Supplemental Table S1. Genotypes that constitute the * alleles for CYP2C9			
Allele	Constituted by genotypes at:	Amino acid changes	Enzymatic Activity
*1	reference allele at all positions		Normal
*2	C>T at rs1799853	R144C	Decreased
*3	A>C at rs1057910	I359L	Decreased
*4	T>C at rs56165452	I359T	Decreased
*5	C>G at rs28371686	D360E	Decreased
*6	delA at rs9332131	273frameshift	Null
*7	C>A at rs67807361	L19I	
*8	G>A at rs7900194	R150H	Decreased
*9	A>G at rs2256871	H251R	
*11	C>T at rs28371685	R335W	Decreased
*12	C>T at rs9332239	P489S	Decreased
*13	T>C at rs72558187	L90P	Decreased
*14	G>A at rs72558189	R125H	Decreased
*15	C>A at rs72558190	S162X	Null
*16	A>G at rs72558192	T299A	Decreased
*17	1144C>T	P382S	
*18	A>C at rs1057910, A>C at rs72558193, A>T at rs1057911	I359L; D397A	Decreased
*25	delAGAAATGGAA at rs72558188	118frameshift	Null
*33	G>A at rs72558184	R132Q	Decreased
Bases reported on the positive chromosomal strand from Golden Path. See http://www.pharmgkb.org/do/serve?objId=PA126&objCls=Gene for updates on CYP2C9 alleles and nomenclature			

Supplemental Table S2. Minor allele frequencies for CYP2C9 and VKORC1 SNPs in major populations			
Allele	White (n=3062)	Asian (n=1063)	Black (n=645)
CYP2C9*2	0.13	0	0.03
CYP2C9*3	0.07	0.04	0.02
Allele	White (n=2426)	Asian (n=883)	Black (n=643)
VKORC1: -1639G>A (rs9923231)	0.39	0.91	0.11

Frequencies are calculated using the genotype informationfrom subjects in International Warfarin Pharmacogenetics Consortium [38, 54].

Detailed CYP2C9 and *VKORC1* allele frequency information is available on the PharmGKB website (http://www.pharmgkb.org/search/annotatedGene/cyp2c9/variant.jsp, http://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp

Supplemental Table S3. Evidence linking genotype with phenotype

Type of experimental model	Major findings	References	Level of evidence
In vitro	CYP2C9 is the primary enzyme catalyzing the metabolism and inactivation of S-warfarin.	[41, 55, 56]	high
In vitro	CYP2C9*2 is associated with reduced catalytic activity. Substrate affinity is not affected substantially by the *2 haplotype, but the maximum rate of metabolism (Vmax) is reduced to approximately 50% of that for CYP2C9*1 (wild-type).	[55-60]	high
In vitro	CYP2C9*3 is associated with significantly reduced (nearly abolished for homozygotes) function of CYP2C9.	[57-59]	high
clinical	Individuals with CYP2C9*2 and CYP2C9*3 exhibit impaired metabolism of S-warfarin, leading to longer half-life of the drug.	[55, 58, 61-63]	high
clinical	CYP2C9 variants with reduced activity (CYP2C9*5, *6, *8, and *11 alleles) variants contribute to variability in the warfarin maintenance dose for African Americans.	[15, 64-67]	high
clinical	Individuals with CYP2C9*2 and CYP2C9*3 haplotypes	[10, 11, 26, 38, 68, 69]	high

	have reduced warfarin maintenance dose.		
clinical	Individuals with CYP2C9*2 and CYP2C9*3 are likely to require more time to achieve steady state and a stable INR due to longer half-life of the drug.	[70]	high
clinical	At conventional warfarin dose, individuals with CYP2C9*2 and CYP2C9*3 are at increased risk of over-anticoagulation (INR>4).	[70-72]	high
clinical	At conventional warfarin dose, individuals with CYP2C9*2 and CYP2C9*3 are at increased risk of life-threatening bleeding event.	[68, 70, 73, 74]	high
clinical	CYP2C9 rs7089580variant is associated with higher warfarin dose in African Americans.	[75]	moderate
In vitro	-1639G>A variant affects VKORC1 expression.	[76, 77]	high
clinical	VKORC1 is the target for warfarin.	[45, 78]	high
clinical	VKORC1: -1639G>A variant is associated with reduced maintenance dose of warfarin in caucasians, asians and blacks. It may explain much of pharmacological variability in warfarin therapy.	[10, 11, 26, 38, 54, 76, 77, 79, 80]	high

clinical	Multiple rare nonsynonymous SNPs in VKORC1 (V29L, D36Y, V45A, R58G, V66M, R98W, L128R) confer warfarin resistance.	[45, 81-83]	high
clinical	At conventional warfarin dose, individuals with VKORC1:-1639G>A have no increased risk for major or monor bleeding event in africanamericans or caucasians.	[73]	moderate
clinical	At conventional warfarin dose, individuals with VKORC1:-1639G>A have no difference in time to stable INR in africanamericans or caucasians.	[80]	moderate
clinical	VKORC1-8191 (rs61162043) variant is associated with higher warfarin dose in African Americans.	[75]	moderate
clinical	A variant of CYP4F2 (rs2108622, V433M) affects enzyme activity and is associated with warfarin dose, where patient with TT genotype requires approximately 1mg/day more warfarin than patients with CC genotype.	[2, 3, 5, 7-10, 12-15]	moderate
clinical	Variant rs339097 in CALU predicts higher warfarin dose	[19, 20]	low/mod

	in African Americans populations, with the G allele of rs339097 associated with 14.5% higher therapeutic warfarin dose.		
clinical	rs11676382 in GGCX was shown to be a significant (p=0.03) predictor of residual dosing error and was associated with a 6.1% reduction in warfarin dose (95% CI: 0.6%-11.4%) per G allele.	[24, 25]	low/mod
clinical	rs12714145/rs7568458 in GGCX is not associated with warfarin dose .	[10, 18, 25, 27, 71]	low/mod

Supplemental Table S4. Additional variants associated with warfarin dose		
Gene	**Variant**	**Effect**
CYP4F2	C>T at rs2108622	Allele T is associated with increased dose of warfarin.
CALU	A>G at rs339097	Allele G is associated with increased dose of warfarin.
GGCX	C>G at rs11676382	Allele G is associated with decreased dose of warfarin.

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C9* and *VKORC1* Genotypes and Warfarin Dosing – ONLINE SUPPLEMENT

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S1. Other genes with evidence for an impact on warfarin dose requirements.

CYP4F2:   CYP4F2 is a primary liver vitamin K1 oxidase that catalyzes the metabolism of vitamin K1 to hydroxyl vitamin K1 and removes vitamin K from the vitamin K cycle [1](Figure 1). It acts as an important counterpart to VKORC1 in limiting excessive accumulation of vitamin K. A non-synonymous variant of *CYP4F2* (rs2108622, V433M) was first shown to affect enzyme activity and associated with warfarin dose in 3 independent white cohorts [2, 3]. Patients carrying the *CYP4F2* rs2108622 TT genotype required approximately 1mg/day more warfarin than patients with the CC genotype. Furthermore, including *CYP4F2* variant in the dosing models showed an improvement in the overall predictability of warfarin dose, in addition to functional variants in *CYP2C9, VKORC1* and clinical factors [4]. This correlation has been confirmed in many subsequent studies in multiple racial groups and rs2108622 contributes about 1 to 7% of mean weekly warfarin dose variance [5-11]. However, there are also contradictory reports showing that the contribution of this variant to warfarin dose was negligible [12-15].

CALU: Calumenin, encoded by gene *CALU*, is a Ca2+-binding Protein retained in the endoplasmic reticulum. It binds to gamma—glutamyl carboxylase (GGCX) as an inhibitory chaperone to inhibit the vitamin K cycle and also affects the activity and warfarin sensitivity of VKORC1 [16].   Genetic variations in *CALU* have been studied for their effect on warfarin dosing. One patient homozygous for the *CALU* rs2290228 mutant allele was found with exceptionally high warfarin requirement (20mg/d) [17]. However, this SNP and other *CALU* SNPs (rs11653, rs2307040, rs339054 and rs1006023) have not been shown to be significantly associated with warfarin dose in other studies [18]. Recently, a new variant, rs339097 in *CALU* has been identified that predicts higher warfarin dose in African Americans populations, with the G allele of rs339097 associated with a 14.5% higher therapeutic warfarin dose [19]. Since variations in *VKORC1, CYP2C9* and *CYP4F2* genes only account for ~10% of the warfarin dose variations in African Americans, in contrast to ~35% in whites, identifying this additional SNP in *CALU* may help with prediction of warfarin dose, especially in African American population. This variant is also more common in African Americans with minor allele frequencies of 11–14%, but only 0.2% in Caucasians. The correlation between rs339097 and higher warfarin dose requirement was recently confirmed in a study of 207 Egyptian patients [20].

GGCX : Background: Gamma-glutamul carboxylase (GGCX) is a critical component of the vitamin K cycle (Figure 1) and catalyzes the post-translational carboxylation of vitamin K-dependent proteins [21]. Many of these vitamin K-dependent proteins (clotting factors F2, F7, F9, F10 and protein C, S, Z) are involved in coagulation cascades. GGCX mediates the conversion of glutamate (Glu) residues to gamma carboxyl glutamate (Gla) on these proteins to make them functionally active with the reduced vitamin K serving as an essential cofactor. Rare non-synonymous mutations in *GGCX* have been linked with clotting disorders such as vitamin K-dependent clotting factor deficiency (VKCFD1, [22]) and PseudoxanthomaElasticum (PXE)-like disorder with multiple coagulation factor deficiency [23]. Due to its pivotal role in the blood coagulations, genetic variations in the *GGCX* gene have been investigated for their impact on warfarin maintenance dose. One variant, rs11676382, was found to be associated with warfarin dose and explained 2% of total variance [24]. This finding was confirmed in a large cohort (985 patients, mostly whites) where rs11676382 was shown to be a significant (p=0.03) predictor of residual dosing error and was associated with a 6.1% reduction in warfarin dose (95% CI: 0.6%-11.4%) per G allele [25]. Another variant in *GGCX*, rs12714145, was shown to be associated with warfarin dose in a Swedish cohort (201 patients, [26], but failed to be replicated in subsequent studies [10, 18, 25, 27].

S2. Examples ofwarfarin pharmacogenetic testing options

At the time of this manuscript writing, four *CYP2C9*/*VKORC1* genotyping platforms have been approved by the U.S. FDA:

1. Infiniti® Warfarin Assay from AutoGenomics, Inc. (Vista, CA); alleles interrogated:
   CYP2C9*2, **3*, and *VKORC1* -1639G>A

2. eSensor® Warfarin Sensitivity Test from GenMark Diagnostics, Inc. (Carlsbad, CA); alleles interrogated: *CYP2C9*2*, **3*, and *VKORC1* -1639G>A

3. Verigene® Warfarin Metabolism Nucleic Acid Test from Nanosphere (Northbrook, IL); alleles interrogated: *CYP2C9*2*, **3*, and *VKORC1* c.174-136C>T (1173C>T)

4. eQ-PCR^{TM} LC Warfarin Genotyping Kit from TrimGen (Sparks, MD); alleles interrogated:
   CYP2C9*2, **3*, and *VKORC1* -1639G>A

AutoGenomics, Inc., also offers the expanded Infiniti® CYP450 2C9-VKORC1 Assay that includes *CYP2C9*2*, **3, *4, *5, *6* and *11, *VKORC1* -1639G>A, and six additional VKORC1 variants, which is not currently FDA-approved. GenMark Diagnostics, Inc., also has a research use only eSensor® Warfarin Plus Test that includes *CYP2C9*2*, **3, *5, *6, *11, *14, *15, *16*, *VKORC1* -1639G>A, and *CYP4F2* V433M. Other commercial *CYP2C9*/*VKORC1* assays not currently approved by the FDA include the xTAG™ CYP2C9+VKORC1 Kit from Luminex Molecular Diagnostics (Toronto, ON, Canada) that interrogates CYP2C9*2, *3, *4, *5, *6, VKORC1 -1639G>A, and six additional *VKORC1* 'warfarin resistant' mutations (V29L, V45A, R58G, V66M, R98W, L128R), and the SimpleProbe Warfarin assay from Idaho Technology Inc. (Salt Lake City, UT) that interrogates *CYP2C9*2*, **3* and *VKORC1* -1639G>A.

In addition to commercial assays, various other LDTs have been reported that utilize real-time PCR allelic-discrimination (TaqMan, Applied Biosystems, Foster City, CA) (20733952), Pyrosequencing (Biotage, Uppsala, Sweden) (18480003), melting curve analysis (17661181), the Affymetrix DMET™ Plus Panel Kit (Affymetrix, Santa Clara, CA), and restriction fragment length polymorphism (RFLP) analyses. Illumina® (San Diego, CA) also has a pharmacogenetic testing panel that includes CYP2C9 and VKORC1 (VeraCode ADME Core Panel), which has an FDA 510k exemption that allows its BeadXpress platform to be used clinically. Any clinical genetic or molecular pathology laboratories using these assays still need to implement these

tests using Clinical Laboratory Improvement Amendments (CLIA) standards.

Given the number of different molecular assays available to interrogate *CYP2C9* and *VKORC1*, no specific Current Procedural Terminology (CPT) code exists for warfarin genotyping; however, it is the responsibility of the service provider to determine proper coding based on the genotyping platform used. The costs of *CYP2C9*/*VKORC1* testing are not generally covered by insurance companies at the time of this manuscript writing. However, for some pharmacogenetic testing, a pre-authorization letter to insurance providers by a referring physician, with or without a letter of medical necessity, may assist in obtaining reimbursement for *CYP2C9*/*VKORC1* genotyping. If this is a concern, whenever possible the insurance provider should be contacted prior to ordering *CYP2C9*/*VKORC1* genotyping.

Several academic clinical laboratories offer *CYP2C9/VKORC1* testing along with some reference laboratories (e.g., see http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp).

S3. Summary of rating system used to grade evidence[28].

Rating system for quality of evidence and strength of recommendation

A three-tiered system is used to describe the quality of evidence linking phenotype to genotype in Supplemental Table S3 as follows:

      Level 1 (HIGH): the evidence includes consistent results from well-designed, well-conducted studies.

      Level 2 (MODERATE): the evidence is sufficient to determine the effects, but the strength of evidence is limited by the number, quality, or consistency of the individual studies, by the inability to generalize to routine practice, or by the indirect nature of the evidence.

      Level 3 (LOW/WEAK): the evidence is insufficient to assess the effects on health outcomes because of the limited number of studies, insufficient power of the studies, important flaws in their design or in the way they were conducted, gaps in the chain of evidence, or lack of information.

A three-tiered system is also used to rate recommendations:

      A: strong recommendation for the statement

      B: moderate recommendation for the statement

      C: optional recommendation for the statement

S4: Currently existing randomized clinical trials evidence base for pharmacogenetic-guided initiation of warfarin

A number of prospective studies have demonstrated the feasibility of initiating warfarin therapy based on pharmacogenetic (PG) -guided dose prediction algorithms [29-36]. Several of these studies were randomized, controlled clinical trials comparing PG-based dosing to clinical algorithms based on standard dosing or on clinical factors excluding genotype[29-33]. These randomized clinical trials to date have been limited by diverse issues, including study design and sample size.

Hillman et-al performed a small (n=38) pilot trial of *CYP2C9* guided and clinical-based dose initiation versus standard dosing (5mg/day). Model-based dosing predicted final stable dose modestly better, but percent INR time-in-range and percent INR$\geq$4 did not differ between groups[32].

Caraco et-al reported on a randomized study in patients guided by *CYP2C9* genotype-guided or a clinical-dosing control algorithm. Of 283 patients randomized, 98 were withdrawn for taking at least one incorrect dose, leaving 185 patients to be included in the per-protocol analysis[30]. (An intention-to-treat analysis was not performed, and the study was not blinded.) PG-arm patients were reported to achieve both first and stable therapeutic INRs earlier and spent more time in the therapeutic range.

CoumaGen was a randomized study of PG-guided warfarin initiation versus standard care (5mg/day after a load), masked to patients (n=200) and investigators[29]. Among randomized trials, it first incorporated both *CYP2C9* and *VKORC1* genotyping, as well as age and weight, into the PG-algorithm, and it analyzed results by intention to treat. PG-guided dosing predicted stable maintenance dose significantly better. The primary endpoint of percent of out-of-range INRs and the secondary endpoint of time-in-therapeutic range were not met. However, those in 2 pre-specified genetic subgroups of interest (i.e., those with either multiple

variants or with no variants, who were anticipated to require substantially less than or more than the population average maintenance dose, respectively) experienced an absolute 10% reduction in out-of-range INRs with PG-guidance (p=0.03). The secondary endpoints of the number of dose-adjustments and non-protocol INRs also were reduced.

Huang et-al created, then tested (single-blind) a PG-algorithm in Chinese patients undergoing valve replacement (n=156)[33]. The initial dose in the standard control group was 2.5mg/day. The primary endpoint, the time to achieve a stable warfarin maintenance dose, was shorter in the PG-arm. The secondary endpoint of time in therapeutic range also favored PG-guidance.

The Medco-Mayo Warfarin Effectiveness Study enrolled 896 patients initiating warfarin therapy through physicians volunteering to participate in the study and matched them to a historical control group in the healthcare system who had received standard therapy (n=2,688)[31]. Genotyping was performed for *CYP2C9* and *VKORC1.* Unadjusted analysis showed a 28% lower hospitalization rate at 6 months. However, genotyping results were not delivered until a median of 32 days after entry, hence any impact on the critical first 2 weeks of dose-finding could not have occurred in the majority, and hospitalizations for non-bleeding/thromboembolism rates were found to be similarly reduced, raising the question of whether differences may have been due to selection bias (i.e., enrolling physicians practiced more careful warfarin and general medical management than those of historical controls, a "Hawthorne Effect"). Taken together, these studies are helpful in defining realistic effect sizes and genotype-specific expectations (i.e., PG-guidance is likely to be of benefit primarily in those patient subgroup in whom algorithm dosing will have a substantial impact on dose-selection, e.g., >1 mg/d improvement) as well as the need for blinded, randomized trial design to avoid selection biases, and careful monitoring to insure accurate, per-protocol dosing in the majority of enrollees, but leave definitive assessment of the role of PG-guided therapy in general clinical practice to be decided by the large ongoing randomized trials.

S5. Ongoing controlled clinical trials testing pharmacogenetic-guided warfarin dosing

Clarification of Optimal Anticoagulation through Genetics (COAG)

NCT00839657

The Clarification of Optimal Anticoagulation through Genetics (COAG) trial is a multicenter, double-blind, randomized trial comparing two approaches to guiding warfarin therapy initiation: 1) initiation of warfarin therapy based on algorithms using clinical information and an individual's genotype using genes known to influence warfarin response ("genotype-guided dosing"), or 2) only clinical information ("clinical-guided dosing"). The primary study objective is to determine whether the use of genetic and clinical information for selecting the dose of warfarin during the initial dosing period will lead to improvement in stability of anticoagulation relative to a strategy that incorporates only clinical information (without genetics) for the initial dosing period. " Each study arm will include a baseline dose-initiation algorithm and a dose-revision algorithm applied over the first 4-5 doses of warfarin therapy. Further dose adjustment will be the same between arms using a standardized dose-adjustment protocol. Participants will be followed in the study for up to 6 months. The primary outcome is the percentage of time participants spend within the therapeutic INR range (PTTR) during the first four weeks of therapy.

The EUropeanPharmacogenetics of AntiCoagulant Therapy(EU-PACT)

NCT01119300

The EUropeanPharmacogenetics of AntiCoagulant Therapy (EU-PACT) trialsare single-blind, randomized controlled trials to assess the safety and clinical utility of genotype-guided dosing of the three main coumarins used in Europe: acenocoumarol, phenprocoumon and warfarin[37]. The warfarin trial is currently recruiting and is aiming to include over 900 patients with atrial fibrillation or venous thromboembolism in the Uk and Sweden. Patients are randomized to either

genotype-guided dosing (intervention arm) or to standard dosing (control arm). Patients in the intervention arm are genotyped for CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910) and VKORC1 -1639G>A (rs9923231) with a rapid genotyping method prior to starting therapy which provides genotyping results within 2-3 hours. Warfarin intervention patients are given a three day loading dose based on the IWPC pharmacogenetic maintenance dose algorithm [38] and the predicted elimination half-life of warfarin for each CYP2C9 genotype [39]. After the first 3 days of therapy, they are dosed according to a modified version of apharmacogenetic warfarin dose revision algorithm [34]. The follow-up time is 3 months and the primary outcome measure is the percentage time in therapeutic INR range. Secondary outcomes are 1) time to reach therapeutic INR; 2) number of dose adjustments; 3) incidence of over-anticoagulation (INR>4.0); 4) number of minor and major bleedings during the first 3 months; 5) recurrence of thrombosis; 6) utility of near-patient genotyping test for routine clinic use; 7) number of thrombotic events; 8) quality of life reported by the patient; 9) cost effectiveness.

GIFT

NCT01006733

The Genetic InFormatics Trial (GIFT) of Warfarin Therapy to Prevent DVT is a multi-centered, randomized controlled trial of 1600 high-risk participants beginning warfarin therapy. GIFT participants will be randomized to either clinical- or pharmacogenetic-guided warfarin dosing. Participants are Medicare beneficiaries (age 65 years or older) who are scheduled for 1 month of warfarin therapy for venous thromboembolism (VTE) prophylaxis after elective hip or knee arthroplasty. The primary hypothesis is that pharmacogenetic dosing decreases the composite risk of: a non-fatal VTE, non-fatal major hemorrhage, death, and an INR$\geq$4.0. The trial is funded by the NIH (1R01 HL097036) with reimbursement of genotyping by the Centers for Medicare & Medicaid Services (CMS), using the Coverage with Evidence Development (CED) mechanism. The doses for GIFT are generated by www.WarfarinDosing.org, a process that has been granted an investigational device exemption (IDE) by the US FDA. Enrollment began in 2011 and will conclude in 2015.

Pharmacogenetic dosing of warfarin: a controlled randomized trial

The Taiwan Warfarin Consortium is currently conducting the "Pharmacogenetic dosing of warfarin: a controlled randomized trial" study which aims to determine whether Pharmacogenetics guided dosing can improve safety for warfarin treatment. The study consists of three arms: dose calculated using the IWPC algorithm, dose calculated using the Taiwan algorithm, and standard care (fixed initial dose). Subsequent dose adjustments for all three arms are based on INR. The study aims to recruit at least 200 patients for each arm and aims to complete the project by Dec 2012. The primary outcomes of the study are the time it takes to reach stable therapeutic INR and how long the stable INR can be maintained. The secondary outcomes are the number of adverse events and the number of dose adjustment required to reach stable therapeutic INR. The study is funded by Academia Sinica and the National Science Council in Taiwan.

Warfarin Adverse Events Reduction for Adults Receiving Genetic Testing at Therapy Initiation (WARFARIN)NCT01305148

This is randomized double-blinded interventional trial where patients are randomized to warfarin dosing based on the GenoSTAT test plus clinical factors, or clinical factors alone, using the warfarindosing.org website. Eligible patients must be 65 years or older and they will be followed for 90 days to determine if there are fewer hospitalizations and/or deaths in the group having genotype-guided dosing. Target sample size is 4,300 and the trial is expected to complete in December 2012. The primary endpoint is the incidence of warfarin-related clinical events, including major hemorrhage and thromboembolic events at 30 days after the initial dose, in those guided with pharmacogeneticsvs clinical information to define the initial warfarin dose. Secondary endpoints include the number of INR tests, major and minor hemorrhagic events, out of range INRs in the first 30 days, and prescriber adherence to dosing recommendation.

The above trials include large national or international trials. This is not intended to be a summary of all ongoing warfarin pharmacogenetics trials. Additional warfarin pharmacogenetics trials can be found at www.clinicaltrials.gov.

Supplement S6. Detailed information not included in main text.

Warfarin

Warfarin is administered as a racemic mixture of *R*- and *S*- stereoisomers. S-warfarin is 3-5 times more potent as a vitamin K antagonist than R-warfarin [40]. The stereoisomers are extensively metabolized by different hepatic microsomal enzymes. S-warfarin is metabolized predominantly to 7- and 6- hydroxyl metabolites via CYP2C9 (Figure 1), whereas R-warfarin is mainly metabolized via CYP3A4 with involvement of CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C18 and CYP2C19 [41-44].

Warfarin exerts its anticoagulant effect through inhibition of its molecular target Vitamin K epoxide reductase complex (VKORC1) [45]. VKORC1 catalyzes the conversion of oxidized Vitamin K to reduced Vitamin K with the help of microsomal epoxide hydrolase (EPHX1). Warfarin blocks this reaction, which leads to decreased availability of the reduced Vitamin K that serves as a cofactor for gamma-glutamyl carboxylase (GGCX), and blocks the formation of functionally active clotting factors, leading to reduced coagulation [25, 46-48].

Other considerations.

Clinical factors. As highlighted in the dosing algorithms, and through the histogram in Figure 2, clinical/demographic factors also significantly influence warfarin dose variability, the most significant of these being body size and age. These factors are accounted for in the formal pharmacogenetics dosing algorithms but should be considered if using the dosing table, which only accounts for *CYP2C9* and *VKORC1* genotype. An additional factor that is known to affect INR stability is patient non-adherence [49, 50]. As with any drug, the patient should be counseled to ensure that there is an understanding of the importance of adherence to the prescribed warfarin regimen. In addition, genotype does not alter the importance of patient adherence.

Drug interactions. Drug interactions are common with warfarin, and significant interactions include both enzyme induction and enzyme inhibition. Smoking also causes enzyme induction. The dosing algorithms take into account some, but not all of the clinically important drug interactions with warfarin. Therefore, it is important to interpret the results of genetic testing in the context of other co-administered drugs.

Other genes. In addition to *CYP2C9* and *VKORC1*, there are several other genes that may influence variation in warfarin dose and response. The most widely replicated of these is a nonsynonymous SNP in *CYP4F2*. Most clinical genotyping platforms do not currently include this SNP, nor do the dosing tables or algorithms. However, this SNP may have increasing utilitization in the near future. Variants in *CALU* and *GGCX* have been shown to affect warfarin dose and contribute to warfarin dose variations in some but not all populations. Further details on these three genes are available below in Supplement S2 and in Supplement Table S3. The effects of these variants are weaker than those of *CYP2C9* and/or *VKORC1*.

Incorporation of genetic information into initial warfarin dose. The use of a different initial warfarin dose (or "loading dose") is controversial and plays different roles in different regions of the world, based on experience and local standards. For example, in the UK and Sweden, it is conventional to use loading doses and several loading dose regimens having been devised. The advantage is quicker time to therapeutic INR, but the major disadvantage is a higher risk of over-anticoagulation early on during therapy. A loading dose algorithm incorporating *CYP2C9* and *VKORC1* genotypes is currently being tested in the European randomized controlled trial EU-PACT (clinicaltrials.gov/ct2/show/NCT01119300).

Use of a loading dose is less common in the U.S. However, due to the very long half-life associated with *CYP2C9* *2 and *3 variants, there is evidence suggesting that with pharmacogenetics-guided dosing, it may be preferable to not consider *CYP2C9* genotype for the first one to three warfarin doses. Then, subsequent doses consider *CYP2C9* genotype, and doses are thus reduced to accommodate the decreased metabolism of S-warfarin conferred by the *2 and *3 genotypes. Inherent to EU-PACT and to trials in the US (COAG and GIFT), is the protocol to initiate. This approach is being taken in the US-based trials (COAG and GIFT) and has been tested prospectively [51] and should decrease the time until reaching a steady-state warfarin level in patients with these SNPs [52].

Alternative therapies to warfarin
For over five decades coumarin anticoagulants, the most popular of which is warfarin, have been the only oral anticoagulants available world-wide. The recent approval of dabigatran provides an alternative to warfarin therapy in those with atrial fibrillation [53], with other oral anticoagulants on the horizon (e.g. rivaroxaban). While dabigatran is not known to be influenced by genetic variability in *CYP2C9* and *VKORC1*, its pharmacokinetics or efficacy may be influenced by other genes. Advantages to dabigatran include its rapid onset of

anticoagulation, dosing simplicity with only two doses utilized (normal dose, and renal impairment dose), and lack of need for monitoring. There are also disadvantages, which include twice daily dosing, dependence on renal function for elimination, the lack of ability to monitor, lack of an antidote, costs, limited amounts of clinical trial data relative to warfarin, and a 30 day shelf life once opened, among others.   As new oral anticoagulants gain market share, reliance on warfarin will decline. However, warfarin will continue to be widely utilized world-wide.

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