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The pharmacogenetics of the response to warfarin in Chinese

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Warfarin is a commonly used oral anticoagulant with a narrow therapeutic range and large interindividual variability in daily dose. Compared with Caucasians, Chinese are known to require lower doses of warfarin. Differences between Caucasians and Chinese in the allelic frequencies of two genes, *CYP2C9* and *VKORC1*, largely explain the difference in dose requirement. There are other genetic polymorphisms that may further explain the response to warfarin. The *VKORC1* genotype is an important determinant of response to warfarin in Chinese, but some genetic variants found in other ethnic groups that have a large effect on warfarin response and dosing are not commonly found in Chinese. Therefore, it is important to recognize and beware of ethnic differences in the pharmacogenetics of the response to warfarin, especially in the design of algorithms to aid dosing in clinical practice.

Introduction

Warfarin, a commonly used oral anticoagulant, is indicated for the prevention and treatment of thromboembolic events in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation and prosthetic heart valves. It is a racemic mixture of *S*-warfarin and *R*-warfarin, with *S*-warfarin being the more active isomer and having a greater therapeutic effect. As shown in Figure 1, these enantiomers are extensively metabolized by various cytochrome P450 enzymes. *R*-Warfarin is mainly metabolized by cytochrome P450 1A2 (CYP1A2), CYP2C19 and CYP3A4, while *S*-warfarin is predominantly metabolized by CYP2C9. Both enantiomers affect the coagulation cascade by inhibiting the activity of vitamin K epoxide reductase complex 1 (VKORC1) and thus interfering with the activation of clotting factors II, VII, IX and X (Figure 1). Warfarin has a narrow therapeutic window, with potentially life-threatening consequences for under- or overdosing; therefore, frequent monitoring of its effect, as measured by the international normalized ratio (INR), is warranted. Moreover, the large interindividual variations in dose response make warfarin dosing a challenging task. In general, the initial phase of warfarin dosing requires 4–6 weeks of frequent clinic visits, blood tests and fine adjustment of dosage. Besides patients' clinical characteristics, such as age, gender, bodyweight, concurrent medications, diet, comorbidities and patient compliance level [1], genetic variations have also been shown to have a large influence in warfarin dosing.

Two genes, *CYP2C9* and *VKORC1*, have been identified as important genetic determinants of warfarin dosing and have been studied intensively over the last decade. The most common *CYP2C9* genotype among all ethnic groups is *CYP2C9*1*, found in around 80% of Caucasians and 95% of Chinese [2]; however, a major difference is observed between the Caucasians and Chinese in the allelic frequency of *CYP2C9*2* (Table 1). About 10–15% of Caucasians harbour this allele, but is absent in most Chinese. Gene variants of *CYP2C9* are associated with a lower warfarin dose requirement. In a meta-analysis by Lindh *et al*. [3], carriers of *CYP2C9*2* and *CYP2C9*3* alleles required lower warfarin doses than carriers of the wild-type *CYP2C9*1* genotype (19.6% lower warfarin dose for those with **1/*2* genotype than those with **1/*1* genotype; 33.7% lower for **1/*3* genotype; 36.0% lower for **2/*2* genotype; 56.7% lower for **2/*3* genotype and 78.1% lower for **3/*3* genotype).

Different allelic frequencies are also observed with the two most common single nucleotide polymorphisms (SNPs) in the *VKORC1* gene, −1639G>A (rs9923231) and 1173C>T (rs9934438) (Table 2). Around 35% Caucasians carry the CC genotype of the 1173C>T variant, but only about 15% carry the TT genotype; however, the majority of Chinese (69–85%) carry the TT genotype, while only a handful of them (1–6%) carry the CC genotype. Similar findings are seen with the −1639G>A variant. Allelic frequency is the highest in the GG genotype (36%) and lowest in the AA genotype (15%) with the Caucasian

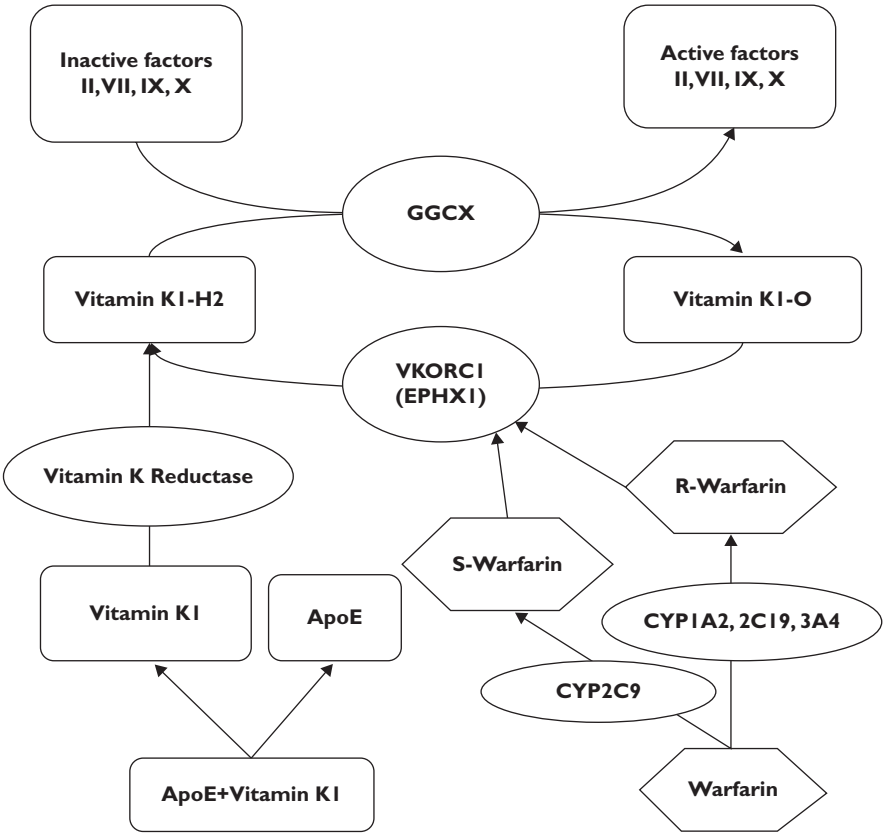

Figure 1

Mechanism of action for warfarin. Circulatory vitamin K_1, being carried by apolipoprotein E (ApoE), is taken up by receptors. It is then reduced to vitamin K_1H_2 by vitamin K reductase. The reduced vitamin K_1H_2, as a cofactor for γ-glutamyl carboxylase (GGCX), converts the inactive Factors II, VII, IX and X to the active forms that are required for coagulation. Vitamin K epoxide reductase complex 1 (VKORC1) and possibly epoxide hydrolase 1 (EPHX1) catalyse the reduction of vitamin K_1O. Warfarin, after being metabolized by cytochrome P450 isoforms to *R*-warfarin and *S*-warfarin, inhibits VKORC1, decreases the amount of vitamin K_1H_2 and thus interferes with the activation of clotting factors

Table 1

Allelic frequencies of selected polymorphisms in *CYP2C9* in different countries/regions

*2C9*1* (wild-type) (%)	*2C9*2* (rs 1799853) (%)	*2C9*3* (rs1057910) (%)	Country/ region	Reference
76	13	11	Israel	[20]
83	12	5	USA	[35]
82	11	7	Sweden	[36]
77.2	14.9	7.9	Italy	[37]
98	0	2	Singapore*	[29]
95.3	0	4.7	Malaysia†	[38]
97	0	3	Taiwan	[30]
96	0	4	China	[39]

*Subjects comprised Chinese, Malays and Indians, with Chinese being the predominant group. †Subjects were all Malaysian Chinese.

Table 2

Allelic frequencies of selected polymorphisms in *VKORC1* in different countries/regions

Reference SNP	Genotypes			Country/region	Reference
rs9934438	CC (%)	CT (%)	TT (%)		
(1173C>T)	36.8	46.9	16.3	Italy	[40]
	36.1	50.7	12.7	USA	[13]
	34	49	17	France	[41]
	1	14	85	China	[41]
	1.11	14.76	84.13	China	[19]
	6	25	69	Hong Kong	[42]
rs9923231	AA	AG	GG		
(–1639G>A)	14.9	48.9	36.2	Sweden	[36]
	16.5	48.2	35.3	Sweden	[43]
	79.8	18.3	1.9	Taiwan	[44]
	83.7	15.7	0.6	China	[39]
	85.76	13.29	0.95	China	[19]

Table 3

Summary of algorithms for warfarin dosage in Chinese populations

Study	*VKORC1*	*CYP2C9**	Age	Weight or body surface area	Other factors	Subjects' ethnicity	R^2	Dosage variation explained (%)	Reference
Gu *et al.*	•	•	•	Weight	+ *EPHX1* + *CYP2C9* C_{-65}	Han Chinese in China	0.743	74.3†	[18]
Huang *et al.*	•	•	•	Body surface area	–	Chinese in China	0.541	54.1	[45]
Miao *et al.*	•	•	•	Weight	–	Han Chinese in China	0.628	62.8	[39]
Sandanaraj *et al.*	•	•	•	Weight	–	Chinese in Singapore	Not reported	74.2	[46]
Tham *et al.*	•	•	•	Weight	–	Asians in Singapore	Not reported	60.2	[47]
Wang *et al.*	•	•	•	Weight	+ *EPHX1* + *CYP2C9* C_{-65}	Han Chinese in China	0.402	40.2	[19]
Wen *et al.*	•	•	•	Body surface area	+ Hypertension	Han Chinese in Taiwan	Not reported	62‡	[48]
Wu *et al.*	•	•	•	Weight	+ Smoking + Height + Gender + *CYP2C9* inhibitor§	Various ethnicities in San Francisco¶	Not reported	59	[49]
Yang *et al.*	•	•	•	Weight	–	Han Chinese in China	0.513	51.3	[50]
You *et al.*	•	•	•	Weight	+ Vitamin K	Chinese in Hong Kong	0.68	68	[42]

*Apart for the studies by Sandanaraj *et al.* [46] and Wu *et al.* [49], *CYP2C9*2* polymorphism was excluded. †In patients without concomitant medication; 70.4% of the variation was explained in patients with concomitant medication, including amiodarone, simvastatin, allopurinol, acetaminophen, fluvastatin, atorvastatin, carbamazepine and omeprazole. ‡From a single hospital site; 48.2% of the variation was explained with multiple sites. §Included amiodarone or sulfamethaoxazole. ¶Ethnicity included Caucasians, African-Americans, Asians (mostly Chinese), Hispanic-Americans and other (possibly mixed ethnicities).

population. The opposite trend is observed with the Chinese population; only 1% has the GG genotype and 83% the AA genotype. Yang *et al.* [4] reported that carriers with genotypes –1639GG and –1639GA required warfarin doses 102 and 52% higher, respectively, than those with –1639AA. When compared with the carriers with genotype 1173TT, carriers with genotypes 1173CC and 1173 CT required a dose of warfarin 97 and 44% higher, respectively.

Warfarin dosing algorithm

Several warfarin dosing algorithms that incorporate clinical characteristics and genetic information have been developed for better estimation of warfarin dosing. None of these algorithms was intended to replace the requirement of INR monitoring, but to increase the accuracy and reduce the trial-and-error approach of warfarin dosing, especially during the initial phase. As shown by the International Warfarin Pharmacogenetics Consortium study [5], the addition of genetic information to clinical information increased the accuracy of dose estimation when compared with the clinical algorithm or fixed-dose approach and was especially beneficial to patients with higher risk of overdosing or underdosing.

As mentioned earlier, ethnicity is one of the important factors that influence warfarin dose requirement, and variations in allelic frequencies among different ethnic groups have been observed. It comes as no surprise that ethnic-specific dosing algorithms have been developed, and some of them were for the Chinese. Chinese patients are known to be more sensitive to warfarin; they require lower doses of warfarin than Caucasians. In the study by Yu *et al.* [6], the mean dose of warfarin in Hong Kong Chinese was 3.3 mg daily, while the usual warfarin daily dose for Caucasians was 4–6 mg. Moreover, as shown in a study by You *et al.* [7], the Chinese had a high incidence of major bleeding, such as gastrointestinal bleeding, gross haematuria or haemoptysis, even when the INR was slightly increased but still within the therapeutic range. Studies that have included genotype information in the dosing algorithms for the Chinese population are summarized in Table 3. The use of clinical factors (for example, age, weight/body surface area, gender and concurrent medications) alone can account for approximately 20% of warfarin dose variability [8]. With the introduction of genetic factors into the algorithm, a higher percentage of dosage variation can be explained. As shown in Table 3, between 48 and 74% of the dose variation can now be explained with the incorporation of *VKORC1* and *CYP2C9* genotypes. One notable difference in most of the algorithms listed in Table 3, when compared with other algorithms for Caucasians, is the inclusion of the *CYP2C9*3* variant but not the *CYP2C9*2* variant. The main reason for the exclusion of the *CYP2C9*2* variant in the algorithms is mostly due to its rarity in the Chinese population, as shown in Table 1 [2, 9].

Other genetic polymorphisms

Although the incorporation of *CYP2C9* and *VKORC1* can explain more warfarin dosage variation than clinical

Table 4

Summary of the effects of other genetic polymorphisms that might influence warfarin dosage

Gene	Reference SNP	Country/region	Minor Variant	Frequency (%)	Contribution to dose variance (%)	Reference
CYP4F2	rs2108622	USA	T	30	2	[11]
		USA	T	25	4	[12]
		USA	T	31.15	5	[13]
		China	T	28	4	[14]
		Singapore*	T	17	3	[15]
		Taiwan	T	23.6	Not significant	[16]
		Singapore*	A†	24.4	3	[51]
EPHX1	rs4653436	USA	A	31.8	Not significant	[13]
		China	A	24.85	Not reported‡	[18]
		China	A	25.31	Not reported‡	[19]
	rs1877724	Taiwan	T	31.95	1.84	[16]
		Singapore*	T	34.8	0.8	[51]
	rs1051740	Israel	C	25	Not significant	[20]
	rs2234922	Israel	G	24.2	Not significant	[20]
GGCX	rs12714145	Sweden	A	40.8	Not significant	[23]
		USA	A	29.7	Not significant	[25]
		China	A	34.3	2.3	[26]
		China	T	41.19	Not significant	[19]
		Taiwan	A	32.3	Not significant	[16]
	rs11676382	USA	G	7.55	0.3	[25]
		Taiwan	G	0	Not significant	[16]
ApoE		Sweden	ε4	19.1	6§	[28]
		Singapore¶	ε4	7	Not significant	[29]
***CYP2C9 C*$_{-65}$**	rs9332127	USA	C	0	Not significant	[30]
		Taiwan	C	5.8	Not reported**	[30]
		China	C	4.25	Not reported**	[19]
		China	C	4.35	Not reported**	[18]

*Subjects comprised of Chinese, Malays and Indians, with Chinese being the predominant group. †Genotypes were reported in reverse orientation. ‡Although the contribution to dose variance was not reported, it was reported that subjects with the A allele required a higher dose of warfarin. §Within the *CYP2C9*1/*1* group, with age as a covariate. ¶Subjects comprised Chinese, Malays and Indians, with Chinese being the predominant group. **Although the contribution to dose variance was not reported, it was reported that subjects with the C allele required a lower dose of warfarin.

factors alone, there is at least 26% of the dose variability that remains unaccounted for. Other genes, such as *CYP4F2*, epoxide hydrolase 1 (*EPHX1*), γ-glutamyl carboxylase (*GGCX*), apolipoprotein E (*ApoE*) and *CYP2C9 C*$_{-65}$, have been investigated recently. A summary of the effects of these genetic polymorphisms on warfarin dosage is listed in Table 4.

CYP4F2 is another cytochrome P450 enzyme that is involved in the metabolism of vitamin K, and its polymorphism could result in altered vitamin K levels as well as warfarin dose requirements [10]. About 30% of the Caucasian population carries the minor allele of SNP rs2108622, which explains 2–5% of the variance in dose [11–13]. A study by Cen *et al*. [14] showed that 28% Han Chinese carried a variant copy of *CYP4F2* and reported that this polymorphism contributed to about 4% of the variance in warfarin dose of the Chinese population. Likewise, Singh *et al*. [15] reported that 17% of Asians (predominant with Chinese) carried the minor allele of *CYP4F2*. It was estimated that approximately 3% of the variation in warfarin dosage variance can be explained by *CYP4F2*. However, a study by Lee *et al*. [16] did not find that this polymorphism significantly influenced warfarin dosage in Chinese. Nonetheless, similar contributions of this SNP (2–5%) to warfarin dose variance were observed in both Caucasian and Chinese populations.

Epoxide hydrolase 1 is another subunit of VKORC1 (Figure 1), which is located in the endoplasmic reticulum [17]. A study by Carlquist *et al*. [13] in the USA showed that the frequencies of the genotypes GG, GA and AA for SNP rs4653436 were 44, 48.2 and 7.7%, respectively. However, no difference was found in warfarin dosage requirement among the different alleles. Gu *et al*. [18] and Wang *et al*. [19] reported that approximately 55% of the Chinese population carried the GG genotype, 41% the GA genotype and 4% the AA genotype. Both studies showed that there was a small but significant correlation between polymorphism of *EPHX1* and warfarin dosing requirement. Gu *et al*. [18] demonstrated that patients with GG or GA genotypes required lower warfarin dosage than those with AA genotype, while Wang *et al*. [19] showed that *EPHX1* was one of the significant variables to the warfarin dosing algorithm. A study by Loebstein *et al*. [20] has shown that two other SNPs (rs1051740 and rs2234922) were not signifi-

cant in contributing to the warfarin dose variance. However, another SNP (rs1877724), reported by both Lee *et al*. [16] and Chan *et al*. [21], was shown to have an additional contribution to dose variance by 0.8–1.8%. Although more studies are needed before firm conclusions can be drawn, it appears that *EPHX1* variants have different impacts in Caucasian and Chinese populations. Similar frequencies of minor alleles of *EPHX1* variants were reported, around 25–35%, in the two populations, but *EPHX1* variants added relatively small but significant contributions to warfarin dosage variance in the Chinese but not in the Caucasians.

As shown in Figure 1, GGCX is another enzyme essential for the vitamin K-dependent clotting factors and coagulation pathway [22]. Wadelius *et al*. [23] reported that the frequency of the A allele (minor allele) of SNP rs12714145 was 40.8% and that carriers of this allele would have a higher warfarin dosage requirement (3.3% more than those with the G allele) [24]. However, the allele did not contribute significantly to additional warfarin dosage variance. King *et al*. [25] also found that this SNP did not have any impact on warfarin dose prediction. The minor allelic frequency of this SNP in the Chinese population, as reported by Lee *et al*. [16], Wang *et al*. [19] and Huang *et al*. [26], is around 32–40%. Huang *et al*. [26] demonstrated that this variant could account for 2.3% of the variance of individual warfarin dose requirement, whereas Lee *et al*. [16] and Wang *et al*. [19] could not detect such a significant association. Lee *et al*. [16] also pointed out that a significant association of the *GGCX* polymorphism with warfarin dosing was observed in the Caucasian and Japanese populations, but this association could not be replicated in the Han Chinese population. Another SNP of *GGCX*, rs11676382, was reported by Lee *et al*. [16] and King *et al*. [25]. While King *et al*. [25] reported that 7.55% of Caucasians carried the minor allele (G allele) and contributed 0.3% to warfarin dosage variance, neither study could detect the G allele in the Chinese population. Unlike *EPHX1*, which has similar allelic frequency but different impact in different ethnicities, the impact from *GGCX* variants, if any, was small and similar across different ethnic groups.

Apolipoprotein E is a glycoprotein that plays a central role in the uptake of vitamin K [27]. Allelic frequencies of *ε2*, *ε3* (wild-type) and *ε4*, as reported by Kohnke *et al*. [28], were 6.0, 74.9 and 19.1%, respectively, in a Swedish population. They demonstrated that *ε4* homozygous patients required a significantly higher warfarin dose (56.9 mg week^{-1}) than those with one or no *ε4* alleles (34.3 and 34.6 mg week^{-1}, respectively). Lal *et al*. [29] studied the influence of *ApoE* genotype on warfarin dose requirement in Asian patients (predominantly Chinese); 78% of the subjects carried the wild-type genotype, but no significant influence on warfarin dosing requirement was found among different *ApoE* genotypes.

Besides the most common *CYP2C9*2* and *CYP2C9*3* alleles, other *CYP2C9* polymorphisms have also been studied and identified. A novel genotypic polymorphism, *CYP2C9* C_{-65} (rs933127), was reported in Taiwan Han Chinese by Chern *et al*. [30]. The frequency of C_{-65} variant allele (GC or CC genotype) was 5.8% for the Taiwan Han Chinese, but not detectable in Caucasians. Carriers of this variant allele were found to require significantly lower daily warfarin doses than those with the GG genotype. Gu *et al*. [18] reported that Han Chinese with GC or CC genotypes required lower warfarin dosages (0.9 $\pm$ 0.2 mg day^{-1}) than those with the GG genotype (3.3 $\pm$ 1.2 mg day^{-1}). Similar findings were shown by Wang *et al*. [19]. Both Wang *et al*. [19] and Gu *et al*. [18] found that this variant allele was one of the strong predictors of warfarin dosage and was incorporated into their dosage algorithms.

The studies on polymorphisms of *CYP4F2*, *EPHX1*, *GGCX*, *ApoE* and *CYP2C9* C_{-65} showed that these have minimal and often undetectable effects on warfarin requirement, yet they have demonstrated that their impacts are subject to the prevalence of genetic variants in the ethnic population. One good example of how this difference can affect the capability of warfarin dosing algorithms to explain dose variability is the prevalence of *CYP2C9*8* among African-Americans. *CYP2C9*8*, another *CYP2C9* polymorphism, was reported by Scott *et al*. [31] as the most prevalent variant allele among African-Americans, instead of *CYP2C9*2* or **3*. Approximately one in 11 (0.047) African-Americans were carriers of this variant allele, while only one in 50 (0.010) Asians were carriers of this allele. As a result of lower frequencies of the more common alleles (e.g. *CYP2C9*2* or **3*), the warfarin dosing algorithm explains dose variability less well in African-Americans than in Caucasians. Thus, identification and incorporation of ethnic-specific genetic factors may facilitate better prediction of warfarin dosage in algorithms.

Possible pitfalls when evaluating results in Chinese/Asian populations

When Asians from China, Hong Kong, Taiwan, Singapore, Malaysia, Vietnam and other Southeast Asian or Asian countries are combined as a single group for investigation, information pertinent to the study (patient demographics and results) should be broken down into each ethnic group, because differences exist among ethnic groups. For example, Lee *et al*. [32] demonstrated that out of the five East Asian populations (Han Chinese from Taiwan, India, Indonesia, Philippines, Thailand and Vietnam) that they have studied, the *VKORC1* haplotype structure in the Indian population was significantly different from the other four Asian populations. The H7 haplotype was the major haplotype in the Indian population (76%), whereas H1 haplotype was the predominant one in the rest of the populations studied. A similar finding was shown in a study by Gan *et al*. [33]; the allelic frequency distribution of *VKORC1*

genotypes was similar in the Chinese and Malay populations but different in the Indian population. The genotype frequencies for *VKORC1* −1639AA and −1639GG for all the study participants were 50 and 21%, respectively. When broken down by patients' ethnicity, however, the genotype frequencies for −1639AA and −1639GG were 67 and 6%, respectively, for Chinese and 7 and 80%, respectively, for Indians [33]. This study demonstrated that extra care should be taken when results are pooled from different populations, even from the same geographical area.

Another possible pitfall happens when pooling results of the Han Chinese population of different regions. Although Han Chinese is the largest subethnic group in China, numerous subethnic groups are found in China. Different allelic frequencies have been found among different Chinese subethnic groups, as shown by Ross *et al*. [34]. The C allele of *CYP2C9*3* is absent in the Han population; however, it was present in more than 10% of the Tu, Tujia and Xibo subethnic groups. All Han and Oroqen populations were found to be carriers of the T allele of *VKORC1* SNP rs9923231, while only 75% of the She population were carriers of this allele. With the growth in China's urbanization and globalization, more ethnic minorities who used to live in rural communities are moving to the big cities. With interethnic marriages, the ethnic minorities will be less genetically and culturally distinct. This means that ethnic minorities will be less easily identified by their names, their place of abode and their cultural habits.

Conclusions

There is no doubt that different genotype compositions exist between different ethnic groups; the concept of 'one size fits all' might not be applicable to warfarin dosing algorithms. Although there may still be pharmacogenetic factors influencing warfarin response that have eluded us, what we already know serves to heighten our awareness of the important contribution of genetic polymorphism to dosage variability. Warfarin, a medication with a narrow therapeutic window that is commonly used, is a good starting point for personalized medicine and demonstrates its potential and importance. A better understanding of the genetic polymorphisms in individuals can facilitate the dosing of warfarin in a more accurate and timely manner that could lead to better clinical outcomes.

Competing Interests

There are no competing interests to declare.

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