

# Warfarin Pharmacogenetics

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April 3 2008



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SCHOOL OF  
MEDICINE

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## I. Warfarin Background

- A. Clinical Use
- B. Mechanism

## II. Pharmacogenetics

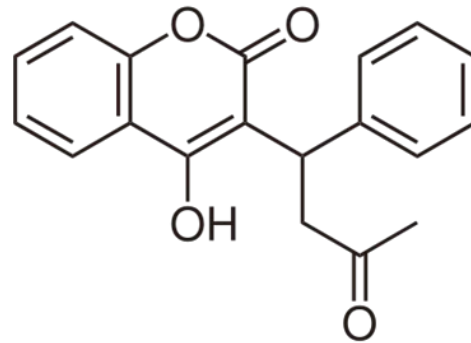
- A. Pharmacokinetics: **CYP2C9**
- B. Pharmacodynamics: **VKORC1**
- C. Others

## III. FDA Recommendation

- A. PGx Testing
- B. Techniques

## IV. Algorithm-mediated Dose Selection

# I. Warfarin Background



# I. Warfarin Background

- One of the most widely used anticoagulants.
  - Wisconsin Alumni Research Foundation (WARF); Coumadin®
  - ~2 million new prescriptions/year
- Used for prevention of thrombosis and embolism.
  - Atrial fibrillation
  - Heart valve prosthesis
  - Recurrent stroke
  - Deep vein thrombosis
  - Pulmonary embolism
- Impairs synthesis of vitamin K dependent clotting factors:
  - Factor II, VII, IX, X, protein C and protein S
- Inhibits vitamin K reductase – key enzyme in vitamin K recycling.

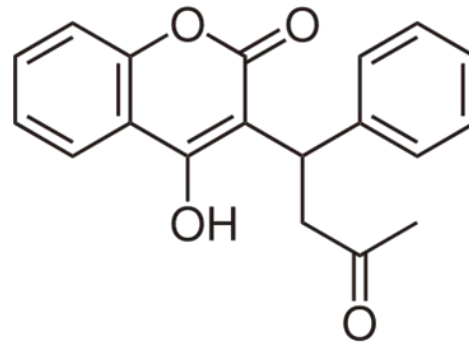
# I. Warfarin Background

- Complicated clinical use:
  - Wide inter-individual differences in drug response
  - Narrow therapeutic range
  - High risk of bleeding or stroke
- Hemorrhage risk is greatest during first weeks to months of therapy.
  - Second most common drug, after insulin, to send patients to ER
  - Under-used because of its toxicity
- Requires frequent monitoring by international normalized ratio (INR) blood test.
  - Normal range ~1
  - Dosing is adjusted to maintain a therapeutic range of ~2-3

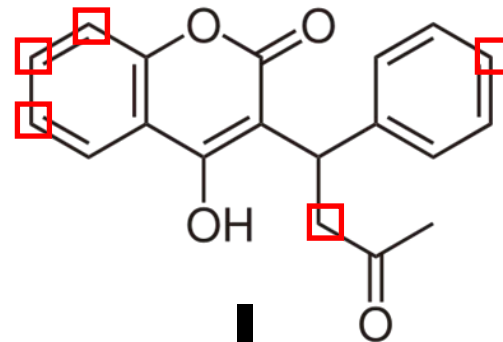
# I. Warfarin Background

- Warfarin dosing variability is due to many factors:
  - Drug-drug interactions
  - Diet (vitamin K)
  - Alcohol
  - Smoking
  - Genetics
- Two generalized clinical scenarios can occur:
  - **Warfarin 'sensitivity'** = decreased dosage: frequent and leads to INR > target range. Increased risk of severe bleeding events.
  - **Warfarin 'resistance'** = increased dosage: infrequent and leads to INR < target range. Increased risk of embolism/stroke.

## II. Warfarin Pharmacokinetics

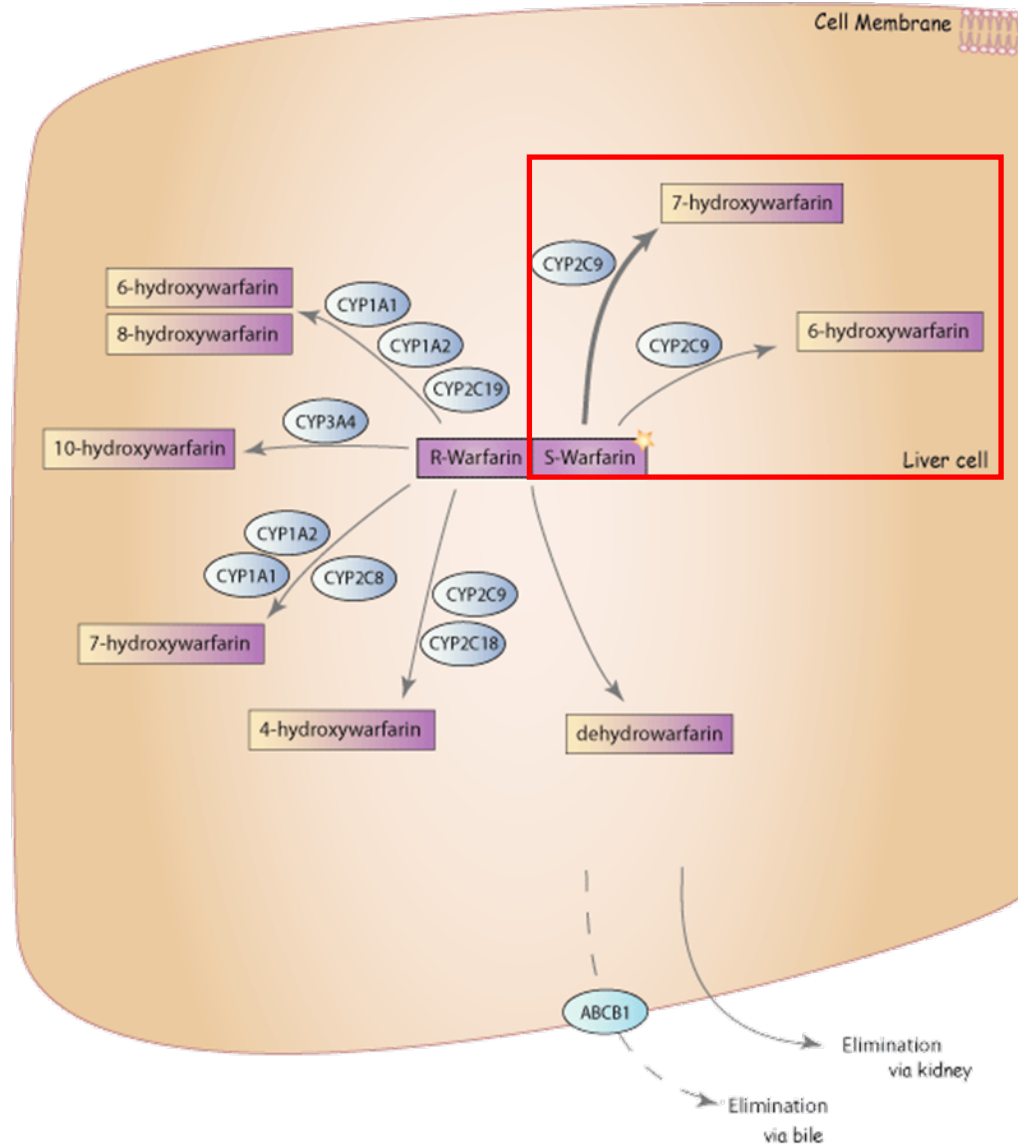


**CYP450**



**EXCRETION**

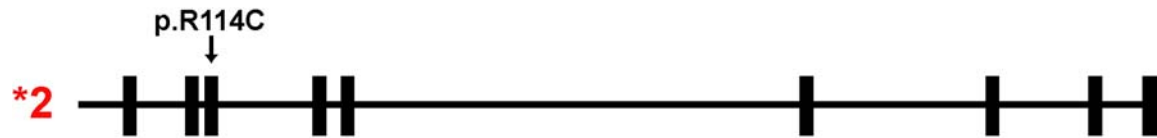
# II. Warfarin Pharmacokinetics



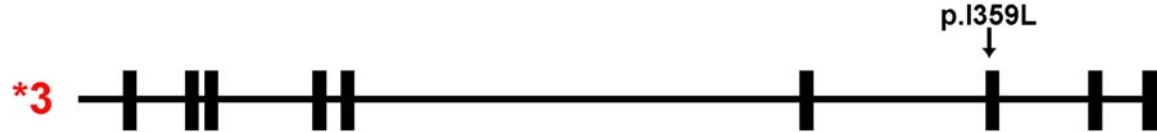
## II. Warfarin Pharmacokinetics

- **CYP2C9** (10q24) is major enzyme involved in warfarin metabolism.
  - Required for excretion of more polar metabolite.
- Polymorphic **CYP2C9** variants with decreased activity result in deficient warfarin clearance.
  - ~30 known alleles: <http://www.cypalleles.ki.se/cyp2c9.htm>
  - \*2 and \*3 most common deficient alleles among most ethnic groups.
- Individuals who carry deficient **CYP2C9** alleles are **sensitive** and have lower warfarin dose requirements.

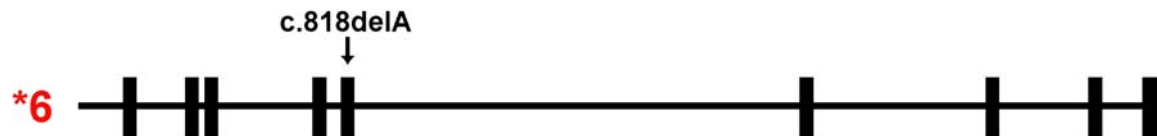
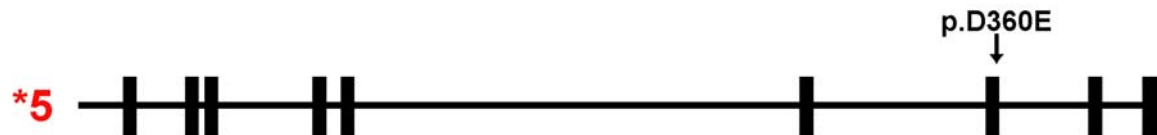
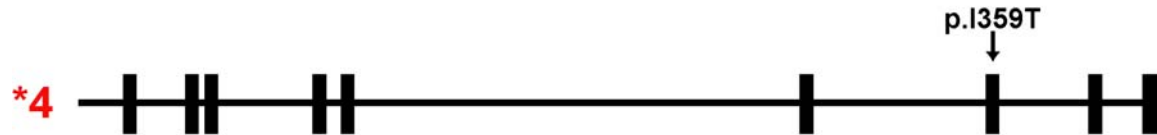
# II. Warfarin Pharmacokinetics



~25% dose reduction

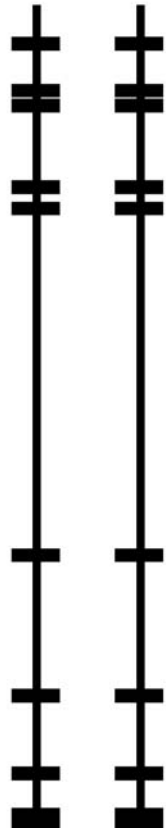


~35% dose reduction



## II. Warfarin Pharmacokinetics

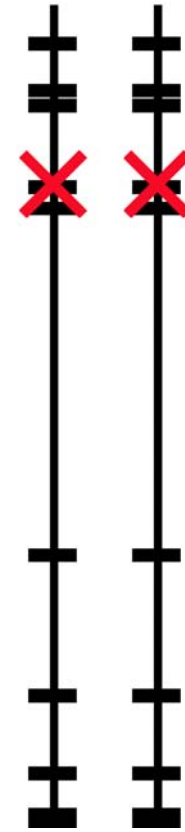
Extensive  
Metabolizer (EM)



Intermediate  
Metabolizer (IM)

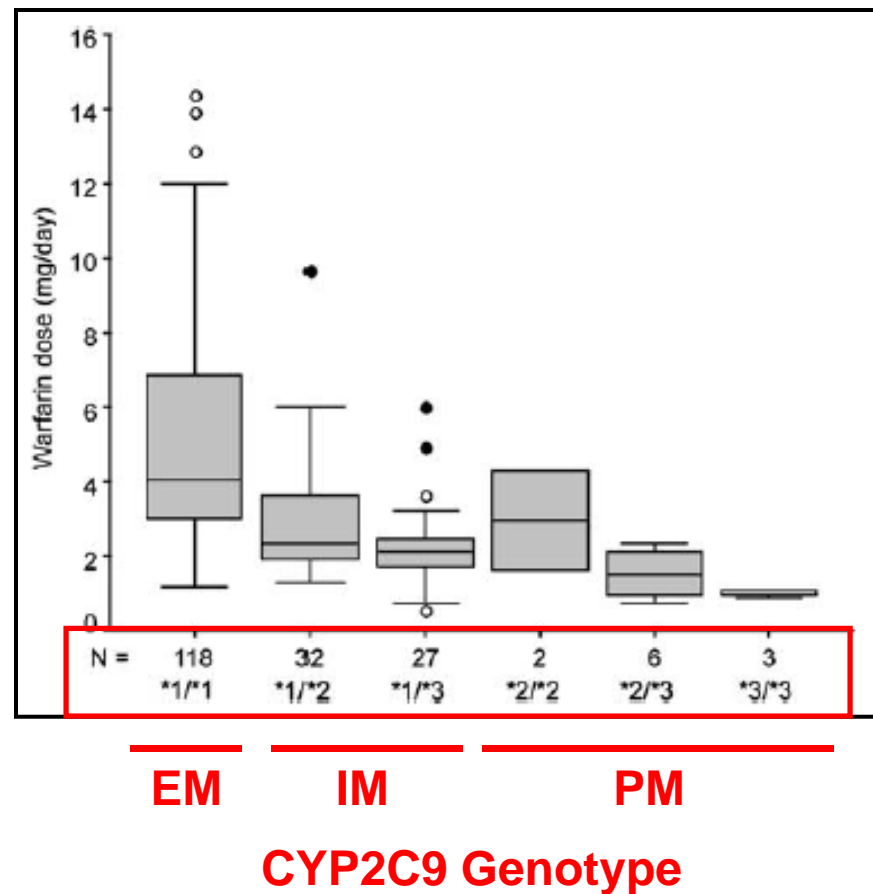


Poor  
Metabolizer (PM)



# II. Warfarin Pharmacokinetics

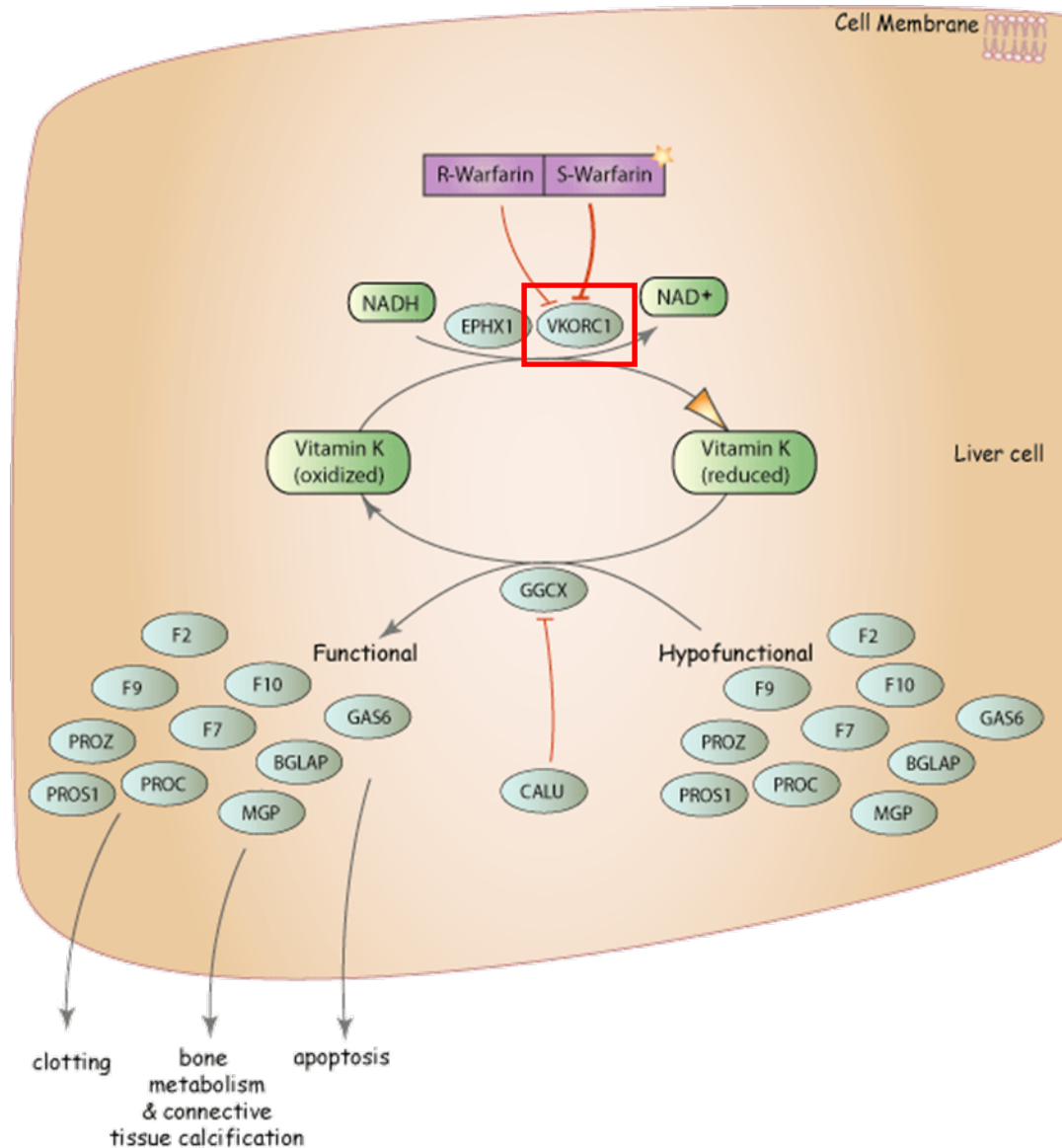
Allele CYP2C9	Frequency	Metabolizer
*1*1 (wild-type)	56 %	Extensive 100%
*1*2 (variant)	22 %	Intermediate 50-70%
*1*3 (variant)	14 %	
*2*2 (variant)	3 %	Poor 10-15%
*2*3 (variant)	4 %	
*3*3 (variant)	1 %	



## II. Warfarin Pharmacodynamics

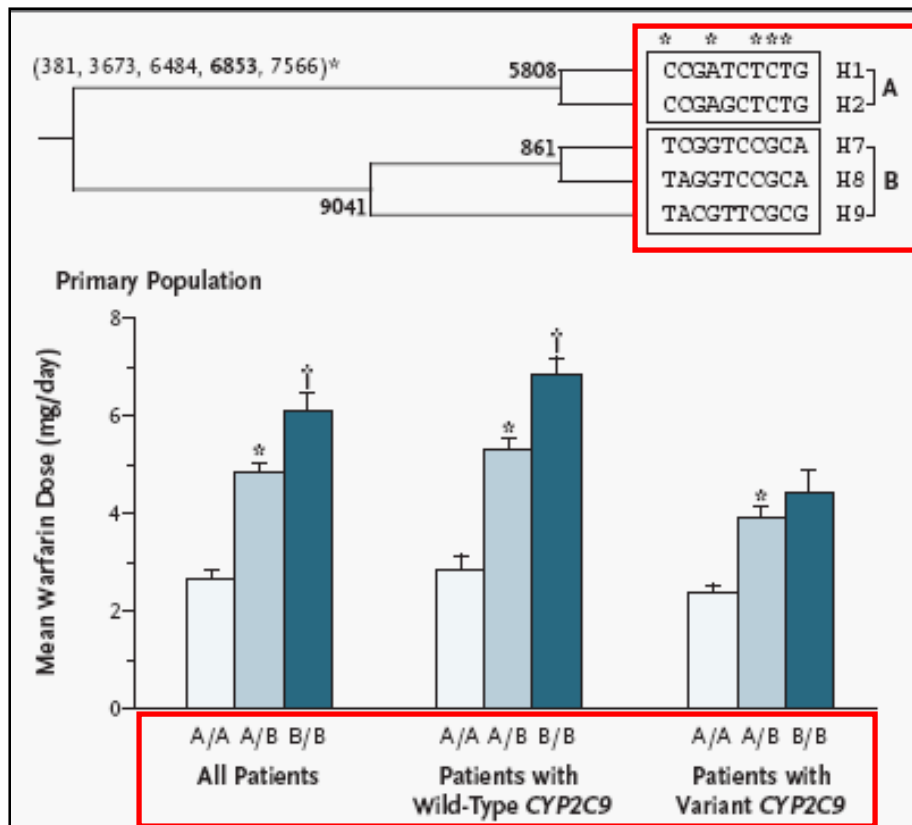
- Vitamin K epoxide reductase complex subunit 1 (**VKORC1**) is major target of warfarin inhibition.
- Inhibition of **VKORC1** by warfarin decreases the regeneration of reduced vitamin K.
- Reduced Vitamin K is necessary for gamma-carboxylation of coagulation factors.

# II. Warfarin Pharmacodynamics



# II. Warfarin Pharmacodynamics

- **VKORC1** gene (16p11) has only recently been identified (2004).
- Common **VKORC1** SNPs associated with therapeutic warfarin dose.



**Two haplotype groups (A and B) associated with dose**

Rieder MJ, et al., *N Engl J Med.* 2005 2;352(22):2285-93.

# II. Warfarin Pharmacodynamics

- Five **VKORC1** SNPs are in strong linkage disequilibrium.

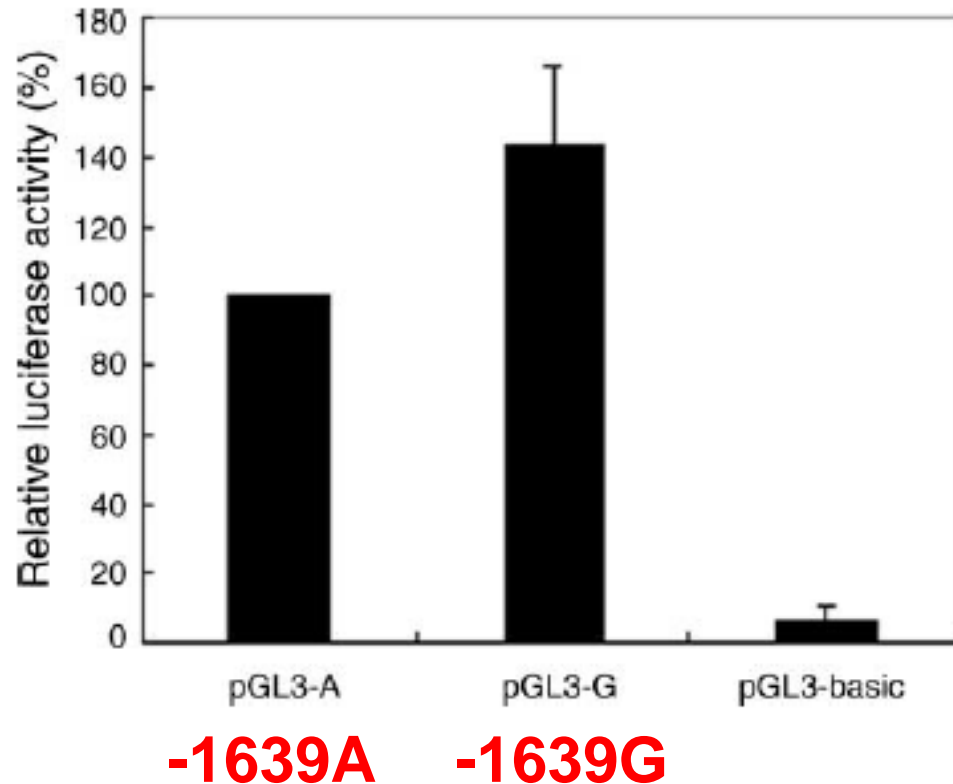
marker nucleotide position nucleotide change region	M2	M3	M8	M9	M13	M16	M17	M18	M19	M20	M21	M23	M25	M26	haplotype	frequency [%]		
	3673	3859	5347	5440	5808	6009	6484	6663	7566	8026	8773	9041	9810	10066		Europeans (GER) n=200	Africans (AFR) n=23	Chinese (CHN) n=24
AYS87020 (reference sequence)	G	G	G	C	T	C	C	G	C	A	C	G	A	C	VKORC1*1	< 0.1	31	< 0.1
	A	-	-	-	-	T	C	T	-	-	-	-	-	VKORC1*2A	12	n.a.	n.a.	
	A	-	G	-	T	C	T	-	-	-	-	-	-	VKORC1*2B	30	42	14	
	-	-	-	-	-	-	-	-	-	-	A	-	-	VKORC1*3A	26	n.a.	n.a.	
	-	-	-	-	-	-	-	-	G	-	A	-	-	VKORC1*3B	8	n.a.	n.a.	
	-	-	-	T	-	-	-	-	G	-	A	-	-	VKORC1*3C	1	n.a.	n.a.	
	-	A	A	-	-	-	-	-	-	-	A	-	-	VKORC1*3D	1	38	43	
	-	-	-	-	-	-	-	-	-	-	A	-	T	VKORC1*3E	1	n.a.	n.a.	
	-	-	-	-	-	-	-	-	-	T	A	-	-	VKORC1*3F	0.5	21	< 0.1	
	-	-	-	-	T	-	-	-	-	-	-	-	-	VKORC1*4A	19	n.a.	n.a.	
	-	-	-	-	T	-	-	-	-	-	-	G	-	VKORC1*4B	1	20	12	

↑  
**-1639G>A**

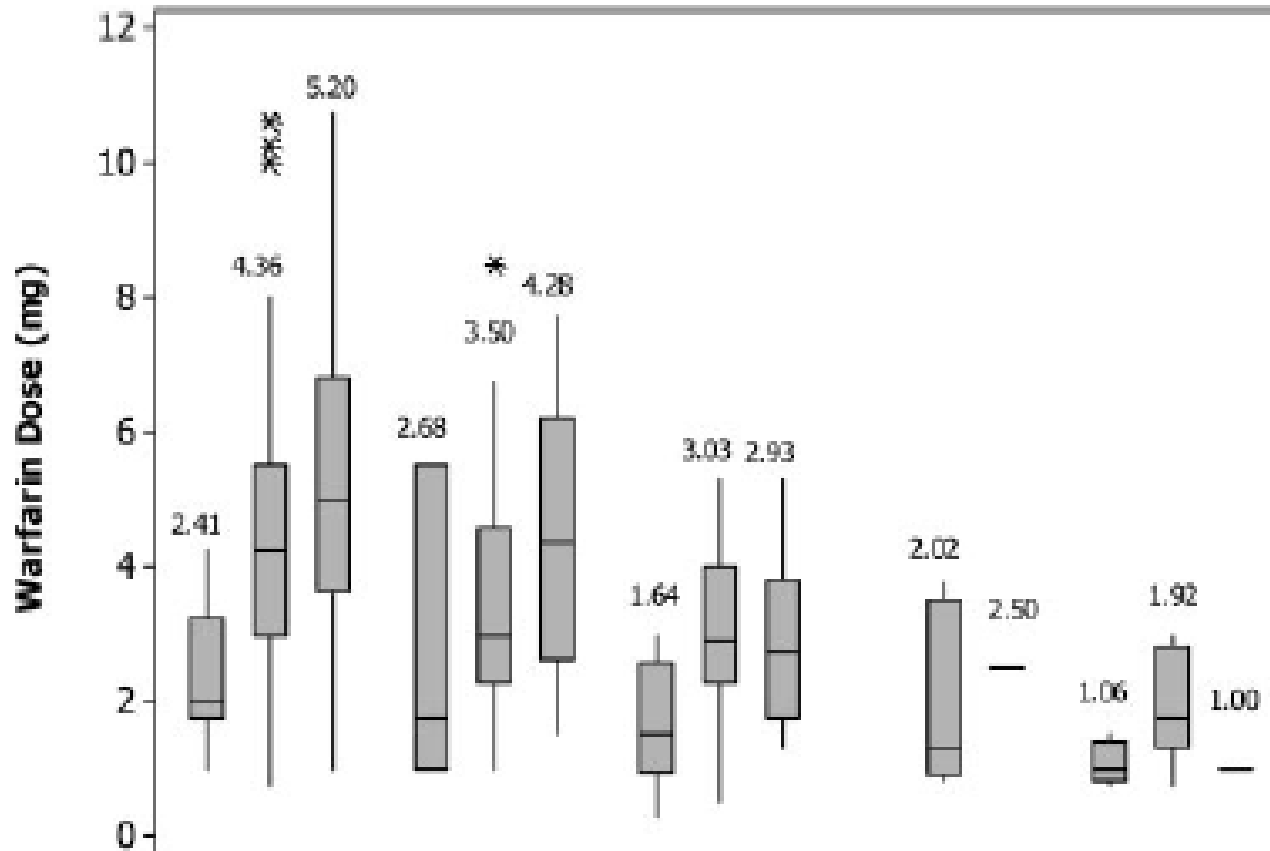
↑  
**1173C>T**

## II. Warfarin Pharmacodynamics

- -1639G>A results in reduced hepatic expression of **VKORC1**, which is likely responsible for decreased warfarin requirements.



# II. Warfarin Pharmacodynamics



VKORC1 Genotype	AA	GA	GG	AA	GA	GG	AA	GA	GG	AA	GA	GG			
CYP2C9 Genotype	*1*1 (n=163)			*1*2 (n=66)			*1*3 (n=42)			*2*2 (n=8)			*2*3/*3*3 (n=11)		

**EM**

**IM**

**PM**

**CYP2C9 Genotype**

# II. Warfarin Pharmacodynamics

- Warfarin resistance is due, in part, to **VKORC1** coding region mutations.

**D36Y**

**Table 1. Genotypes in the warfarin-resistant and -sensitive patient groups**

Patient no.	Sex	Age, y	Weight, kg	Dose, mg/wk	CYP2C9 genotypes	VKORC1 haplotypes	VKORC1 Asp36Tyr
<b>Warfarin-resistant group</b>							
1	F	42	52	185	*1/*1	*1/*3	Wt/Mut
2	M	60	90	140	*1/*1	*1/*4	Wt/Mut
3	F	84	51	138	*1/*1	*1/*4	Wt/Mut
4	F	53	70	135	*1/*2	*1/*4	Wt/Mut
5	M	53	90	123	*1/*1	*1/*2	Wt/Mut
6	F	34	82	123	*1/*1	*1/*3	Wt/Mut
7	M	60	66	115	*1/*1	*3/*4	Wt/Wt
8	M	32	80	110	*1/*1	*3/*3	Wt/Wt
9	F	35	65	105	*1/*1	*3/*4	Wt/Wt
10	F	55	72	95	*1/*1	*4/*4	Wt/Wt
11	F	40	53	95	*1/*1	*3/*4	Wt/Wt
12	M	55	91	80	*1/*3	*1/*2	Wt/Mut
13	F	43	55	80	*1/*1	*2/*3	Wt/Wt
14	F	48	65	80	*1/*1	*2/*3	Wt/Wt
15	F	31	80	88	*1/*1	*3/*3	Wt/Wt
<b>Warfarin-sensitive group</b>							
1	M	80	76	13	*1/*3	*2/*2	Wt/Wt
2	M	55	74	12	*1/*1	*2/*2	Wt/Wt
3	M	60	70	12	*1/*3	*2/*2	Wt/Wt
4	F	59	65	12	*1/*3	*2/*2	Wt/Wt
5	M	82	71	11	*1/*1	*2/*2	Wt/Wt
6	M	78	70	10	*1/*2	*2/*3	Wt/Wt
7	F	69	68	7	*3/*3	*1/*3	Wt/Wt
8	M	85	88	7	*3/*3	*2/*4	Wt/Wt

# II. Warfarin Pharmacodynamics

- Warfarin sensitive and resistance markers occur at different frequencies in various ethnic subgroups.

Table 4. *CYP2C9* and *VKORC1* Combined Genotype Frequencies

<i>CYP2C9</i> Genotype (Predicted Metabolizer Phenotype <sup>a</sup> )	VKORC1 g.-1639G → A	AJ			SJ		
		n <sup>b</sup>	Frequency (%)	No. of p.D36Y Carriers	n <sup>b</sup>	Frequency (%)	No. of p.D36Y Carriers
<b>*1/*1 (EM)</b>							
	G/G	49	18.8	9 <sup>c</sup>	9	11.3	1
	G/A	81	31.2	10	14	17.5	0
	A/A	38	14.6	0	13	16.3	0
<b>*1/*2 or *1/*3 (IM)</b>							
	G/G	26	10.0	2	11	13.8	0
	G/A	38	14.6	3	17	21.3	0
	A/A	20	7.7	0	6	7.5	0
<b>*2/*2, *2/*3, or *3/*3 (PM)</b>							
	G/G	1	0.4	1	2	2.5	0
	G/A	6	2.3	2	5	6.3	0
	A/A	1	0.4	0	3	3.8	0

<sup>a</sup> EM, extensive metabolizer; IM, intermediate metabolizer; and PM, poor metabolizer.

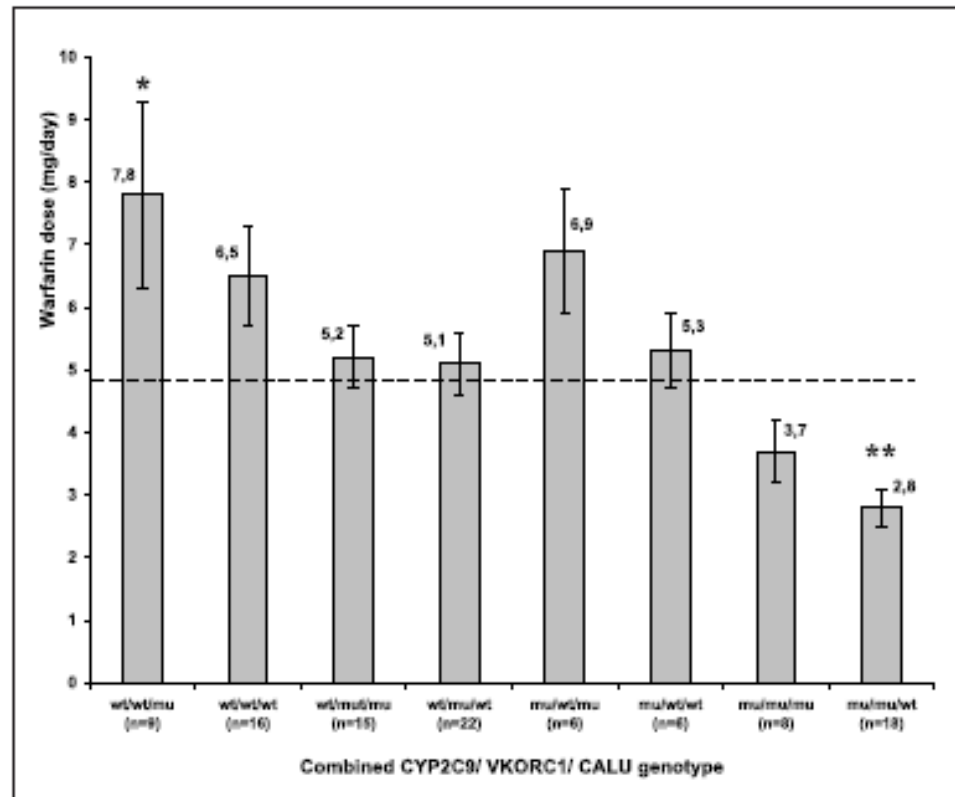
<sup>b</sup> Number of subjects.

<sup>c</sup> One p.D36Y homozygote was found in this group.



## II. Other Genes Involved in Warfarin Variability

- Genotyping of 100 patients for SNPs in 5 genes (**CYP2C9**, **VKORC1**, **CALU**, **GGCX**, **EPHX1**) within the warfarin pathway identified significant dosing association with **CALU-R4Q** variant as well as **CYP2C9** and **VKORC1**.



## II. Other Genes Involved in Warfarin Variability

- Genotyping of 201 patients for SNPs in 29 genes within the warfarin pathway identified significant dosing association with **VKORC1**, **CYP2C9**, **PROC**, and non-genetic factors (age, bodyweight, comedications, indication)  
→ accounted for **62% of variability**.
- Weaker associations with other genes (**EPHX1**, **GGCX**, **ORM1-2**) could explain up to ~10%, but needs to be validated in larger cohort.

# III. FDA Recommends Warfarin Label Revision



U.S. Food and Drug Administration



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## FDA News

FOR IMMEDIATE RELEASE  
August 16, 2007

**Media Inquiries:**  
Karen Riley, 301-827-6242  
**Consumer Inquiries:**  
888-INFO-FDA

**FDA Approves Updated Warfarin (Coumadin) Prescribing Information**  
*New Genetic Information May Help Providers Improve Initial Dosing Estimates of the Anticoagulant for Individual Patients*

- Explains that an individual's genetic makeup (**CYP2C9** and **VKORC1**) may influence response to the drug.
- Testing *may* help optimize the use of warfarin and lower the risk of bleeding complications from the drug.



### III. FDA Recommends Warfarin Label Revision

- **ACMG Policy Statement published February 2008:** ACMG Working Group on Pharmacogenetic Testing of CYP2C9, VKORC1 Alleles for Warfarin Use. *Genet Med.* 2008;10(2):139-50.
  - Insufficient evidence at this time to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naïve patients.
  - Prospective clinical trials are needed to provide evidence of benefit, disadvantage, and costs.
  - Although not fully endorsed, “CYP2C9 and VKORC1 testing may be useful, and warranted, in determining the cause of unusual therapeutic responses to warfarin therapy.”

### III. FDA Recommends Warfarin Label Revision

- **February 2008:** A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. *Genet Med.* 2008;10(2):89-98.
  - Review literature to address analytical validity, clinical validity, clinical utility, and ethical, legal, and social implications.
  - Overall analytic sensitivity and specificity will be 98% or higher for CYP2C9 genotyping, but not enough information available on VKORC1 testing.

# III. FDA Recommends Warfarin Label Revision

**Table 2**  
Analytic validity of *CYP2C9* (restricted to the \*2 and \*3 variants) and *VKORC1* testing

Reference	Year	Assay method	Referent method	<i>CYP2C9</i>					Analytic specificity (*1, *1)
				Analytic sensitivity (test result/referent result)					
				(*1, *2)	(*2, *2)	(*1, *3)	(*3, *3)	(*2, *3)	
Hillman et al. <sup>22</sup>	2004	LightCycler	Sequencing	2/2	1/1	—	1/1	1/1	4/4
Pickering et al. <sup>23</sup>	2004	Luminex, eSensor	Sequencing	15/15	1/1	13/13	—	2/2	70/70
Wen et al. <sup>24</sup>	2003	Microarray	Sequencing	—	—	7/7	—	—	13/13
Zainuddin et al. <sup>25</sup>	2003	Nested PCR	Sequencing	3/3	—	5/5	2/2	2/2	28/28
Eriksson et al. <sup>21</sup>	2002	Pyrosequencing	PCR-RFLP	9/9	—	5/5	—	—	9/9
Aquilante et al. <sup>19</sup>	2004	Pyrosequencing	PCR-RFLP	—	—	—	—	—	—
Burian et al. <sup>20</sup>	2002	LightCycler	PCR-RFLP	27/27	1/1	10/10	1/1	1/1	79/79
<i>Total</i>				56/56	3/3	40/40	4/4	6/6	203/203
Third Wave Tech	2006	Invader, Tag-It, Pyro	Sequencing	9/9	3/3	6/6	2/2	6/6	9/9
ARUP Laboratory	2006	Invader, Tag-It	Sequencing	9/9	—	1/1	—	—	21/21
LabCorp	2006	Invader, Tag-It	PCR-RFLP	6/6	1/1	5/5	1/1	4/4	5/5
				<i>VKORC1</i>					
				AB	AA				BB
Third Wave Tech	2006	Invader, Pyro	Sequencing	16/16	12/12				7/7
ARUP	2006	Invader	Sequencing	10/10	4/4				17/17
LabCorp	2006	Invader	PCR-RFLP, sequencing	10/10	5/5				7/7

ARUP, Associated Regional and University Pathologists.

### III. FDA Recommends Warfarin Label Revision

- **February 2008:** A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. *Genet Med.* 2008;10(2):89-98.
  - Gaps in knowledge:
    - which variants to include in panel
    - external proficiency testing
    - validated dosing algorithms
    - evidence of clinical utility, economics
    - ethical, legal, and social implications

# III. FDA Recommends Warfarin Label Revision

- The College of American Pathologists (CAP) has established a working group (CAP/ACMG/others) to develop an annual Pharmacogenomics (PGx) Survey.
  - Twice per year participating clinical labs receive 25  $\mu$ g of DNA:
    - CYP2C19
    - **CYP2C9**
    - CYP2D6
    - UGT1A1
    - **VKORC1**



College of American Pathologists



American College of Medical Genetics  
Medical Genetics: Translating Genes Into Health®

# IV. Algorithm-mediated Dose Selection

- Several groups have attempted to estimate the optimum initial warfarin dose needed to maintain stable and optimum anticoagulation using genetic and non-genetic variables.
- **Examples:**

## **Sconce E, et al (2005):**

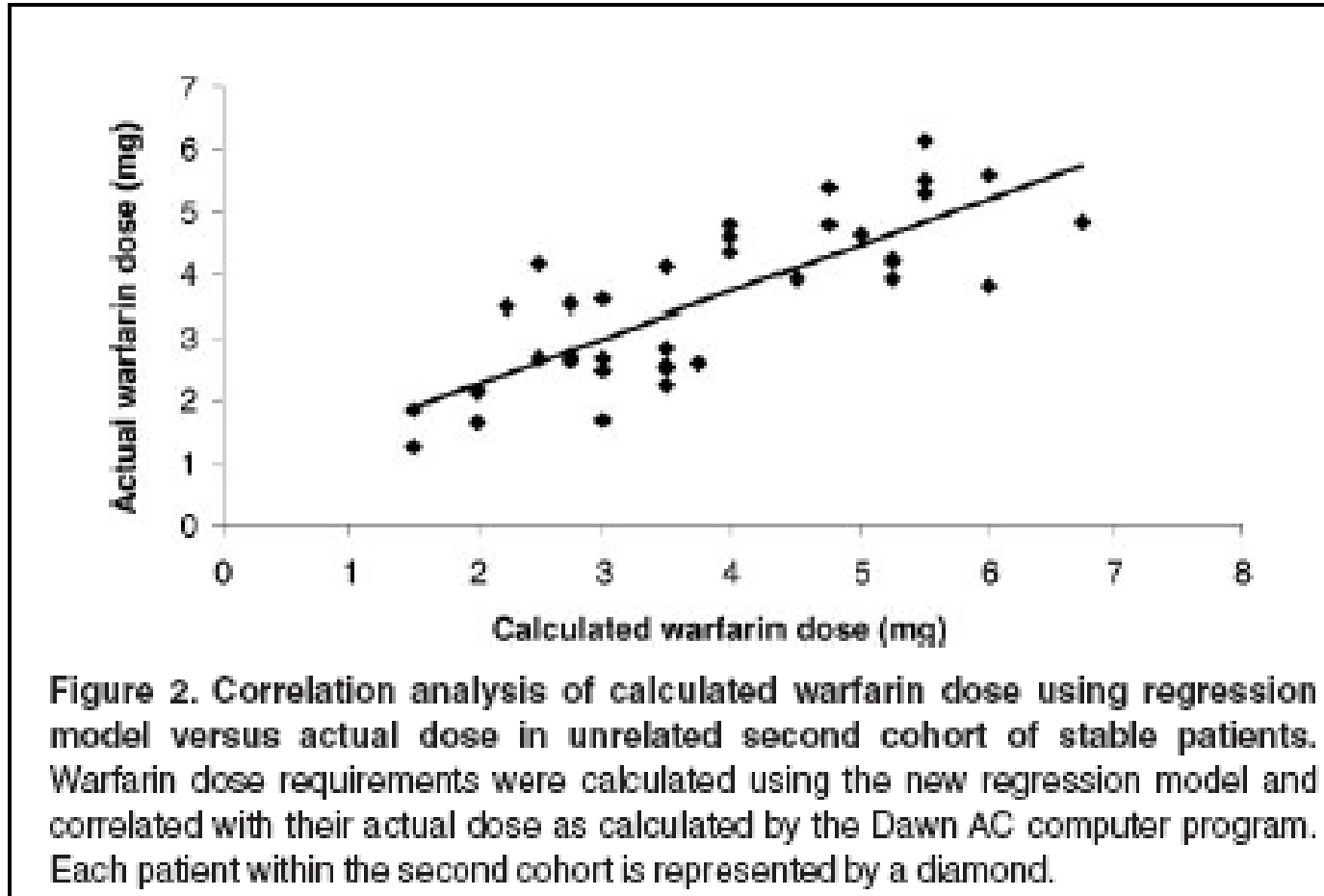
$$\sqrt{\text{dose (mg/day)}} = 0.628 - 0.0135(\text{age}) - 0.240(2C9^*2) - 0.370(2C9^*3) - 0.241(\text{VKORC1-1639}) + 0.0162(\text{height})$$

## **Gage B, et al (2008):**

dose (mg/day) =

$\exp[0.9751 - 0.3238 \times \text{VKOR3673G>A} + 0.4317 \times \text{BSA} - 0.4008 \times \text{CYP2C9}^*3 - 0.00745 \times \text{age} - 0.2066 \times \text{CYP2C9}^*2 + 0.2029 \times \text{target INR} - 0.2538 \times \text{amiodarone} + 0.0922 \times \text{smokes} - 0.0901 \times \text{African-American race} + 0.0664 \times \text{DVT/PE}]$ , where the SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous, and race is coded as 1 if African American and 0 otherwise.

# IV. Algorithm-mediated Dose Selection



# IV. Algorithm-mediated Dose Selection

## WARFARIN DOSING

www.WarfarinDosing.org

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User:  
Patient:  
Version 13.1  
Build : Mar 26, 2008

### Required Patient Information

Age:  Sex:  Ethnicity:

Race:

Weight:  lbs or  kgs

Height: ( feet and  inches) or ( cms)

Smokes:  Liver Disease:

Indication:

Baseline INR:  Target INR:

CYP2C9 Genotype:   Randomize & Blind

VKORC1-1639/3673 Genotype:

Amiodarone/Cordarone® Dose:  mg/day

Statin/HMG CoA Reductase Inhibitor:

Any azole (eg. Fluconazole):

Sulfamethoxazole/Septtra/Bactrim/Cotrim/Sulfatrim:

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> ESTIMATE WARFARIN DOSE

# IV. Algorithm-mediated Dose Selection

## WARFARIN DOSING

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User:

Patient: 0

Version 13.1

Build : Mar 26, 2008

### Estimate of Warfarin Dose

Estimated loading dose: 5.0 mg for initial warfarin dose.

Estimated therapeutic dose: 3.3 mg/day.

Today's prescribed dose:  mg.



(Slide the Pointer to the dose you would like to prescribe today.)

Patient Code (e.g. BG or 007)\*:

Email address to save patient under\*:

When would you like an email to remind you to check the INR: In  hours.

\* All information entered into this site is kept confidential. Your e-mail address will not be shared, sold, or rented. It is required to save and to access this record.

### Recommendations

We developed this initial dose algorithm from 1015 patients and prospectively validated in 292 additional patients starting warfarin where the R2 was 54% and the median absolute error was 1.0 mg/day ([Clin Pharmacol Ther](#) 2008).

To get a better estimate of the therapeutic dose, first save this record by entering a patient code and your email address. Then, return to this site after 1, 2, and/or 3 warfarin doses and enter that day's INR.

# IV. Algorithm-mediated Dose Selection

## Box 1. Published warfarin dosing algorithms.

### University of Newcastle, Newcastle, UK [23]:

Square root of dose (mg) =  $0.628 - 0.0135(\text{age}) - 0.240(\text{CYP}^*2) - 0.370(\text{CYP}^*3) - 0.241(\text{VKORC1} -1639) + 0.0162(\text{height})$   
Where  $\text{CYP}^*2$  and  $^*3$  are the number of alleles present, if any, and  $\text{VKORC1} = 1$  for GG, 2 for GA and 3 for AA, and height in cm.

### University of Louisville, KY, USA [45]:

In dose (mg) =  $1.35 - 0.008(\text{age}) + 0.116(\text{sex}) + 0.004(\text{weight}) - 0.376(\text{VKORC1} -1639 -M) + 0.271(\text{VKORC1} W) - 0.307(2\text{C9}^*2) - 0.318(2\text{C9}^*3)$

Where sex = 0 for female, 1 for male,  $\text{VKORC1} M, W = 0,0$  for GA, 1,0 for AA and 0,2 for GG,  $\text{CYP}^*2, ^*3$  are the number of alleles present, if any, and weight in pounds.

### Uppsala University, Uppsala, Sweden [37]\*:

Dose (mg) =  $(15.5 - 23.2[\text{VKORC1} T/T] - 11.5[\text{VKORC1} T/C] + 34.4[2\text{C9}^*1/^*1] + 29.7[2\text{C9}^*1/^*2] + 23.9[2\text{C9}^*1/^*3] + 13.7[2\text{C9}^*2/^*2] + 14.3[2\text{C9}^*2/^*3] - 0.316[\text{age}] + 20.6[\text{if comeds are } 2\text{C9} \text{ inducers}] + 2.16[\text{if no } 2\text{C9} \text{ interactions}] + 0.222[\text{weight}] - 4.65[\text{if not treated for heart valve replacement}])/7$

Where  $\text{VKORC1} = 1$  for TT, TC or CC, comeds inducers = 1 if present, if no  $2\text{C9}$  interactions = 1, and weight in kg.

\*Algorithm written by Niclas Ericsson, Panos Deloukas, Leslie Chen and Mia Wadelius.

### National University Hospital, Singapore [46]:

Log dose (mg) =  $0.838 - 0.005(\text{age}) + 0.003(\text{weight}) - 0.189(2\text{C9}^*3) - 0.283(\text{VKORC1} 383\text{CC}) - (0.119 \times \text{VKORC1} \text{ TC})$

Where weight is in kg,  $2\text{C9}^*3, \text{VKORC1} \text{ TT or TC} = 1$ , if present.

### University of California, San Francisco, CA, USA [Unpublished Observations]:

Log dose =  $1.10837 - 0.03597^*(2\text{C9}^*2) - 0.21622^*(2\text{C9}^*3) - 0.00218^*(\text{age}) - 0.08091^*(\text{Asian}) - 0.00365^*(\text{African-American}) + 0.08583^*(\text{gender}) - 0.00257^*(\text{height}) - 0.03838^*(\text{Hispanic}) - 0.11285^*(\text{inhibitors}) + 0.06889^*(\text{other ethnicity}) + 0.03087^*(\text{smoking}) + 0.02287^*(\text{VKORC1} -1639) + 0.00162^*(\text{weight}) - 0.07326^*(\text{VKORC1} 2255\text{TC}) - 0.32939^*(\text{VKORC1} 2255\text{TT})$

Where Asian = 1, if present, African-American = 1, if present, Hispanic = 1, if present, male = 1, female = 2, height in cm, inhibitors = 1, if present, smoking = 1, if present,  $\text{VKORC1} -1639 = 1$  if GG, 2 if GA and 3 if AA,  $\text{VKORC1} 2255 = 1$  if GG, 2 if GA and 3 if AA, and weight in kg.

CYP: Cytochrome P450; VKORC1: Vitamin K epoxide reductase.



## I. Warfarin Background

- A. Uses – AF, DVT, strokes
- B. Mechanism – Impairs vitamin K dependent clotting factors

## II. Pharmacogenetics

- A. Pharmacokinetics: CYP2C9 – EM, IM, PM
- B. Pharmacodynamics: VKORC1 – -1639G>A (1173C>T), D36Y
- C. Others – GGCX, CALU, EPHX1

## III. FDA Recommendation

- A. PGx Testing – CYP2C9 and VKORC1
- B. Techniques – Molecular assays available with good sen./spec.

## IV. Algorithm-mediated Dose Selection

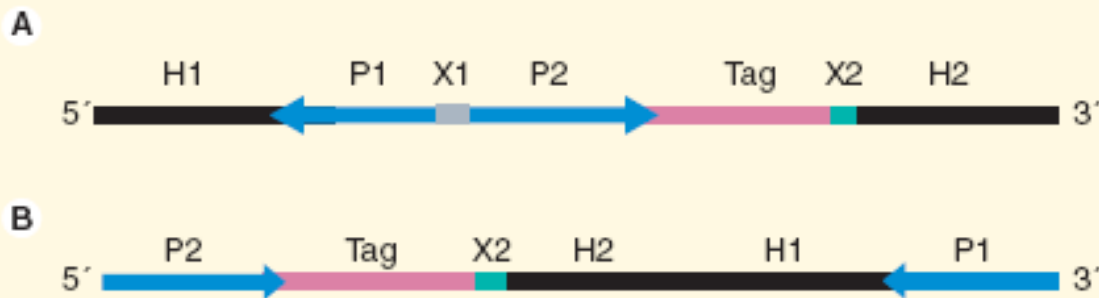
– Multiple regression equations available that include genetic/non-genetic variables but require prospective validation in pan-ethnic cohorts.

## **CYP4F2 genetic variant alters required warfarin dose.**

Caldwell MD, Awad T, Johnson JA, Gage BF, Falkowski M, Gardina P, Hubbard J, Turpaz Y, Langae TY, Eby C, King C, Brower A, Schmelzer JR, Glurich I, Vidaillet HJ, Yale SH, Zhang KQ, Berg RL, Burmester JK.

**Blood. 2008 Feb 4; [Epub ahead of print]**

**Figure 1. Molecular inversion probe before (A) and after (B) inversion.**



H1 and H2 are regions of genomic homology; P1 and P2 represent primer binding sites; X1 and X2 indicate probe cleavage sites; and the Tag is a probe-specific barcode, which hybridizes to a complementary sequence on an Affymetrix Tag Array.

**Figure 2. Standard Targeted Genotyping Assay workflow.**

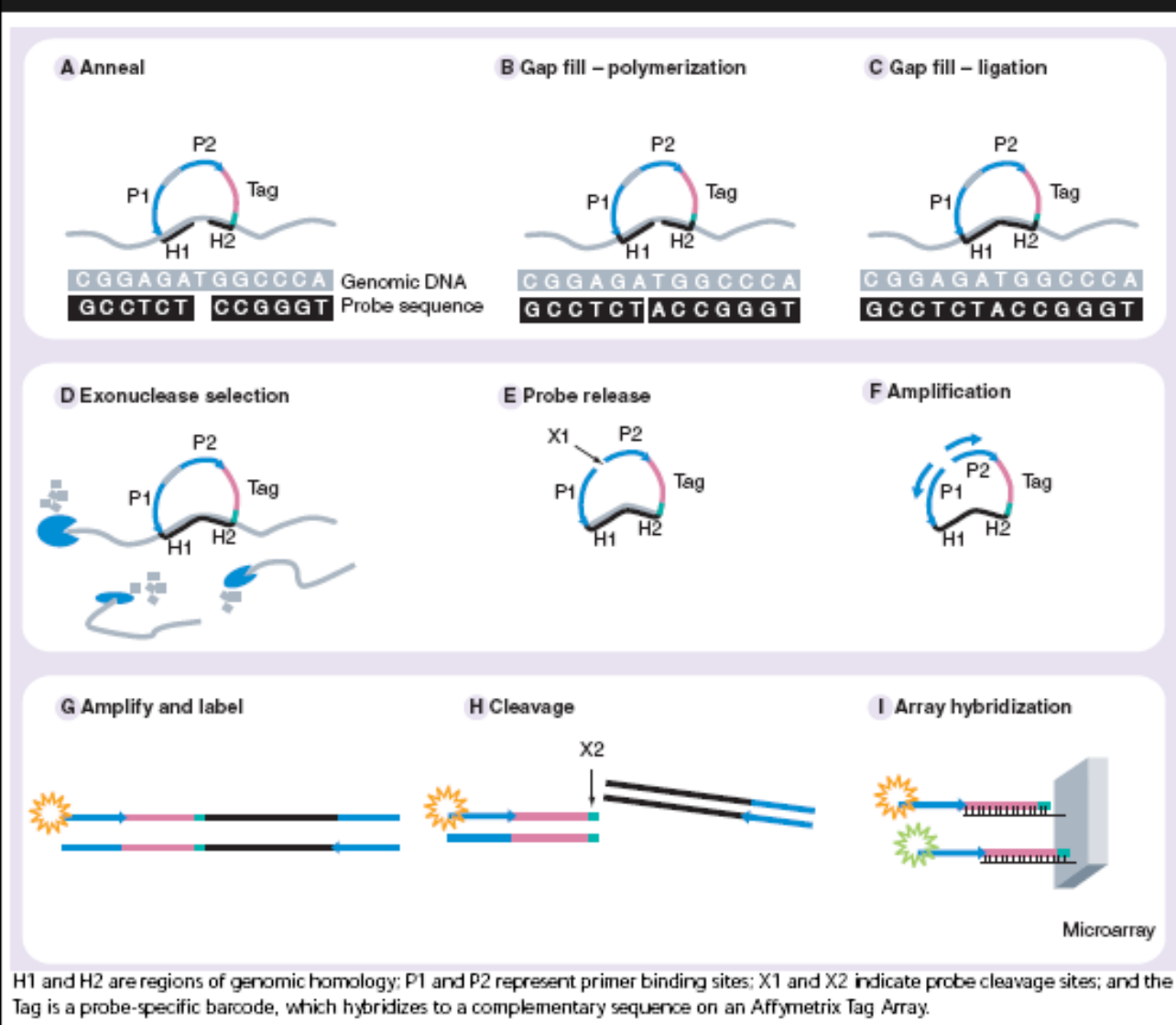


Table 1. Genes containing SNPs with &gt;1% minor allele frequency in the Marshfield population

DMET metabolism						DMET transport and other genes	
Gene	SNP count	Gene	SNP count	Gene	SNP count	Gene	SNP count
ADH1B	3	CYP2C18	4	GSTM4	2	ABCB1	14
ADH4	4	CYP2C19	1	GSTO1	1	ABCB4	9
ADH7	2	CYP2D6	7	GSTP1	3	ABCB11	15
ALDH1A1	1	CYP2E1	7	HNMT	1	ABCC1	10
ALDH2	1	CYP2F1	2	MAOB	1	ABCC2	8
ALDH3A1	2	CYP2J2	1	NAT1	7	ABCC3	3
AOX1	1	CYP2S1	1	NAT2	6	ABCC4	12
CDA	2	CYP3A1	2	NQO1	4	ABCC5	3
CHST1	1	CYP3A4	2	POR	1	ABCC6	4
CHST2	1	CYP3A43	3	PTGIS	1	ABCG2	1
CHST3	13	CYP3A5	1	SULT1A1	1	AHR	2
CHST5	4	CYP3A7	1	SULT1A2	1	ATP7A	1
CHST7	1	CYP4A11	1	SULT1A3	1	ATP7B	10
CHST10	5	CYP4B1	6	SULT1C1	1	NR3C1	3
CHST11	7	CYP4F2	7	SULT1C2	1	PPARD	38
CHST13	2	CYP4F8	4	SULT1E1	2	PPARG	1
CHST8	1	CYP4F11	5	SULT2A1	1	RALBP1	3
COMT	2	CYP4F12	4	SULT2B1	2	SLC10A1	1
CYP11A1	1	CYP4Z1	1	SULT4A1	2	SLC10A2	7
CYP11B1	10	CYP51A1	3	TBXAS1	2	SLC13A1	2
CYP11B2	4	CYP7A1	1	TPMT	3	SLC15A1	5
CYP17A1	3	CYP8B1	1	UGT1A1	5	SLC15A2	5
CYP19A1	5	DPYD	2	UGT1A3	3	SLC16A1	2
CYP1A1	2	EPHX1	7	UGT1A4	1	SLC19A1	2
CYP1A2	6	FMO1	4	UGT1A6	2	SLC22A1	7
CYP1B1	1	FMO2	10	UGT1A7	1	SLC22A2	2
CYP20A1	2	FMO3	6	UGT2A1	2	SLC22A3	2
CYP24A1	4	FMO5	1	UGT2B4	2	SLC22A4	3
CYP2A13	3	FMO6	4	UGT2B11	1	SLC22A5	3
CYP2A6	13	GSTA1	1	UGT2B15	1	SLC22A6	1
CYP2A7	3	GSTA2	4	UGT2B28	1	SLC22A8	2
CYP2B6	8	GSTA4	4	UGT8	1	SLC28A1	8
CYP2C8	2	GSTA5	1	XDH	4	SLC28A2	1
CYP2C9	2	GSTM3	2			SLC28A3	2
						SLC29A1	1
						SLC5A6	2
						SLC7A5	1
						SLC7A7	5
						SLCO1A2	3
						SLCO1B1	5
						SLCO1B3	4
						SLCO2B1	1
						SPG7	2

DMET, drug-metabolizing enzymes and transporters; SNP, single nucleotide polymorphism

## CYP4F2 genetic variant alters required warfarin dose.

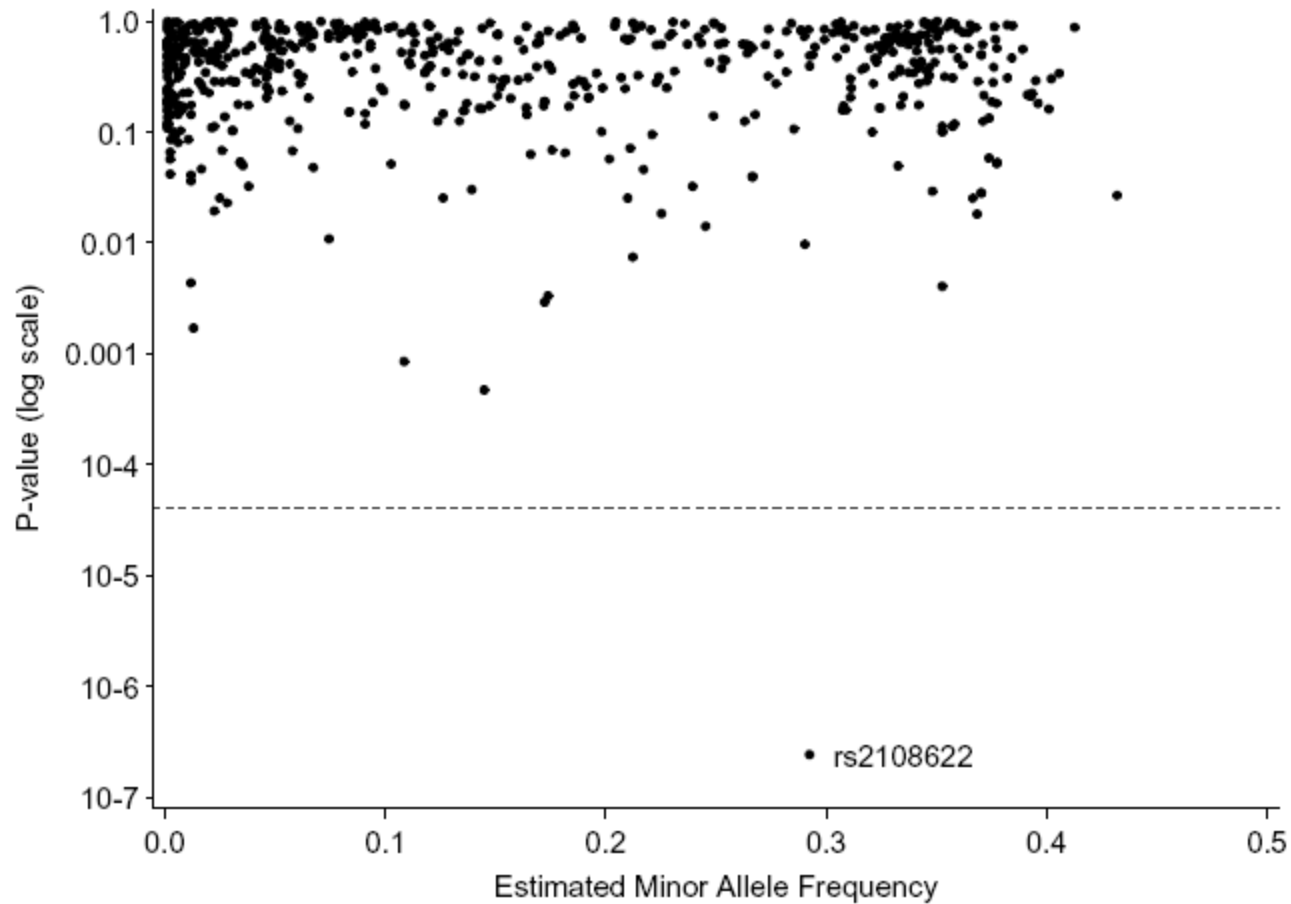


Figure 1

## CYP4F2 genetic variant alters required warfarin dose.

<b>Table 2. Genotype by site</b>			
	<b>Marshfield (%)</b>	<b>University of Florida (%)</b>	<b>Washington University in St. Louis</b>
<b>CYP2C9</b>			
*1/*1	64.69	71.19	64.31
*1/*2	18.98	15.93	20.07
*1/*3	12.45	8.81	11.52
*2/*2	1.43	3.39	1.49
*2/*3	2.04	0.68	1.86
*3/*3	0.41	0.00	0.74
<b>VKORC1</b>			
GG	38.78	36.99	37.92
GC	48.37	48.63	47.21
CC	12.86	14.38	14.87
<b>rs2108622</b>			
CC	49.59	47.80	52.42
CT	42.04	44.75	40.15
TT	8.37	7.46	7.43

## CYP4F2 genetic variant alters required warfarin dose.

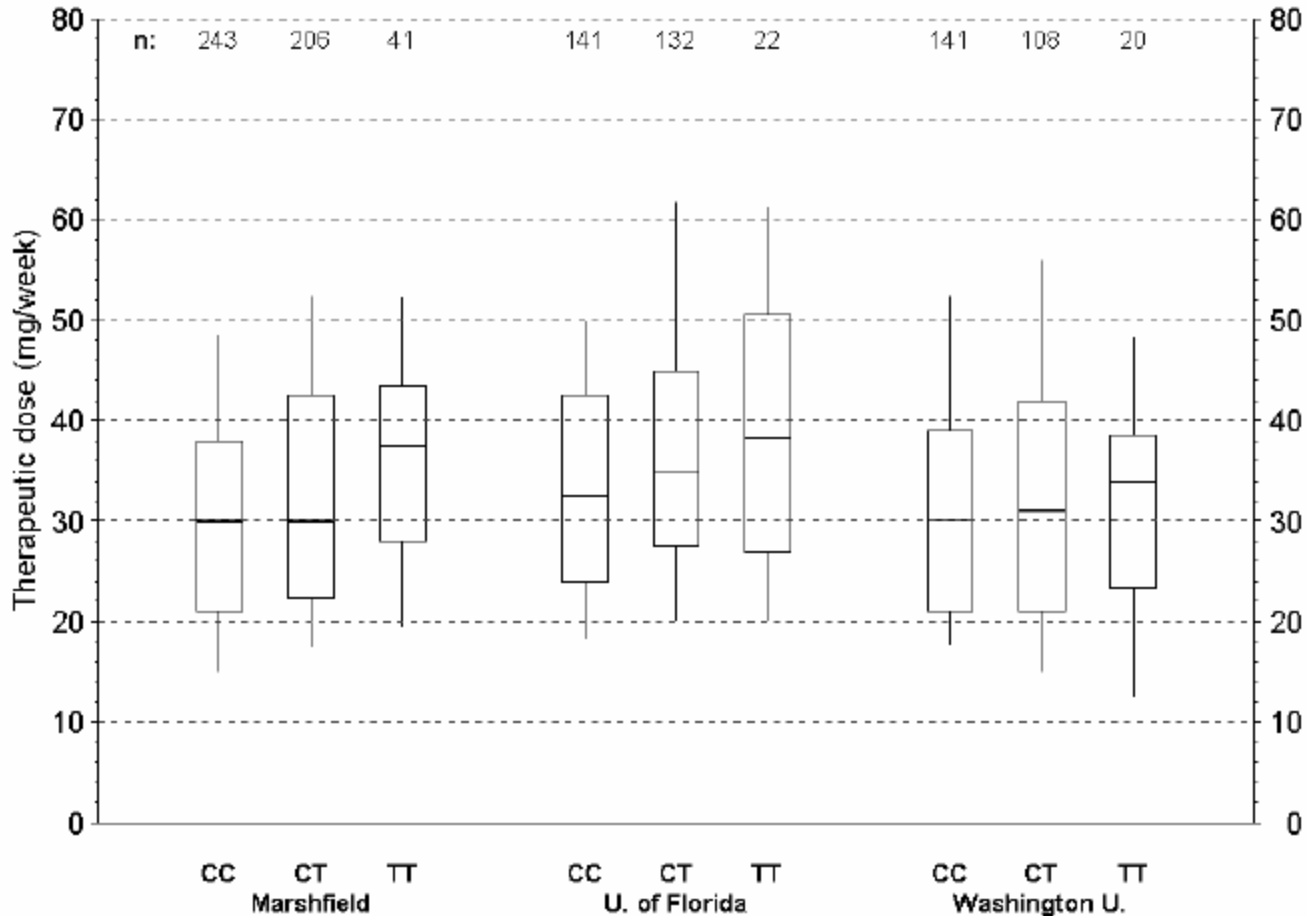


Figure 2

## CYP4F2 genetic variant alters required warfarin dose.

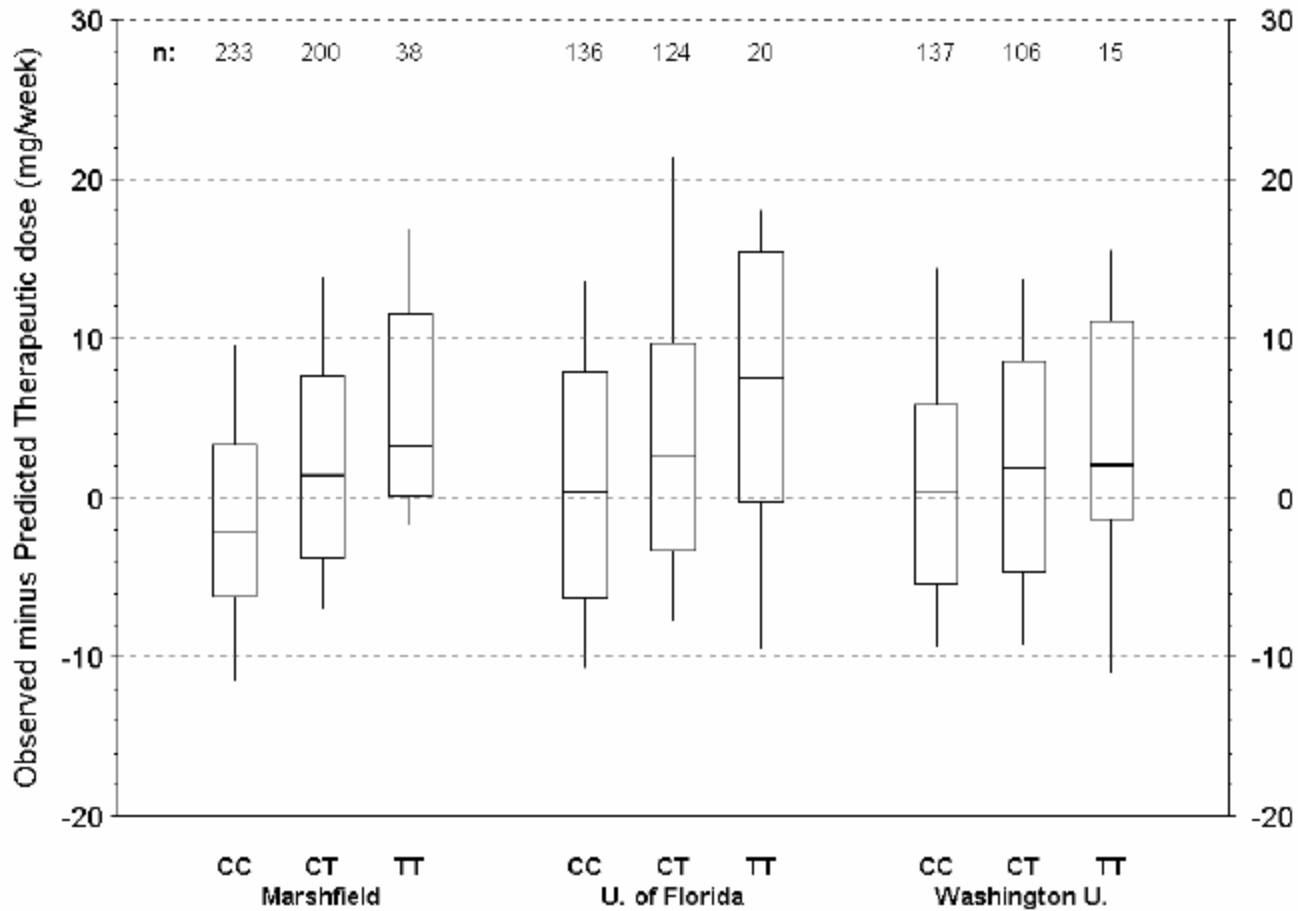


Figure 3

## CYP4F2 genetic variant alters required warfarin dose.

Predictor/predictor group	Adjusted R <sup>2</sup>
Clinical only	0.17
Clinical plus CYP2C9 and VKORC1	0.54
Clinical plus CYP2C9 and VKORC1 and CYP4F2	0.56

Clinical variables were: gender, age, body surface area, and target international normalized ratio.