TIMELINE FOR SELECTED STUDIES REFLECTING ON THE USE OF GENOTYPE IN DOSING WARFARIN

1980 - CYP2C9 SEQUENCED

1992 – Rettie, et al – CYP2C9 converts S-warfarin enantiomer to inactive S-7 hydroxy warfarin

1995 – Furuya, et al - First Known study linking CYP2C9 Genotype and warfarin dose

1996 – SullivanKlose, et al - Allelic variants of CYP2C9 gene *2 Cys for Arg 144, *3 Leu for Ile 359

1996 – Stubbins, et al Defined frequencies in Caucasian populations

1996 – Steward, et al – Demonstrated *3 allelic variant associated with diminished clearance of S-warfarin (elevated S:R ratio)

1998 – Takahashi, et al - CYP2C9 allelic variants affect S-warfarin clearance

1999 - Aithal, et al – Showed a strong association between CYP2C9 genotype and warfarin sensitivity. Suggested association hemorrhagic complications and genotype (n=36 low dose, n=52 random dose, n=100 control)

2000 – Freeman, et al – Confirmed CYP2C9 genotype frequencies and confirmed that mutant alleles were associated with reduced weekly warfarin dose (n=38)

2000 – Taube, et al – Confirmed CYP2C9 genotype association with warfarin sensitivity in large patient population (n=561 random dose)

2001 – Loebstein, et al – At optimized steady state, individual sensitivity to warfarin is determined by CYP2C9 genotype and age. (n=156 random patients)

2001- Leung, et al – Novel polymorphisms at 4 positions (Ile181Leu, His184Pro, Gln192Pro, Leu208Val identified in Hong Kong Chinese population. The 208 polymorphic alleles existed at high frequency and associated with lower warfarin dose. (n=89) Low prevalence of *2 and *3 alleles

2001 – Tabrizi, et al – Expanded population from Freeman study. (n=120 Caucasian and 33 African American patients) Found that weekly warfarin dose was affected by age and CYP2C9 genotype. No effect of gender or ethnicity. CYP2C9 polymorphisms less frequent in African Americans.

2002 – Lee, et al - Excellent review of CYP2C9 in-vitro and human data

2002 – Hermida, et al - *2 and *3 variants affect acenocoumarol metabolism as well (n=113 random dose patients)

2002 – Higashi, et al – (n=185retrospective random dose patients) Patients having at 1 variant CYP2C9 allele had an increased risk of above-range INR values. This group also required more time to achieve stable dosing. Suggested patients with a variant genotype had an increased risk of serious or life-threatening bleeding event.

2002 – Scordo, et al – (n=93 stable patients) Confirmed the effect of CYP2C9 polymorphisms on warfarin dose in an Italian population

2002 – Linder, et al – Confirmed association with age and CYP2C9 genotype on warfarin dose. (n=56)

2003 – Takahashi, et al – (n=90 Japanese and 47 Caucasian patients receiving warfarin) Japanese patients have lower allelic frequencies for the 5 CYP2C9 variants.

2003 – Lee, et al – Could not find CYP2C9 polymorphisms in low dose warfarin cohort of Korean patients (n=71 regular dose and 19 in low dose group)

2004 – Rost, et al – Description of VKORC1 and demonstration that mutations in VKORC1 cause warfarin resistance

2004 – D'Andrea, et al – (147 patients) VKORC1 and CYP2C9 together can explain 35% of variance in warfarin dose

2005 – Sanderson, et al – Meta-analysis of strength and quality of existing evidence about CYP2C9 gene variants and clinical outcomes in warfarin-treated patients. Patients with *2 or *3 genotypes have lower mean daily warfarin doses and a greater risk of bleeding. (Nine studies included 2775 patients)

2005 - Voora, et al – Prospective study of perioperative pharmacogenetics-based dosing of warfarin. Elective surgery. No standard treatment group. Patients with variant achieved a stable therapeutic dose without excessive delay. Still increased risk for adverse outcome (primarily INR>4)

2005 – Wadelieus – VKORC1 and GGCX polymorphisms associated with warfarin dose. VKORC1 larger impact than CYP2C9. (29-30% of variance vs. 12%)

2005 – Hillman, et al – Prospective trial of clinically relevant genotyping for CYP2C9 prior to prescribing warfarin. Can genotype with rapid turn-around

2005 – Sconce, et al – Age, CYP2C9 and VKORC1 genotypes can explain 55% of variance in warfarin dose.