

# Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update

JA Johnson<sup>1</sup>, KE Caudle<sup>2</sup>, L Gong<sup>3</sup>, M Whirl-Carrillo<sup>3</sup>, CM Stein<sup>4</sup>, SA Scott<sup>5</sup>, MT Lee<sup>6</sup>, BF Gage<sup>7</sup>, SE Kimmel<sup>8,9</sup>, MA Perera<sup>10</sup>, JL Anderson<sup>11</sup>, M Pirmohamed<sup>12</sup>, TE Klein<sup>3</sup>, NA Limdi<sup>13</sup>, LH Cavallari<sup>1</sup> and M Wadelius<sup>14</sup>

This document is an update to the 2011 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C9* and *VKORC1* genotypes and warfarin dosing. Evidence from the published literature is presented for *CYP2C9*, *VKORC1*, *CYP4F2*, and rs12777823 genotype-guided warfarin dosing to achieve a target international normalized ratio of 2–3 when clinical genotype results are available. In addition, this updated guideline incorporates recommendations for adult and pediatric patients that are specific to continental ancestry.

Warfarin is a widely used anticoagulant with a narrow therapeutic index and large interpatient variability in the dose required to achieve target anticoagulation. Common genetic variants in *CYP2C9*, *VKORC1*, *CYP4F2*, and the *CYP2C* cluster (e.g., rs12777823), plus known nongenetic factors, account for ~50% of warfarin dose variability. This document is an update to the 2011 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C9* and *VKORC1* genotypes and warfarin dosing and aims to assist in the interpretation and use of *CYP2C9*, *VKORC1*, *CYP4F2*, and rs12777823 genotypes to estimate therapeutic warfarin dose among patients with a target international normalized ratio (INR) of 2–3, should clinical

genotype results be available to the clinician. The CPIC of the National Institutes of Health's Pharmacogenomics Research Network develops peer-reviewed gene/drug guidelines that are published and updated periodically on <https://cpicpgx.org/guidelines/> and <http://www.pharmgkb.org> based upon new developments in the field.<sup>1</sup> These guidelines were written with a global audience in mind, although the majority of the data that underpin these guidelines arise from people of European ancestry, East Asia, and African Americans.

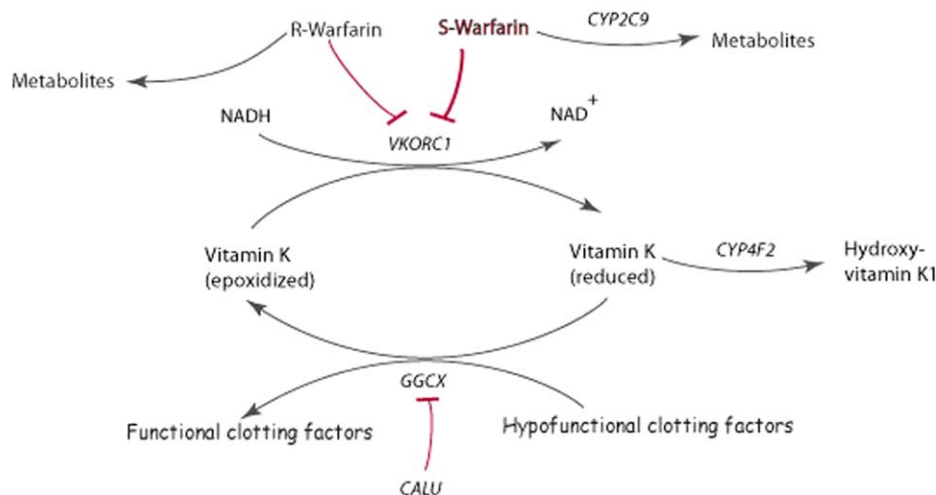
## FOCUSED LITERATURE REVIEW

The **Supplement** includes a systematic literature review on *CYP2C9*, *VKORC1*, *CYP4F2* and other relevant genes/genotypes that have been associated with warfarin dosing. This systematic review forms the basis for the recommendations contained in this guideline. Although some of these genes have also been associated with dose of other coumarin anticoagulants, the recommendations below are specific to warfarin.

## DRUG: WARFARIN

Warfarin (Coumadin and others) is the most commonly used oral anticoagulant worldwide, with annual prescriptions in the

<sup>1</sup>Department of Pharmacotherapy and Translational Research, College of Pharmacy, and Center for Pharmacogenomics, University of Florida, Gainesville, Florida, USA; <sup>2</sup>Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; <sup>3</sup>Department of Biomedical Data Science, Stanford University, Stanford, California, USA; <sup>4</sup>Division of Clinical Pharmacology Vanderbilt Medical School, Nashville, Tennessee, USA; <sup>5</sup>Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA; <sup>6</sup>Laboratory for International Alliance on Genomic Research, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan; National Center for Genome Medicine; Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan; Genomic Medicine Institute, Geisinger Health system, Danville, Pennsylvania, USA; <sup>7</sup>Department of Internal Medicine, Washington University in St. Louis, St. Louis, Missouri, USA; <sup>8</sup>Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA; <sup>9</sup>Department of Medicine and Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA; <sup>10</sup>Department of Medicine, University of Chicago, Chicago, Illinois, USA; <sup>11</sup>Intermountain Heart Institute, Intermountain Medical Center, and Department of Internal Medicine (Cardiology), University of Utah School of Medicine, Salt Lake City, Utah, USA; <sup>12</sup>Department of Molecular and Clinical Pharmacology; The Wolfson Centre for Personalised Medicine; Institute of Translational Medicine, University of Liverpool, Liverpool, UK; <sup>13</sup>Department of Neurology and Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA; <sup>14</sup>Department of Medical Sciences, Clinical Pharmacology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden. Correspondence: JA Johnson (Johnson@cop.ufl.edu)



**Figure 1** Schematic representation of warfarin metabolism and its mechanism of action. Warfarin is administered via a racemic mixture of the *R*- and *S*-stereoisomers. *S*-warfarin is 3–5 times more potent than *R*-warfarin and is metabolized predominantly to 7- and 6-hydroxyl metabolites via CYP2C9. Warfarin exerts its anticoagulant effect through inhibition of its molecular target VKORC1, which in turn limits availability of reduced vitamin K, leading to decreased formation of functionally active clotting factors. These clotting factors are glycoproteins that are posttranslationally carboxylated by gamma-glutamyl carboxylase (GGCX) to Gla-containing proteins. The endoplasmic reticulum chaperone protein calumenin (CALU) can bind to and inhibit GGCCX activity. The metabolism of reduced vitamin K to hydroxyvitamin K1 is catalyzed by CYP4F2, which removes vitamin K from the vitamin K cycle (adapted from warfarin pharmacokinetics (PK) and pharmacodynamics (PD) pathways at PharmGKB, <http://www.pharmgkb.org/do/serve?objId=PA451906&objCls=Drug#tabview=tab4>).

western world typically equaling 0.5–1.5% of the population.<sup>2</sup> It is prescribed for the treatment and prevention of thromboembolic disorders.<sup>3</sup> Although highly efficacious, warfarin dosing is notoriously challenging due to its narrow therapeutic index and wide interindividual variability in dose requirements, even among patients with the same target INR.<sup>4</sup> Complications from inappropriate warfarin dosing are among the most frequently reported adverse events to the US Food and Drug Administration (FDA) and one of the most common reasons for emergency room visits.<sup>5</sup>

Warfarin is usually dosed empirically: an initial dose is prescribed, typically followed by at least weekly measurement of the INR and subsequent dose adjustment. The initial dose is often based on population averages (e.g., 4–5 mg/day), but in some settings, it is common to use loading doses during the first few days of anticoagulation. Irrespective of the method used to initiate warfarin, stable doses to achieve an INR of 2–3 range from 1–20 mg/day. The iterative process to define the appropriate dose can take weeks to months and during this period, patients are at increased risk of over- or under-anticoagulation, and thus risk of bleeding or thromboembolism.

#### Warfarin pharmacology and pharmacokinetics

**Figure 1** highlights key elements of warfarin pharmacology and pharmacokinetics. Warfarin inhibits vitamin K epoxide reductase complex<sup>6</sup> and is administered as a racemic mixture, with *S*-warfarin being more potent than *R*-warfarin.<sup>3</sup>

#### GENES: CYP2C9, VKORC1, AND CYP4F2

There is substantial candidate gene literature evaluating associations with warfarin dose requirements, as well as several reported genomewide association studies (**Supplemental Tables S1–S7**).

The genes with the strongest literature support, and for which we make recommendations for use in warfarin dosing, are *CYP2C9*, *VKORC1*, and *CYP4F2*. Additionally, genomewide association studies have identified an independently significant single nucleotide polymorphism (SNP) in the *CYP2C* cluster,<sup>7</sup> which has also been incorporated into this updated recommendation.

#### CYP2C9 and warfarin

*CYP2C9* is a hepatic drug-metabolizing enzyme in the cytochrome P450 (CYP450) superfamily,<sup>8</sup> and is the primary metabolizing enzyme of *S*-warfarin (**Figure 1**). *CYP2C9* has over 60 known variant alleles (<http://www.cypalleles.ki.se/cyp2c9.htm>; **CYP2C9 allele definition table**<sup>9</sup>). Individuals homozygous for the reference *CYP2C9* allele (*CYP2C9\*1*) have the “normal metabolizer” phenotype. Each named *CYP2C9* star (\*) allele is defined by one or more specific SNPs and, to date, and 18 alleles have been associated with decreased enzyme activity (**CYP2C9 allele definition table**<sup>9</sup>). The two most common decreased function alleles among individuals of European ancestry are *CYP2C9\*2* (c.430C>T; p.Arg144Cys; rs1799853) and *CYP2C9\*3* (c.1075A>C; p.Ile359Leu; rs1057910).<sup>8</sup> *CYP2C9* allele frequencies differ between racial/ethnic groups.<sup>8,10</sup>

*In vitro* and *in vivo* studies suggest *CYP2C9\*2* and *\*3* impair metabolism of *S*-warfarin by ~30–40% and ~80–90%, respectively.<sup>8</sup> Compared to patients homozygous for *CYP2C9\*1*, individuals who inherit one or two copies of *CYP2C9\*2* or *\*3* are at greater risk of bleeding during warfarin therapy,<sup>11,12</sup> require lower doses to achieve similar levels of anticoagulation, and require more time to achieve a stable INR<sup>11</sup> (**Supplemental Table S1**). Additional *CYP2C9* alleles (*CYP2C9\*5*, *\*6*, *\*8*, and *\*11*) are associated with decreased function of the *CYP2C9* enzyme and

contribute to dose variability. These alleles are found with the highest frequency among those of African ancestry, and collectively are more common than *CYP2C9*\*2 and \*3 in that population (*CYP2C9* frequency table<sup>9</sup>).

#### **VKORC1 and warfarin**

*VKORC1* encodes the vitamin K epoxide reductase protein, the target enzyme of warfarin.<sup>6</sup> *VKORC1* catalyzes the conversion of vitamin K-epoxide to vitamin K, which is the rate-limiting step in vitamin K recycling.<sup>13</sup>

A common variant upstream of *VKORC1* (c.-1639G>A, rs9923231) is significantly associated with warfarin sensitivity and patients with one or two -1639A require progressively lower warfarin doses than -1639G/G homozygotes.<sup>10,14–18</sup> The -1639G>A polymorphism is present on a haplotype that affects *VKORC1* protein expression (*VKORC1* allele definition table<sup>19</sup>).<sup>18</sup>

Other common *VKORC1* SNPs or haplotypes do not further improve warfarin dose prediction.<sup>10,16</sup> The c.-1639G>A allele frequency varies among different ancestral populations (*VKORC1* frequency table<sup>19</sup>), and largely explains the differences in average dose requirements between whites, blacks, and Asians.<sup>10,17</sup> Several rare nonsynonymous *VKORC1* variants confer warfarin resistance (high dose requirements) and are detailed in **Supplemental Table S2**.<sup>20</sup>

#### **CYP4F2 and warfarin**

*CYP4F2* is a primary liver vitamin K oxidase that catalyzes the metabolism of vitamin K to hydroxy-vitamin K1 and removes vitamin K from the vitamin K cycle<sup>21</sup> (**Figure 1**). It acts as an important counterpart to *VKORC1* in limiting excessive accumulation of vitamin K. The nonsynonymous variant *CYP4F2*\*3 (c.1297G>A; p.Val433Met; rs2108622) was first shown to affect enzyme activity and associated with warfarin dose in three independent white cohorts (*CYP4F2* gene definition table<sup>24</sup>).<sup>22–24</sup> Furthermore, including this *CYP4F2* variant in warfarin dosing models that included *CYP2C9*, *VKORC1*, and clinical factors improved the accuracy of dose prediction.<sup>25</sup> This correlation has been confirmed in subsequent studies with those of European and Asian ancestry, although not those of African ancestry.<sup>26,27</sup> Two large meta-analyses (one in Han Chinese that pulled in substantial Chinese literature) provide the best estimates for the influence data of *CYP4F2*\*3 on warfarin dose requirements.<sup>26,27</sup> They suggest statistically significant but modest impacts of 8–11% higher warfarin doses in A allele carriers (**Supplemental Table S3**).

#### **CYP2C rs12777823 and warfarin**

rs12777823 is a SNP in the *CYP2C* cluster near the *CYP2C18* gene on chromosome 10 and is associated with a clinically relevant effect on warfarin dose through significant alterations in warfarin clearance, independent of *CYP2C9*\*2 and \*3.<sup>7</sup> This association was first identified through a genome-wide association study in African Americans ( $P = 1.51 \times 10^{-8}$ ) and confirmed in a replication cohort ( $P = 5.04 \times 10^{-5}$ ); meta-analysis of the two cohorts together produced a  $P$  value of  $4.5 \times 10^{-12}$ . This study concluded that African Americans who are heterozygous or

homozygous for the rs12777823 A allele require a dose reduction of ~7 or 9 mg/week, respectively.<sup>7</sup> Regression analysis showed that addition of this SNP improves the dosing algorithm published by the International Warfarin Pharmacogenetics Consortium (IWPC) by 21%. Further studies have demonstrated the importance of this SNP in African Americans.<sup>28</sup> Although this variant is common in other ethnic populations, an association with warfarin dose has only been detected among African Americans, suggesting it is not the underlying cause but likely inherited with other variant(s) on a haplotype that influences warfarin dose in this population. Of note, an association was not observed in a cohort of Egyptians, thus it is not possible to make broad statements about this allele in people of continental African ancestry. Most African Americans are of West African ancestry; it is unknown whether similar associations are present in individuals from other parts of Africa.

#### **Genetic test interpretation**

**CYP2C9.** Clinical laboratories typically report *CYP2C9* genotype results using the star (\*) allele nomenclature system and an interpretation that includes a predicted metabolizer phenotype (*CYP2C9* allele definition table<sup>9</sup>). Most FDA-approved *CYP2C9* tests include only \*2 and \*3, which is not as informative for African ancestry populations; however, some clinical laboratories may offer expanded *CYP2C9* panels validated as laboratory developed tests (LDTs) (for allele frequencies see: *CYP2C9* frequency table<sup>9</sup>).

**VKORC1.** Clinical laboratories typically report *VKORC1* genotype results by c.-1639G>A (or the linked 1173C>T; rs9934438) genotype (e.g., G/A) and an interpretation on warfarin sensitivity (*VKORC1* allele definition table<sup>19</sup>). Most commercial genotyping platforms do not detect rare *VKORC1* variants that have been associated with warfarin resistance (*VKORC1* frequency table<sup>19</sup>).

**CYP4F2.** Although not as commonly tested for as *CYP2C9* and *VKORC1*, some clinical laboratories may also test for *CYP4F2* using a targeted genotyping laboratory developed test to detect *CYP4F2*\*3 (c.1297G>A, p.Val433Met; rs2108622) variant (*CYP4F2* allele definition table<sup>24</sup>). Results are typically reported by nucleotide (e.g., G/A), amino acid (e.g., Val/Met) or star (\*) allele (\*1/\*3) genotype and an interpretation related to warfarin dosing.

**CYP2C rs12777823.** Given the recent identification of the association between rs12777823 (g.96405502G>A) and warfarin dosing among African Americans, most clinical laboratories do not currently include this non-coding variant in their warfarin pharmacogenetic genotyping panels. However, the increasing accessibility of clinical research genomics programs that return actionable results and the notable effect of this variant among African Americans suggests that some patients may have genotype results for this variant in the future. Results would likely be reported by genotype (e.g., G/A) and an interpretation related to warfarin dosing.

### Genetic test options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (<http://www.ncbi.nlm.nih.gov/gtr/>).

### Incidental findings

No diseases have been linked to common *CYP2C9* variants independent of drug metabolism and response. Similarly, no diseases have been consistently linked to common *VKORC1* and *CYP4F2* variants that are interrogated in warfarin response tests. However, homozygosity for rare coding mutations in *VKORC1* are a known cause of combined deficiency of vitamin K-dependent clotting factors-2 (VKCFD2), which is a rare and potentially fatal bleeding disorder that can be reversed by oral administration of vitamin K.<sup>29</sup>

### Linking genetic variability to variability in drug-related phenotypes

Common variants in *CYP2C9*, *VKORC1*, and *CYP4F2* account for up to 18%, 30%, and 11% respectively, of the variance in stable warfarin dose among patients of European ancestry,<sup>10,16,17,30,31</sup> but because of differing allele frequencies across populations, these variants explain less of the dose variability in patients of other ancestries. In particular, *CYP2C9*\*2 is virtually absent in Asians, and additional *CYP2C9* alleles (e.g., \*5, \*6, \*8, and \*11 alleles) occur almost exclusively in persons of African ancestry and contribute to dose variability in this population. Other genes of potential importance are discussed in the **Supplemental Material**.

Published in 2013, the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) and Clarification of Optimal Anticoagulation through Genetics (COAG) trials examined the efficacy of genotype-guided warfarin dosing in randomized controlled trials.<sup>32,33</sup> In a homogenous European population, the EU-PACT trial showed shorter time to stable dose, improved percent time in therapeutic range, and reduced number of episodes with an INR >4 using a pharmacogenetic dosing algorithm compared to standard dosing.<sup>33</sup> The COAG trial was conducted in an ethnically diverse cohort with 27% of participants of African ancestry.<sup>32</sup> Overall, COAG did not show a difference in time to stable dose, percent time in therapeutic range, reduction in number of episodes with INR >4 or <2, or bleeding risk with a pharmacogenetic dosing algorithm compared to a clinical algorithm. In nonblacks, the pharmacogenetic dosing algorithm arm had more patients whose stable dose was within 1 mg per day of the algorithm-predicted dose (57 vs. 39%, respectively). In contrast, the pharmacogenetic dosing algorithm was less accurate at predicting within 1 mg/day of the stable dose than the clinical algorithm in blacks (38 vs. 48%, respectively).<sup>32</sup> Blacks were more likely to have an INR above range with pharmacogenetic dosing, which could be due to the genotyping panel in the COAG trial being limited to *CYP2C9*\*2, \*3, and *VKORC1* c.-1639G>A. Other variants that influence warfarin dose and are more common in blacks (i.e., *CYP2C9*\*5, \*6, \*8, and \*11 and rs12777823) were not genotyped in the COAG trial and their absence likely

led to significant overdosing in patients with these alleles.<sup>10,34</sup> Consequently, this updated CPIC guideline recommends against pharmacogenetic dosing of warfarin in blacks when only *CYP2C9*\*2 and \*3 genotype results are available.

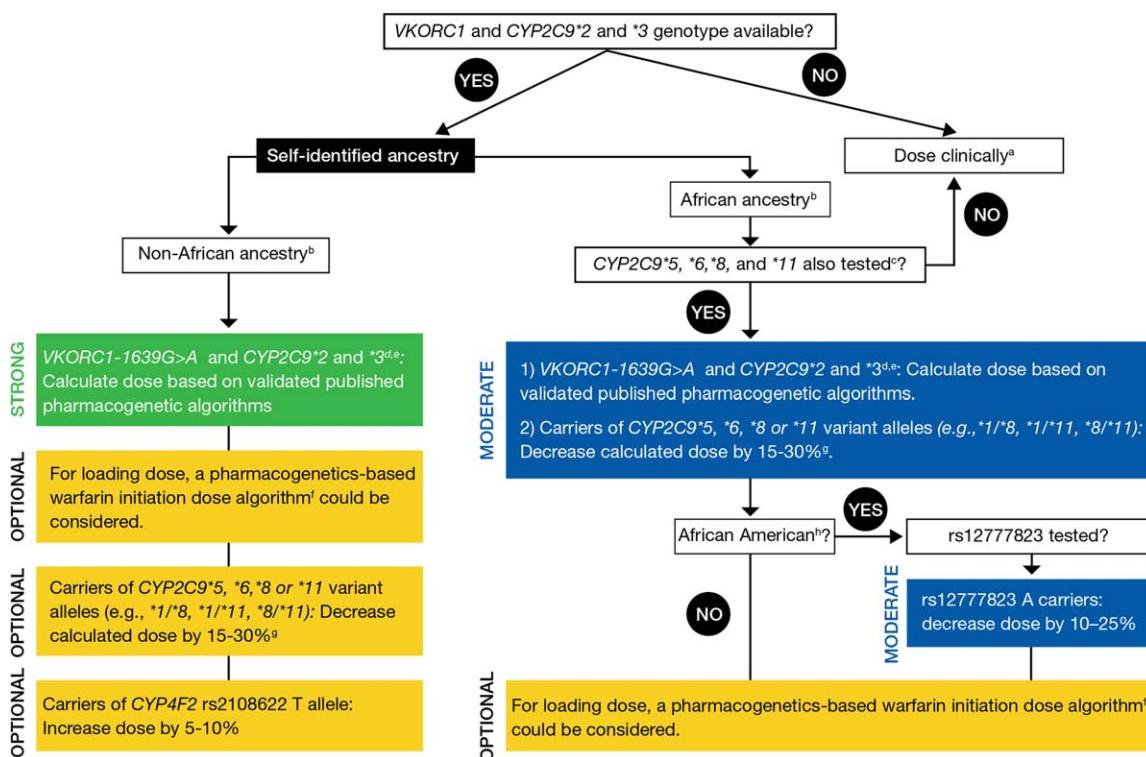
The Genetics-InFormatics Trial (GIFT) was a randomized controlled trial examining the effectiveness and safety of genotype-guided dosing versus clinical algorithm dosing in orthopedic patients with a composite outcome that included symptomatic and asymptomatic venous thromboembolism, major hemorrhage, INR  $\geq 4$ , and death.<sup>35</sup> It is the first warfarin pharmacogenetics trial powered for clinical outcomes. GIFT included genotyping for *CYP2C9*\*2 and \*3, *CYP4F2*\*3, and *VKORC1*-1639, but did not include the African-specific *CYP2C9* alleles or rs12777823. The results of GIFT were presented in early 2017 and revealed a 27% reduction in the composite outcome with genotype-guided versus clinical algorithm dosing, documenting the clinical benefits of a genotype guided approach to warfarin dosing. (<https://www.sciencedaily.com/releases/2017/03/170320091104.htm>)

### Therapeutic Recommendations: Adults

**Recommendations for warfarin maintenance (chronic) dosage based on genetic information.** We use the three-tiered rating system described previously (and in the **Supplemental Material**)<sup>1</sup> in which ratings of strong, moderate, and optional are applied based on the evidence reviewed. The recommendations for dosing based on genotype contained herein include recommendations and are derived from numerous observational and prospective studies, and randomized trials that suggest the ability to more accurately identify stable therapeutic warfarin dose requirements through the use of both genetic and clinical information. Data from prospective studies and randomized controlled trials are equivocal on whether the improvement in dosing prediction by pharmacogenetics dosing leads to improved clinical outcomes. The majority of the literature underpinning these guidelines arises from individuals of European ancestry, African Americans, and East Asians. However, the more limited literature in other populations generally suggests the guidelines are appropriate in them also.

Numerous studies have derived warfarin dosing algorithms that use both genetic and nongenetic factors to predict warfarin dose.<sup>16,17,36,37</sup> Two algorithms perform well in estimating stable warfarin dose<sup>16,17</sup> and were created using more than 5,000 subjects, although as noted above, more recent data suggest they do not perform acceptably in African Americans when used without modification for *CYP2C9* alleles frequently found in the African population.<sup>32</sup> The Gage and IWPC algorithms or minor adjustments to them have also been the algorithms used in both randomized controlled trials and most of the prospective dosing studies. Dosing algorithms using genetic information outperform nongenetic clinical algorithms and fixed-dose approaches in dose prediction, except in African Americans when the algorithm only includes *CYP2C9*\*2 and \*3.<sup>16,17,32</sup> Genetics-based algorithms also better predict warfarin dose than the FDA-approved warfarin label table.<sup>38</sup>

**Pharmacogenetic algorithm-based warfarin dosing.** This guideline recommends that pharmacogenetic warfarin dosing be accomplished through the use of one of the pharmacogenetic dosing



**Figure 2** Dosing recommendations for warfarin dosing based on genotype for adult patients. (a) “Dose clinically” means to dose without genetic information, which may include use of a clinical dosing algorithm or standard dose approach. (b) Data strongest for European and East Asian ancestry populations and consistent in other populations. (c) 45–50% of individuals with self-reported African ancestry carry *CYP2C9*\*5, \*6, \*8, \*11, or rs12777823. If *CYP2C9*\*5, \*6, \*8, and \*11 were not tested, dose warfarin clinically. Note: these data derive primarily from African Americans, who are largely from West Africa. It is unknown if the same associations are present for those from other parts of Africa. (d) Most algorithms are developed for the target INR 2-3. (e) Consider an alternative agent in individuals with genotypes associated with *CYP2C9* poor metabolism (e.g., *CYP2C9*\*3/\*3, \*2/\*3, \*3/\*3) or both increased sensitivity (*VKORC1* A/G or A/A) and *CYP2C9* poor metabolism. (f) See the EU-PACT trial for pharmacogenetics-based warfarin initiation (loading) dose algorithm with the caveat that the loading dose algorithm has not been specifically tested or validated in populations of African ancestry.<sup>33</sup> (g) Larger dose reduction might be needed in variant homozygotes (i.e., 20–40%). (h) African American refers to individuals mainly originating from West Africa.

algorithms described above, as summarized in **Figure 2**. These algorithms, as originally published, are available in the **Supplement** and the dosing algorithm published by IWPC is also online at <http://www.pharmgkb.org/do/serve?objId=PA162372936&objCls=Dataset#tabview=tab2>. The two algorithms provide very similar dose recommendations. The clinical and genetic information used in one or both algorithms is shown in **Text Box 1**. These algorithms compute the anticipated stable daily warfarin dose to one decimal and the clinician must then prescribe a regimen (e.g., an estimate of 4.3 mg/day might be given as 4 mg daily except 5 mg 2 days per week). An additional “dose revision” algorithm, which can be used on days 4–5 of therapy for dose refinement and uses genetic information, was tested in COAG and EU-PACT and can also be used<sup>36</sup> (**Supplemental Table S5**).

It is important to note that these algorithms do not include *CYP4F2*, *CYP2C9*\*5, \*6, \*8, or \*11 or rs12777823, and incorporation of these should be added when results are available, as described in **Figure 2**. The warfarindosing.org website contains both algorithms, the Gage algorithm<sup>16</sup> as the primary algorithm and the IWPC algorithm<sup>17</sup> as the secondary algorithm and can adjust for *CYP4F2*, *CYP2C9*\*5, and \*6. If utilizing warfarindosing.org, the user should be clear on whether the

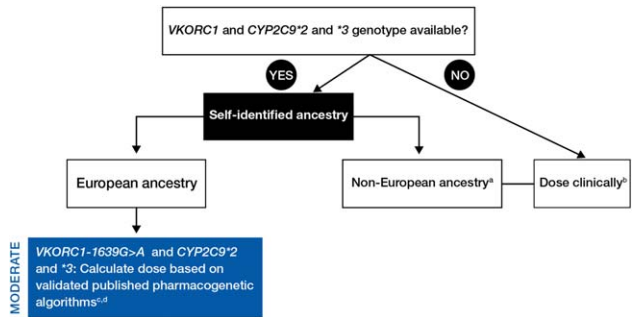
**Text Box 1. Patient characteristics utilized in the Gage (16), or IWPC (17) algorithms or both**

- Age
- Sex
- Race
- Weight
- Height
- Smoking status
- Warfarin indication
- Target INR
- Interacting drugs
  - Inhibitors: Amiodarone, statins, sulfamethoxazole, azole antifungals
  - Inducers: Rifampin, phenytoin, carbamazepine
- Genetic variables
  - *CYP2C9* genotype
  - *VKORC1* genotype
  - Gage algorithm can also incorporate *CYP4F2* and *GGCX* genotypes

algorithm is or is not incorporating genotypes beyond *CYP2C9* \*2 and \*3 and *VKORC1*, which are the only three genotypes in the original version of both algorithms.

**Pharmacogenetics-informed loading (or initiation) dose calculations.** The use of a different initial warfarin dose (or “loading dose”) is somewhat controversial and plays different roles in different regions of the world, based on experience and local standards. Recent data from a diverse US-based cohort suggest that failure to provide a loading dose in patients with zero or one variant alleles in *VKORC1* or *CYP2C9* may delay time to therapeutic INR and reduce time in therapeutic range in the initial month of therapy.<sup>39</sup> A genetically guided loading dose approach was developed by Avery *et al.*<sup>37</sup> and a slightly modified version was successfully implemented in the EU-PACT trial.<sup>33</sup> In COAG *CYP2C9* variant alleles were not considered for the initial dose, providing a small loading dose on day 1. Whether differences in loading dose strategies between the EU-PACT and COAG trials contributed to differing results is not known. If loading doses are to be used, a genetically informed approach to calculating the loading dose may be helpful. The majority of the experience with a genetically informed loading regimen is in those of European ancestry. Determination of maintenance dose would be as described above.

**Non-African ancestry recommendation.** In patients who self-identify as non-African ancestry, the recommendation, as summarized in **Figure 2**, is to: 1) calculate warfarin dosing using a published pharmacogenetic algorithm,<sup>16,17</sup> including genotype information for *VKORC1-1639G>A* and *CYP2C9*\*2 and \*3. In individuals with genotypes associated with *CYP2C9* poor metabolism (e.g., *CYP2C9* \*2/\*3, \*3/\*3) or both increased sensitivity (*VKORC1-1639 A/A*) and *CYP2C9* poor metabolism, an alternative oral anticoagulant might be considered.<sup>12</sup> The bulk of the literature informing these recommendations is in European and Asian ancestry populations, but consistent data exist for other non-African populations. These recommendations are graded as *STRONG*. 2) If a loading dose is to be utilized, the EU-PACT loading dose algorithm that incorporates genetic information could be used.<sup>33</sup> This recommendation is *OPTIONAL*. 3) While *CYP2C9*\*5, \*6, \*8, or \*11 variant alleles are commonly referred to as African-specific alleles, they can occur among individuals who do not identify as, or know of their, African ancestry. If these variant alleles are detected, decrease calculated dose by 15–30% per variant allele or consider an alternative agent. Larger dose reductions might be needed in patients homozygous for variant alleles (i.e., 20–40%, e.g., *CYP2C9*\*2/\*5). This recommendation is graded as *OPTIONAL*. 4) If the *CYP4F2*\*3 (i.e., c.1297A, p.433Met) allele is also detected, increase the dose by 5–10%. This recommendation is also considered *OPTIONAL*. 5) The data do not suggest an association between rs12777823 genotype and warfarin dose in non-African Americans, thus rs12777823 should not be considered in these individuals (even if available).



**Figure 3** Dosing recommendations for warfarin dosing based on genotype for pediatric patients. (a) Data strongest for European ancestry populations and consistent in most Japanese studies. (b) “Dose clinically” means to dose without genetic information, which may include use of a clinical dosing algorithm or standard dose approach. (c) Validated published pediatric pharmacogenetic algorithms include Hamberg *et al.*<sup>42</sup> and Biss *et al.*<sup>41</sup> (d) No studies in children included *CYP2C9*\*5, \*6, \*8, or \*11 genotyping.

**African ancestry recommendation**

In patients of African ancestry, *CYP2C9*\*5, \*6, \*8, \*11 are important for warfarin dosing. If these genotypes are *not* available, warfarin should be dosed clinically without consideration for genotype. If *CYP2C9*\*5, \*6, \*8, and \*11 are known, then the recommendation, as shown in **Figure 2**, is to: 1) calculate warfarin dose using a validated pharmacogenetic algorithm, including genotype information for *VKORC1* c.-1639G>A and *CYP2C9*\*2 and \*3<sup>16,17</sup>; 2) if the individual carries a *CYP2C9*\*5, \*6, \*8, or \*11 variant allele(s), decrease calculated dose by 15–30%. Larger dose reductions might be needed in patients who carry two variant alleles (e.g., *CYP2C9*\*5/\*6) (i.e., 20–40% dose reduction). 3) In addition, rs12777823 is associated with warfarin dosing in African Americans (mainly originating from West Africa). Thus, in African Americans a dose reductions of 10–25% in those with rs12777823 A/G or A/A genotype is recommended. These recommendations are considered *MODERATE*.

In individuals with genotypes that predict *CYP2C9* poor metabolism or who have increased warfarin sensitivity (*VKORC1* c.-1639 A/A) and *CYP2C9* poor metabolism, an alternative oral anticoagulant should be considered (see **Supplemental Material** for definitions of strength of recommendations). As noted above, for non-African ancestry, if a loading dose is to be used, the EU-PACT algorithm<sup>33</sup> that incorporates genetic information could be used to calculate loading dose. This recommendation is *OPTIONAL*. The data do not support an impact on clinical phenotype for *CYP4F2* on warfarin dosing in those of African ancestry and so no recommendation is made for use of *CYP4F2* genotype data in blacks.

**Recommendations for pediatric patients**

As detailed in **Supplemental Table S7**, there is strong evidence for the use of *CYP2C9*\*2 and \*3 and *VKORC1-1639G>A* genotype to guide warfarin dosing in children of European ancestry. The studies in Japanese pediatric individuals are conflicting, as *VKORC1* and *CYP2C9* could not be adequately evaluated due to the low numbers of *CYP2C9* variant carriers. For other

ethnicities, there is no evidence documenting that *VKORC1* and *CYP2C9* are important. Furthermore, there are no data in children that included *CYP2C9*\*5, \*6, \*8, or \*11 genotyping. Based on the current evidence, in children of European ancestry and if *CYP2C9*\*2 and \*3 and *VKORC1-1639* genotype are available, calculate warfarin dosing based on a validated published pediatric pharmacogenetic algorithm (Figure 3).<sup>40,41</sup> A dosing tool that can be used in children of European ancestry is available at <http://www.warfarindoserevision.com>.<sup>42</sup>

### Other considerations

Given the effects of *CYP2C9* on warfarin clearance, and given that the *CYP2C9* variant alleles are associated with reduced warfarin clearance, *CYP2C9* genotype may influence time to onset and offset of anticoagulation, as measured by INR.<sup>43</sup> The **Supplemental Material** summarizes other considerations in the dosing of warfarin, including clinical factors and interacting drugs, some of which are included in the pharmacogenetic dosing algorithms (see **Text Box 1**). Other genes of potential importance are detailed in the **Supplemental Material and Supplemental Table S6**, including *CALU* and *GGCX*. Most clinical genotyping platforms do not include these genes, nor do the dosing tables or published algorithms. The **Supplemental Material** also discusses incorporation of genetic information into the initial dose, and alternatives to warfarin.

### POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

Incorporation of genetic information has the potential to shorten the time to stable INR, increase the time within the therapeutic INR range, and reduce underdosing or overdosing during the initial treatment period.<sup>33</sup> If these benefits are achieved, they could result in a reduced risk of bleeding and thromboembolic events.<sup>12,44</sup> There are also potential risks. For example, using genetic information to guide dosing may lead to false security and inadequate INR monitoring. In particular, there are risks of using pharmacogenetic dosing in those of African ancestry if only *CYP2C9* \*2 and \*3 alleles are included. Genetic-guided dosing may increase the risk for overdosing or underdosing, especially in individuals who carry rare or untested variants and are assigned as “wild-type” by default.<sup>17,32</sup> The cost–benefit of genetic-guided therapy depends on the cost of genotyping and the reduction in adverse events,<sup>45</sup> and most insurance plans do not currently pay for warfarin pharmacogenetic testing. Although there is substantial evidence associating *CYP2C9* and *VKORC1* variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes (see Linking genetic variability to variability in drug-related phenotypes, above). Although genotyping is reliable when performed in qualified laboratories, an additional risk is an error in genotyping or reporting of genotype. Genotypes are life-long test results, so such error could have long-term adverse health implications.

### CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Many pharmacogenetic dosing algorithms are developed for a target INR of 2–3<sup>17</sup> and so their utility for estimating therapeutic

warfarin doses with other target INR ranges is uncertain; however, some algorithms accommodate the target INR explicitly.<sup>16,42</sup> Pharmacogenetic-guided warfarin dosing does not alter the requirements for regular INR monitoring. There are patients for whom genetic testing is likely to be of little or no benefit, including those who already have had long-term treatment with stable warfarin doses and those who are unable to achieve stable dosing due to variable adherence. The greatest potential benefit is early in the course of therapy (before therapy initiation or in the early days of therapy).<sup>36</sup> It is likely that patients on therapy for many weeks to months, with careful INR monitoring, will derive little benefit from subsequent warfarin pharmacogenetics testing.<sup>46</sup>

### DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision-making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of CPIC’s guidelines, or for any errors or omissions.

**SUPPLEMENTARY MATERIAL** is linked to the online version of the article at [www.cpt-journal.com](http://www.cpt-journal.com)

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### CONFLICTS OF INTEREST

J.A.J. is on the CPIC Steering Committee and has no conflicts of interest related to this guideline. T.E.K and M.W.C. are paid scientific advisors to the Rxight Pharmacogenetic Program. S.A.S. is a director of a clinical laboratory that performs *CYP2C9* and *VKORC1* genetic testing. All other authors declare no conflicts of interest related to this guideline.

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