding proteins implicated in the drug's pharmacokinetic and pharmacodynamic processes.Cytochrome P450 family 2 subfamily C member 9 (CYP2C9) is the enzyme primarily responsible for metabolizing the more potent S-enantiomer of warfarin to an inactive metabolite (Figure1).The amino acid sequence is altered by several SNPs in the CYP2C9 gene, which results in lower enzyme activity and warfarin metabolism.Vitamin K epoxide reductase (VKORC1), an enzyme that triggers the activation of downstream clotting components, is inhibited by warfarin to produce its anticoagulant effect [16]. Single nucleotide polymorphism (SNPs) in CYP4F2, which is involved in catalyzing the conversion of free vitamin K to hydroxyl vitamin K, was shown to raise the amount of warfarin that was needed [17].Another gene with variation that affects the dose of warfarin is glutamyl carboxylase (GGCX), which acts as a chaperone for glutamyl carboxylation and contributes to activating clotting factors.

NAD(P)H quinone dehydrogenase 1 (NQO1) helps reduce vitamin K to vitamin K hydroquinone, the activating co-factor for -glutamyl carboxylase [18,19].

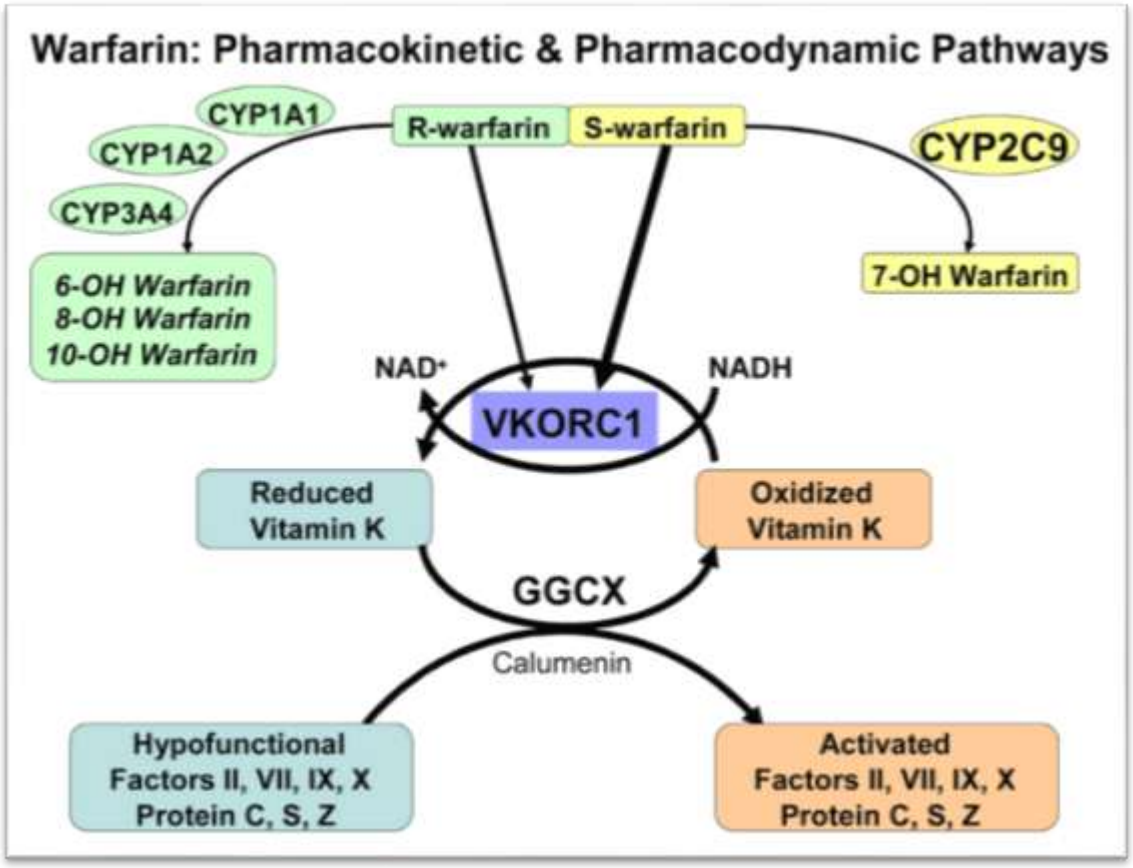

Fig no:1 warfarin genomics in different population

Warfarin Pharmacogenomics in Individuals of European Ancestry

Variants in CYP2C9, VKORC1, and CYP4F2 are thought to account for 9%, 25%, and 2%, respectively, of the variation in warfarin dose requirements in people with European ancestry. [11,20]. The Food & Drug Administration (FDA) of the United States amended the warfarin dosing label in 2010 in response to growing evidence of the influence of CYP2C9 and VKORC1 SNPs on warfarin dose requirements[10]. Based on the genotypes of CYP2C9 and VKORC1, this label contains a table with beginning dose recommendations.Even though the chart is straightforward to use in clinical settings, many other clinical aspects that can have an impact on how much warfarin needs to be administered are not taken into account.The Gauge method and the International Warfarin Pharmacogenetic Consortium (IWPC) algorithm are two of the most often used algorithms to forecast steady warfarin dose [7,13].These algorithms take race and ethnicity into account as a variable and were created in populations with a predominance of European ancestry.The majority of warfarin pharmacogenetic research, particularly those that look at the therapeutic value of genotype-guided warfarin dose, have been carried out in people with European ancestry [21].

Genotype-guided warfarin dose has not been widely adopted in the clinic despite the FDA label update and the availability of these algorithms.The Clinical Pharmacogenetics Implementation

Consortium (CPIC) strongly suggests using a patient's genotype to direct therapy due to the increased predictability to attain a stable dose when compared to standard care [9].It is crucial to note that the CPIC guidelines make the assumptions that genetic information is available at the time warfarin is started and do not include recommendations for the timing of pharmacogenetic testing.The absence of supporting data from randomised prospective trials and the expense of genotyping are two reasons given by opponents of warfarin pharmacogenetic testing.The American College of Chest Physicians (ACCP) advises against using pharmacogenetic testing to direct warfarin prescription due to a lack of data showing an increase in patient outcomes, such as bleeding and thrombotic events [22].While accessible at the time of warfarin commencement, pharmacogenetic information was not addressed in ACCP's guideline.The European Pharmacogenetics of Anti-coagulant Therapy (EU-PACT) group enrolled 454 patients and discovered that initial dosing predictions based on genotype-guided dosing instead of fixed-dosing resulted in a significant improvement in the percent of time patients were able to maintain a stable warfarin dose (67.4% vs. 60.3% time in therapeutic range (TTR), p>0.001)[23].Although a fixed dose would be more accurate for clinical practise, it is unclear whether the pharmacogenetic data or the clinical data used to predict dose were driving the observed benefit. On the other hand, the Clarification of Optimal Anticoagulation through Genetics (COAG) study in 955 patients found no difference in TTR between dosing based solely on clinical factors and predicted warfarin dosing (45.2 versus 45.4% TTR, p=0.91) [24].The warfarin derivatives acenocoumarol and phenprocoumon were examined in a second EU-PACT research using TTR for genotype-guided and clinical algorithms [25].The genotype-guided group's percent TTR was not significantly higher than that of the individuals receiving clinically-guided dose (61.6% vs. 60.2%, p=0.52) in this study.(See Supplementary Materials) [48].

The EU-PACT and COAG investigations used the IWPC and Gauge algorithms, which were developed by persons with primarily European ancestry and contain the variants CYP2C9*2, CYP2C9*3, and VCORC1-1639G>A. The COAG trial included a more diversified population of patients, including 27% AA people, compared to EU-PACT, which included a patient group with 98.5% self-reported European ancestry [24,25]. Individuals with European ancestry accounted for 52% of the variation in warfarin dose explained by the genotype-guided algorithm in COAG, while AAs accounted for as little as 17% [26].The results indicate that European-based genetic algorithms do not reliably estimate warfarin dose in AAs, and the same issue applies to other underrepresented non-European populations.

Warfarin pharmacogenetic variants in different populations

When using warfarin, patients from diverse populations face more serious health concerns than those from Europe.Compared to those of European ancestry, Asians, Latinos, and African Americans (AAs) had increased chances of warfarin-related cerebral haemorrhage outcomes [15]. Additionally, compared to those of European ancestry, TTR (time in therapeutic range) is significantly lower in African Americans, Asians, and Native Americans.African Americans had a lower median TTR than people with European ancestry, according to a warfarin management assessment (59% vs. 62% vs. 68%, p>0.0001) [14].

Similar research revealed that individuals of African, Asian, and Native American descent had lower mean TTRs than patients of European descent [17]. These

findings indicate that genotype-guided warfarin administration may be more advantageous for a variety of populations due to its improved ability to estimate doses accurately.

Early clinical observations of varied warfarin dose requirements by race/ethnicity are partially explained by differences in the frequency of warfarin pharmacogenetic variations. For example, the VKORC1 1639G>A allele is less prevalent in people of African descent, which contributes to the increased warfarin dose required in AAs.People with European, Asain ancestry are more likely to have the CYP2C9*2 and *3 alleles, whereas people with AA ancestry are more likely to have the CYP2C9*8 and *11 alleles.These differences in minor allele frequency (MAF) are compounded by the existence of race-specific variants that contribute to warfarin dose variability. The clinical applicability of genotype-guided algorithms is constrained if significant functional variations for a particular race or ethnic group are not recognised or found. The following is a summary of the literature describing these variations and their frequencies.

Individuals of African Ancestry

Most research on the pharmacogenetics of warfarin in people with African ancestry has been done in AA populations from the US.CYP2C9*2 and CYP2C9*3 are less useful in predicting the warfarin dose requirements in people of African ancestry (AAs) due to their lower prevalence compared to those of European ancestry[28] .CYP2C9*5,*6,*8,*11 and 18786T, rs12777823 in the CYP2C gene cluster, VKORC1 1639G>A, GGCX (CAA) 16/17, and CALU rs339097 are significant warfarin pharmacogenetic variations in AAs.Except for VKORC1 1639G>A, the majority of these mutations show higher MAFs in AAs than in people of European ancestry.For instance, the MAF of the CALU rs339097 is 9% in AAs and less than 1% in Europeans, which translates to an 11–15% higher warfarin dose in AAs[29].In comparison to groups of European ancestry, AAs have ten times more of the GGCX (CAA) 16/17 repeat polymorphism than do communities of European ancestry, which accounts for 2% of the variability in warfarin dose [30] New variations in VKORC1 and CYP2C9 that alter the dosage of warfarin were discovered in a focused resequencing analysis of AAs[31].VKORC1 and CYP2C9 were substantially linked to higher warfarin dosages and an enhanced R2 for the warfarin dosing algorithm.A more recent genome-wide association study (GWAS) of warfarin dose variability in AAs found a substantial correlation with rs12777823 G>A, a variant in a gene whose effects on warfarin dose requirements were unknown at the time[32].In comparison to people with the GG genotype, people heterozygous for the A allele needed 6.92 mg less of warfarin per week, and people homozygous for the allele needed 9.34 mg less.The CYP2C9*5, *6, *8, and *11 alleles are present in almost all populations of African ancestry [18].

Individuals of Asian Ancestry

Asian communities, especially those from China, have been better investigated in terms of warfarin pharmacogenomics than people with European ancestry.With a few exceptions, these studies are more likely to concentrate on creating new algorithms based on clinical data and well-known European variations than on discovering novel variants or demonstrating the therapeutic value of genotype-guided algorithms [10,33,34].Additionally, only a small number of these research have been conducted in Asian populations in the US.The variants identified that are known to significantly influence warfarin dose requirements include CYP2C9*3, VKORC1-1639A, and CYP4F2*3. Similar to populations of European ancestry, the total variability in warfarin dose explained

by CYP2C9*3, VKORC1-1639A, and CYP4F2*3 is estimated at 40–63% in Asian populations34]. Asian populations have a significantly higher (90%) prevalence of the VKORC1-1639 A allele than do people of other races or ethnicities, which helps to explain why Asian patients require lower doses of warfarin[10].Similar to a study in people of European ancestry, variations in the cytochrome p450 oxidoreductase gene have recently been discovered to impact the warfarin dose requirements in Chinese patients [35].

Genotype-guided warfarin dosing algorithms in different populations

In terms of warfarin pharmacogenomic testing, those with a predominance of European ancestry are by far the most well investigated racial or ethnic group.Algorithms that were developed in populations of European ancestry may miss important variants in other race/ethnic groups. Additionally, variations may change in their effects based on the racial or ethnic group, resulting in use of incorrect effect sizes and incorrect dose estimates[36]. The literature analysing the effectiveness of warfarin pharmacogenetic algorithms developed in Europe and also the development of race-specific algorithms in other populations is summarized in the section that follows.

Individuals of African Ancestry

The effectiveness of genotype-guided warfarin dosing algorithms in AAs has been examined in a number of studies (See Supplementary Materials S3) [15]. Comparing AA patients to those of European ancestry, studies that genotype polymorphisms from populations of European ancestry find a comparatively low amount of variance explained [37]. This finding is in line with the findings of the COAG study, which used a European-derived algorithm and found that AAs' unfavorable outcomes increased while their time in the therapeutic range reduced[15] (See Supplementary Materials S2). Following research, AA-specific algorithms were created that take into account CYP2C9*5, *6, *8, *11, and rs12777823 variations with warfarin dose effects in AAs.According to these research, the IWPC (R2=0.26) and other conventional genotype-guided algorithms do better (R2=0.38) [38].Recently, revised warfarin CPIC recommendations advised a race-stratified method for genotype-guided dosage in AAs[13]. This suggests that genotype-guided dosing will not have as much clinical utility in AAs as in individuals of European ancestry in the absence of identifying and incorporating additional variants influencing dose in AAs. In any case, the data highlight the limited amount of prospective randomized trials evaluating variants from AAs in genotype-guided warfarin dosing algorithms.

Individuals of Asian ancestry

Studies that assess the effectiveness of genotype-guided warfarin dosing algorithms in populations of Asian ancestry have been reported in a number of size(See Supplemental Materials, Table S5). There are very few research on Asian populations in the US, with most of them being conducted on people from China, Korea, and Japan. Variants like CYP2C*3 and VKORC1 1639A, which are related with warfarin response in European populations but are much less common in Asian populations, are heavily studied in these studies.The effectiveness of algorithms created in people with Asian ancestry compared to conventional pharmacogenetic algorithms has been assessed in numerous research.Algorithms developed in populations of Asian ancestry perform comparably or slightly better than Gage and/or IWPC algorithms as indicated by R2. This outcome is in line with population similarities to people of European origin in terms of allele frequencies. Similar to the work on

Latinos, these algorithms frequently use distinct clinical characteristics than conventional dosage algorithms and are tested on the same population in which they were developed, which is likely to improve algorithm performance.

Comparatively to other diverse populations, Asian Americans have been examined more thoroughly, yet the body of research highlights the neglect of variants outside of conventional genotype-guided dosage algorithms.The genetic diversity among Asian groups with more African and European ancestry, which is likely to exist in the US, is not likely to be captured by people from China, Korea, and Japan. Therefore, when deciding if and which genotype-algorithms should be employed clinically, it will be crucial to take into account the diversity of other Asian groups.

Overview of Observations and Limitations in the Evidence

While variations tend to affect warfarin dose requirements similarly regardless of race or ethnicity, variations may contribute to warfarin dose variability differently depending on the frequency of these variations. Variants found in populations of European ancestry may account for the majority of variation in warfarin dose for some ethnicities, such as communities of Asian ancestry. However, new variations altering the dose of warfarin have been found in AAs. The discovery of novel polymorphisms impacting warfarin dose in AAs, Latinos, and AI/AN groups, however, raises the possibility that variants found in populations of European ancestry may not adequately capture contributions to the heterogeneity of warfarin dose among other populations. This implies that it may be crucial to incorporate these novel variants in genotype-guided algorithms to increase the predictability of warfarin dosing in a variety of racial/ethnic groups. The majority of studies in diverse race/ethnic groups have sought to replicate associations of known variants rather than identify new variants

In the future, research aiming at finding novel polymorphisms impacting warfarin dose variability will probably be required if genotype-guided therapy is to be used in these groups. Instead of single SNP genotyping, these investigations would have to use sequencing and/or GWAS, which would be more expensive and lead to the discovery of new relationships. Additionally, a sustained effort will probably be needed to find new polymorphisms due to the considerable genomic variety in the US and around the world [39].The accuracy of genotype-guided warfarin dosing algorithms in minority populations has been improved through a number of studies. However, rather than identifying novel variants among other racial/ethnic groups, these studies frequently assess clinical and genetic characteristics obtained from populations of European ancestry.

Future Directions

Warfarin is probably going to continue to be a significant oral anticoagulant despite rising DOAC use. A number of clinical considerations, such as FDA-approved indications, worries about bleeding risk, contraindications in valvular heart disease, and availability/cost of an antidote in the event of overdose, may limit the use of DOACs in certain socioeconomic populations.

Given the significant role that warfarin plays in adverse events, increasing dose accuracy should remain a top objective if the medicine is still widely used in clinical practice[4]. Whether genotype-guided dosing algorithms, clinical algorithms, or other techniques are used to boost dosing accuracy, race and ethnicity must be taken into account because minorities have higher incidence of adverse events and increased dose variability.

Warfarin Dosing Algorithms Selected Using Genotype Information in Various Populations

Any genetic study, including pharmacogenomics, must take race and ethnicity into account.In the past, numerous studies have purposefully excluded people of different racial and ethnic backgrounds in order to rule out population stratification[30].This brings to light one possible explanation for the scant data in non-European racial/ethnic groupings.

Genotype-guided warfarin dosing provides a case study that has broader significance across pharmacogenomics. Moving forward, any implementation of racial/ethnic consideration will likely be necessary for genotype-guided warfarin dose algorithms. More research is required to determine the effects of current variants or new variants in other racial/ethnic groups because the evidence for many drug-gene pairings is mostly found in people of European ancestry. For some populations, it would make sense to employ European-derived algorithms, but this strategy is unlikely to hold true for other populations. It is anticipated that different algorithms will need to be developed for several racial/ethnic groups in order to maximise the utility of pharmacogenomics. This idea is supported by recent results from population pharmacokinetic models[40].

The updated CPIC guidelines for genotype-guided warfarin dosing incorporates substantial changes based on African ancestry [9]. In patients with African ancestry, CPIC now recommends a 15–30% warfarin dose decrease if a patient possesses the CYP2C9*5, *6, *8, or *11 allele and advises against employing genotype–guided dosing if these alleles are not captured.The updated recommendations advise a 10–25% dose reduction in rs12777823 A carriers if patients are African Americans, which refers to people who originate primarily from West Africa. All non-African ancestry patients are managed using the European-derived algorithms from earlier CPIC recommendations, with possible dose reductions for those who carry the CYP2C9*5, *6, or *11 allele as well as the CYP4F2 rs2108622 T allele. It is unclear if a new algorithm needs to be created for portions of ancestral populations. It is important to take into account patient mixing, particularly in US demographics. For the selection of the best algorithms or the inclusion of an admixture variable, admixture mapping may be necessary.

It is unlikely that an accurate algorithm could be developed for each nationality or individual race/ethnic group. There has been some progress in creating these models, and the consideration of mixing will be especially crucial for US populations. Additionally, methods like artificial neural networks and machine learning have been researched

Clinical Implementation of Genotype-Guided Warfarin Dosing Algorithms

Whether clinical implementation is supported by the available evidence is a key factor in determining the future course of warfarin dosing algorithms. The FDA has revised the labelling of warfarin to include genetic data, and recommendations for the clinical translation of genotypes are now accessible[6,9]. The limited clinical utility of pharmacogenetic testing observed in randomized controlled trials performed in individuals of European ancestry may not be generalizable to other race/ethnic groups. Based on the poor performance of genotype-guided algorithms in AAs, additional randomized trials may be needed in AAs and potentially other race/ethnic groups.

Thus a key issue in implementation is the threshold of evidence at which pharmacogenomics testing should be incorporated in the clinic.Some organizations contend that since a current

drug is being improved rather than a new medicinal entity, randomised controlled trials are not necessary. These organizations point to the inclusion of renal dosage adjustments in clinical treatment as well as a number of other clinical modifications that lack sufficient evidence to be supported by randomised controlled trials. Given that personalized care is provided using a randomised treatment scheme, a randomised controlled trial for personalized medicine may seem like a contradiction in terms[43]

Considerations for Pharmacoeconomics

A pharmacoeconomic threshold of evidence is suggested by one argument. That is, the incorporation of genetic testing into practise should occur once the testing has been financially justified because no new drugs are being licensed at this time. The CPIC guidelines, which suggest using Pharmacogenomic data when it is available rather than ordering genetic testing every time a new warfarin prescription is authorized, indirectly promote this strategy by effectively avoiding issues about cost effectiveness [43]. This is a reasonable approach considering that no additional cost is incurred for testing, yet data are still used to improve dosing recommendations.

Warfarin pharmacogenetic testing may have enhanced quality-adjusted life years (QALY) gained, but not to a level where it was cost-effective, according to earlier cost-effective analysis studies conducted in 2009 and 2010 [44-47].The calculated cost-effectiveness ratios of the studies ranged from $50,000 to over $170,000 per QALY, with costs being most significantly influenced by the cost of genetic testing, the clinical outcome, the time it took to receive the results of the genetic testing, and the propensity of high risk patients to bleed or clot while receiving warfarin therapy.

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Genomic information should be available for the majority of patients as standard of care as genotyping becomes more accessible and precise as a result of technological improvements. This would eliminate the need for genotyping ancestral markers and pharmacogenomics variants, as well as making incorporation into clinical care more likely. Implementing pharmacogenomics can be viewed as premature until genome sequencing is routinely performed in clinics. Whatever the case, as more and more patients get access to their genomic information, study into the impact of variations on treatment response will help guide clinical practise.

2. Conclusion:

The majority of genotype-guided warfarin dose research that has been published comes from populations of European ancestry. Additionally, the majority of research in groups with a wider range of genetic backgrounds assesses genetic variance in different populations with European ancentry.Pharmacogenetic testing must be done in these populations, although the frequency and impact of variations may vary depending on race and ethnicity, necessitating additional research in varied communities. The development of race-specific or admixture-based algorithms may enable enhanced safety and efficacy of warfarin beyond that seen in people with European ancestry in some racial/ethnic groupings.Finally, the data from warfarin pharmacogenomics may have broader implications for Pharmacogenomic testing, highlighting the importance of taking race and ethnicity into account when identifying gene-drug combinations and creating guidelines. It is necessary to take into account genotypes that are significant across populations in order to provide a broad benefit from genotype-guided warfarin dose.

Supplementary Material

Refer to Clinical Pharmacogenetics Implementation Consortium (CPIC)

Guideline for Pharmacogenetics-Guided Warfarin dosing[48].

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