

Supplemental Tables and Figures to Horne et al. “Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy” (Thromb Haemost 2012; 107.2)

Authors: Benjamin D. Horne, Petra A. Lenzini, Mia Wadelius, Andrea L. Jorgensen, Stephen E. Kimmel, Paul M. Ridker, Niclas Eriksson, Jeffrey L. Anderson, Munir Pirmohamed, Nita A. Limdi, Robert C. Pendleton, Gwendolyn A. McMillin, James K. Burmester, Daniel Kurnik, C. Michael Stein, Michael D. Caldwell, Charles S. Eby, Anders Rane, Jonatan D. Lindh, Jae-Gook Shin, Ho-Sook Kim, Pantep Angchaisuksiri, Robert J. Glynn, Kathryn E. Kronquist, John F. Carlquist, Gloria R. Grice, Brian F. Gage

Table S1. Characteristics of the 13 contributing sites, including location, sample size available for this study, sample size used, and brief details of each individual study's methods.

Site	N offered (2,022)	N used (1,684)	Ancestral Origin	Usual starting dose of warfarin	Definition of therapeutic dose
Inje University, Busan, South Korea ⁴³	139	139	100% Asian	2.5-5mg	Dose resulting in two in-range INR values following a week of a steady-dose regimen.
Mahidol University, Bangkok, Thailand ¹⁸	47	38	100% Asian	3-5 mg	The dose that keeps patient's INR between 2-3.
Karolinska Institute, Stockholm, Sweden ¹³	653	532	Majority were Caucasian (of Swedish origin)	Various regimens were used. Median doses on days 1, 2 and 3 were 10 mg, 7.5 mg, and 5 mg.	Dose that leads to INR within 2-3 for at least 3 consecutive visits.
Uppsala University, Uppsala, Sweden ⁴⁴	3	3	100% Caucasian	7.5-10 mg	Dose that leads to INR within 2-3 for at least 3 consecutive visits.
University of Liverpool, UK ⁴⁵	178	167	100% Caucasian	Various regimens were used. Most common: 10 mg (63%); 10 mg on first day then 5 mg on next (17%); 3 mg (7%)	Dose that leads to INR within therapeutic range for at least 3 consecutive clinic visits.
University of Alabama, USA ⁴⁶	62	17	52% Caucasian, 47% African, 1% other	Various regimens were used. Most common: 5 mg (61%); 2.5 mg (17.5%); 7.5/10 mg (15%)	Dose that produced an INR in the target range for 3 consecutive visits over a period of at least 2 weeks.
Vanderbilt University, Tennessee, USA ^{14,37}	104	66	92% Caucasian, 8% African	5 mg	Dose given for ≥ 7 days that yielded an INR within the 1.7-3.0 range.
PREVENT (Harvard University), Massachusetts, USA ¹⁹	212	196	88% Caucasian, 9% African, 3% other	3 mg	Dose resulting in two in-range INR values following a week of a steady-dose regimen.
Marshfield Clinic, Wisconsin, USA ³⁴	135	101	100% Caucasian	5 mg	Dose required for two in-range INRs taken at least 3 days apart with no dose change >0.5 mg from 6 days prior to the first INR through the last INR.

Washington University in St. Louis, Missouri, USA ^{12,18}	268	265	82% Caucasian, 16% African, 2% Asian	www.WarfarinDosing.org	Daily dose (mg/day) unchanged for at least 3 days prior to a first in range INR, and 6 days prior to a second in range INR.
Kaiser Permanente Colorado, USA ^{12,18}	30	20	93% Caucasian, 3% African, 4% other	www.WarfarinDosing.org	Daily dose (mg/day) unchanged for at least 3 days prior to a first in range INR, and 6 days prior to a second in range INR.
University of Utah, USA ⁴⁷	48	47	100% Caucasian	3-5mg	Dose that keeps patient's INR between 1.8-2.9.
Intermountain Healthcare, Utah, USA ²	119	87	94% Caucasian, 2% Asian, 2% African, 2% Hispanic	10 mg daily x 2 days, then 5 mg daily on days 3 and 4	Dose on day 8 or later that was associated with ≥ 2 INRs that were measured ≥ 1 week apart but whose values were within 15%.

Supplemental References

43. Kim HS, Lee SS, Oh M, et al. Effect of CYP2C9 and VKORC1 genotypes on early-phase and steady-state warfarin dosing in Korean patients with mechanical heart valve replacement. *Pharmacogenet Genomics*. 2009;19:103-112.
44. Wadelius M, Chen LY, Downes K, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. *Pharmacogenomics J*. 2005;5:262-270.
45. Jorgensen AL, Al-Zubiedi S, Zhang JE, et al. Genetic and environmental factors determining clinical outcomes and cost of warfarin therapy: a prospective study. *Pharmacogenet Genomics*. 2009;19(10):800-812.
46. Limdi NA, Arnett DK, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. *Pharmacogenomics*. 2008;9:511-526.
47. McMillin GA, Melis R, Wilson A, et al. Gene-based warfarin dosing compared with standard care practices in an orthopedic surgery population: A prospective, parallel cohort study. *Ther Drug Monit*. 2010;32(3):338-345.

Figure S1. Weights of recent warfarin doses. Based on a first-order pharmacokinetic model, doses given 2 or 3 days ago have the greatest effect on the current International Normalized Ratio (INR) value.

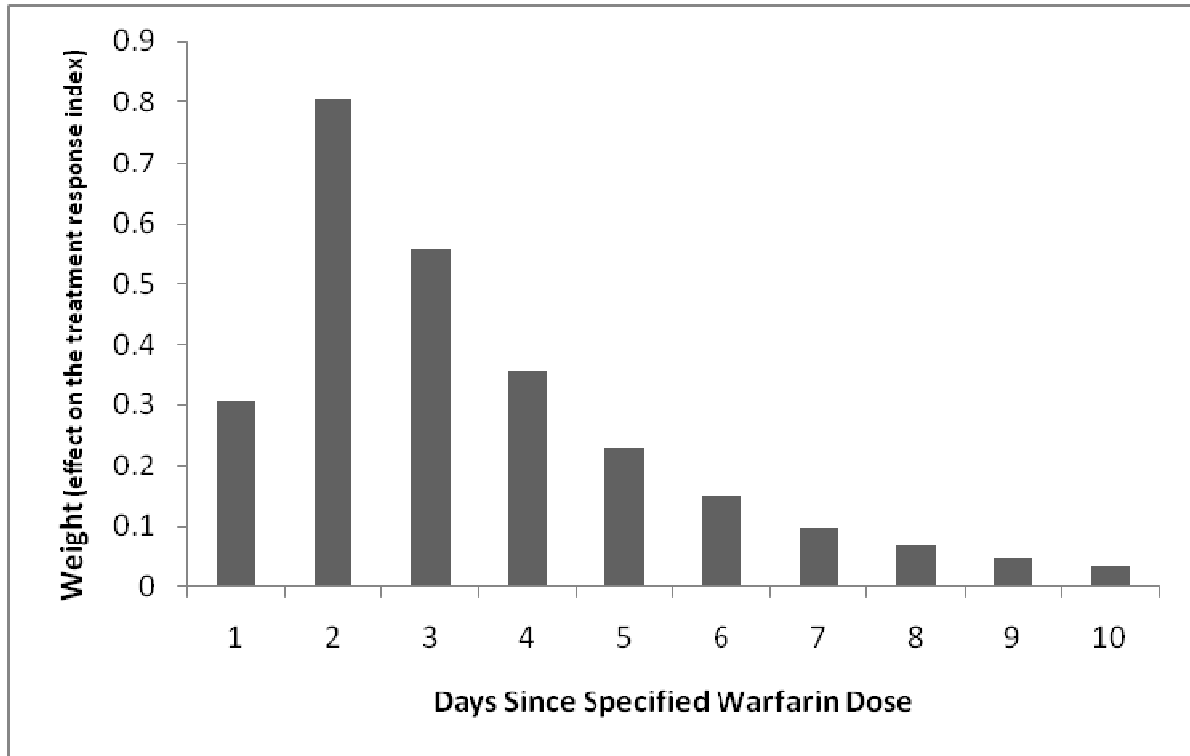
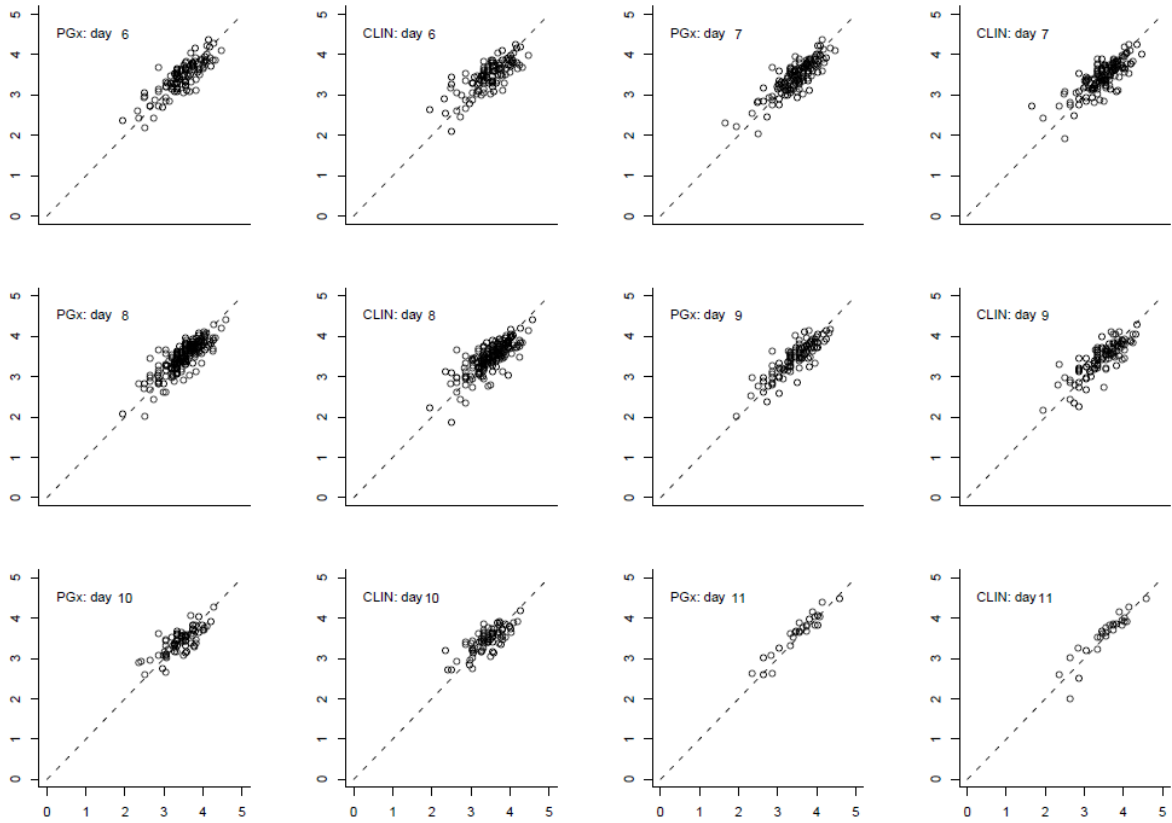


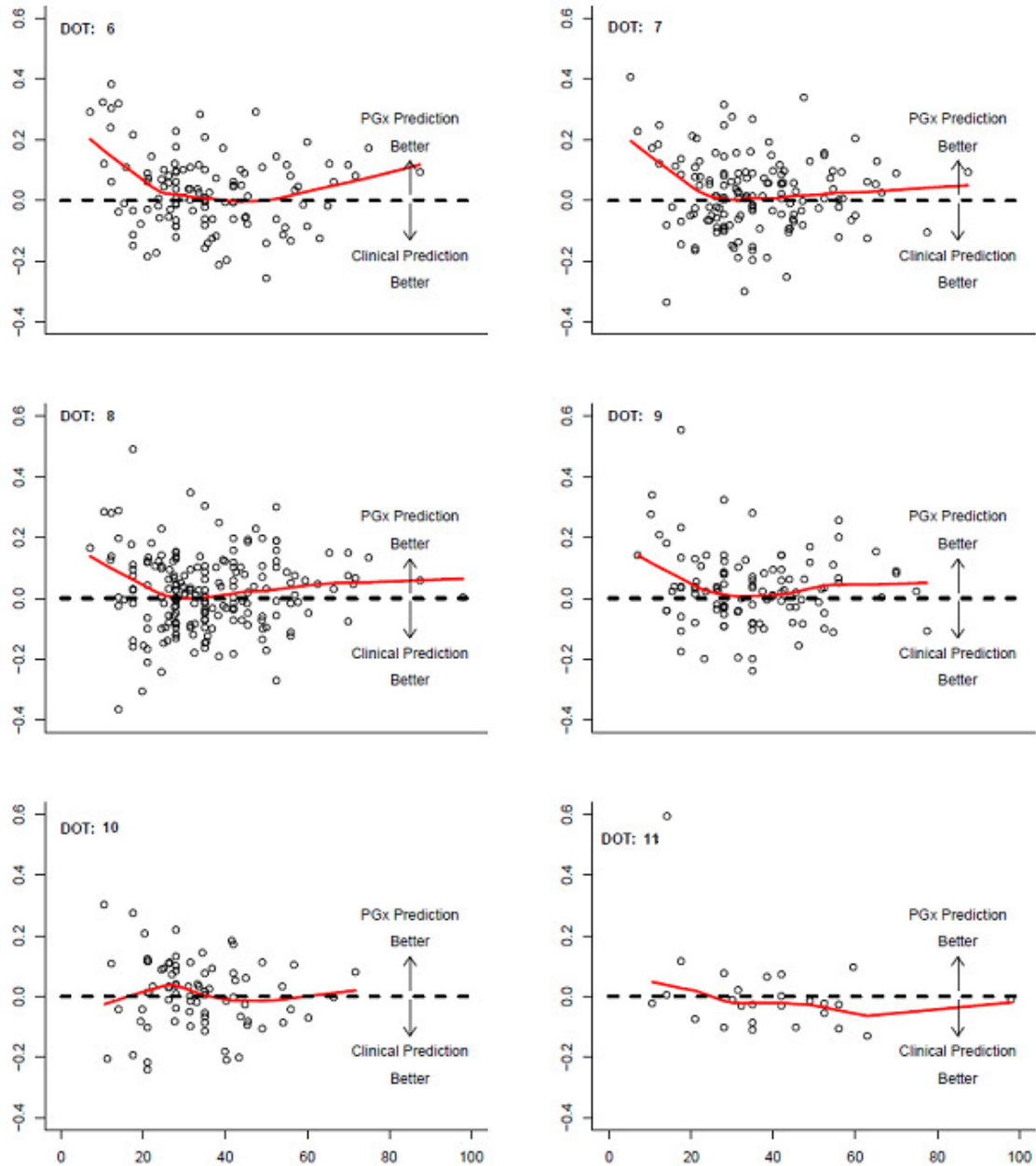
Figure S2. Scatter plots illustrating the correlation between the observed and predicted warfarin dose for PGx and clinical algorithms on each day of therapy that was examined.



Horizontal Axis: log(observed weekly warfarin dose)

Vertical Axis: log(predicted weekly warfarin dose)

Figure S3. Regression lines (red) for the differences between the weekly warfarin doses predicted by the clinical and PGx algorithms on each day of treatment (DOT).



Horizontal Axis: the observed weekly warfarin dose (mg/week)

Vertical Axis: the difference between absolute values of the residuals of the PGx- and clinically-predicted doses