“Knowing how to dose warfarin can be difficult, but with genetic testing we can get patients safely into therapeutic range. We no longer fear overshooting a patient’s INR goal.” Dr Craig J. McCotter, M.D., F.A.C.C

Clinicians are ambivalent about warfarin. Notoriously difficult to dose, fraught with bleeding risk, warfarin is nonetheless a cheap and effective medicine. Clinicians are caught in knowing such, that warfarin, while being an accessible and effective medication with a sixty-year track record and a diverse range of anticoagulation applications, also causes significant adverse drug events in up to twenty-two percent of patients on a yearly basis. As dosing is of the essence, because of its impact on achieving an exact therapeutic level in warfarin’s narrow window, it has become the focus of pharmacogenetic testing. On its own, genetic testing is an academic exercise. Coupled with a useful dosing algorithm, genetic testing for the variability in response to warfarin becomes a powerful clinical tool. In addition to age, gender, and weight, a person’s genetic makeup accounts for up to sixty percent of variability in response to warfarin. Capturing the significance of a patient’s genetic influence on his response to warfarin, with an appropriate dosing algorithm, allows for the personalization of medicine. Old-time medications like warfarin can be tailored to the individual, ushering them in to the twenty-first century.

To understand the applicability of genetic testing for warfarin, one must understand the drug’s background, properties, and metabolism. Warfarin is derived from the phytochemical coumarin. Coumarin’s effects were first noticed in the early nineteen twenties, in North America, when substantial percentages of some livestock herds, having fed on sweet clover silage, had post-procedure hemorrhaging. In the nineteen forties, the coumarin derivative, dicoumerol, was isolated and characterized. Dicoumerol’s relative, warfarin, derived its name from the acronym WARF (Wisconsin Alumni Research Foundation), relating to its birthplace, the University of Wisconsin. Warfarin, otherwise known as 3-(α-acetonylbenzyl)-4-hydroxycoumarin, was put to clinical use in the
nineteen fifties – Eisenhower famously received the drug after suffering a heart attack. Since its advent in clinical practice, warfarin has become well entrenched. Warfarin, today, is the number one anticoagulant prescribed in the United States.

Regarding specific properties, warfarin is a racemic mix of the R- and S-entantiomers, with the latter isomer, S, being the more potent form. Warfarin can be administered either orally or intravenously, travels through the bloodstream bound to albumin, and is metabolized in the liver according to its entantiomer status. S-warfarin is metabolized by the enzyme encoded by CYP2C9. Numerous other drugs are metabolized by the same enzyme; warfarin effect is thus often subject to concurrent medication administration. Warfarin is a competitive antagonist of vitamin K, meaning that warfarin competes with vitamin K for the latter’s binding site on the enzyme, vitamin K epoxide reductase. This enzyme, encoded by VKORC1, helps recycle (reduce) oxidized Vitamin K for use in activating key coagulation factors, II, VII, IX, and X, and proteins C and S. These appropriately named, ‘vitamin K-dependent’ coagulation factors are carboxylated in the presence of vitamin K, by the enzyme gamma glutamyl carboxylase. The carboxyl moiety allows for attachment to the vascular endothelium. Clearly, warfarin inhibition of the recycling of oxidized vitamin K reduces the amount of functional vitamin K-dependent coagulation factors, thereby thinning the blood.

Both genes mentioned above are those two, main genes of focus responsible for the variability in response to warfarin. When there is a change (polymorphism) in the gene sequences of these two genes, variable enzymes, and consequently, enzyme function result. A change in CYP2C9 results in decreased metabolism of warfarin. The wild-type allele, CYP2C9*1, is the normal variant. The alleles CYP2C9*2 through CYP2C9*6 span the gamut from reduced, to minimal, to absent activity. A change in VKORC1, namely a promoter nucleotide change of guanine (G) to adenine (A) at position -1639, results in reduced gene expression, and ultimately, reduced available vitamin K. With all forms of variations, the bleeding risk with warfarin is higher. Given this, patients with CYP2C9 and VKORC1 variations may require lower doses of warfarin to achieve and maintain a therapeutic INR. The prevalence of gene variations for both genes depends on the racial background. Twenty percent of Caucasians, five percent of African-Americans, and two percent of Asians carry at least one variant of CYP2C9. Thirty-seven percent of
Caucasians, fourteen percent of African-Americans, and eighty-nine percent of Asians carry at least one variant of VKROC1.\(^3\)

In 2007, the FDA heralded the importance of warfarin genetic testing by approving the updating of warfarin labeling to explain the influence of genetic makeup on a patient’s response to the drug. This increased recognition of the role of genetics on patient warfarin response was additionally reflected in the increased number of companies offering warfarin genetic testing. Ideally, with warfarin genetic testing, the goal is to facilitate its usage. Four key points towards this end are essential. First, the actual genetic test, for best results, should be based on a reliable and FDA-approved platform. Second, the results of the test should be coupled to an accurate dosing algorithm, for clinical applicability. Third, minimizing product delivery time is important. Providing the results within twenty four hours can help expedite patient care. Finally, the testing must be cost effective. Clinical trials, currently underway, will assist with evaluating this issue.

The future of medicine is the personalization of care. Patients, as unique individuals, not only require tailored medicine for their comfort, but for their well-being. Curtailing the high number of adverse drug events with warfarin requires more than just vigilance; it requires a paradigm shift. Clinicians have grown comfortable with the high failure rates of warfarin, perhaps because it’s an old and familiar medication, not inspiring reappraisal. Yet, this, in and of itself, is the very reason for motivation to action. Complacence should not impede the improvement of care. Knowing the influence of a patient’s genetic makeup on his ability to withstand and undergo treatment, will inevitably improve the treatment itself. Warfarin genetic testing, coupled with a strong dosing algorithm, has the ability to revolutionize the current practice of anticoagulation. With the help of genetic testing, warfarin can be brought into the twenty-first century.
