# Warfarin Sensitivity Genotyping Assay: Genetics and Clinical Overview

<table>
<thead>
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<th>Test Information (v1_020112):</th>
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<tr>
<td>Warfarin Sensitivity Genotyping Assay (CMGDL test code 4003)</td>
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<td>For sample collection, transport and testing information refer to the CMGDL website <a href="http://www.medgen.med.miami.edu">www.medgen.med.miami.edu</a>.</td>
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<td>See the link for additional test ordering information such as CPT codes, test methodology and limitations.</td>
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## Genetics, Epidemiology and Clinical Overview

Warfarin (Coumadin®) is the most commonly prescribed anticoagulant in the United States (Horton 1999; eSensor® Trombophilia Risk Test Product Insert, PI0205REV:A). Warfarin is used to help prevent and treat blood clots. Blood clots are potentially dangerous because they can detach and travel in the bloodstream, where they can get wedged in a blood vessel and block the blood supply to a vital organ such as the lungs, heart or brain. Vitamin K is essential for the production of these clotting factors. Warfarin prevents blood clots by inhibiting the action of vitamin K, thereby preventing the activation of clotting factors.

Warfarin is used in the treatment of atrial fibrillation, venous thrombosis, recurrent stroke and pulmonary embolism. Warfarin is also used for prevention of clot formation in postsurgical patients, especially after cardiac surgery.

However, warfarin exhibits a narrow optimal therapeutic window, a wide inter-individual variation in dosage required, and severe adverse effects of overdosage, primarily due to bleeding (Brunton 2006). The anticoagulant effect of warfarin is measured in terms of the prothrombin time, the time taken for blood clotting to occur in a sample of blood to which calcium and thromboplastin have been added. As a result, the effectiveness of warfarin therapy is typically monitored by frequent measurement of coagulation time (Lowe 2004; Tripodi 2003). This time is expressed as the International Normalized Ratio (INR). The higher the INR, the longer time it takes for blood to clot. If the INR is too high, there is an increased risk of bleeding. If it is too low, there may be an increased risk of clot formation. The goal is to adjust the dose of warfarin so that the INR reaches and stays within a narrow therapeutic range. The initial dose of warfarin is an approximation, generally based on a standard protocol or dosing algorithm. Over the first several weeks on the medication, the patient’s INR is tested regularly and the dose adjusted. The risk of anticoagulant-related bleeding is highest at the beginning of therapy (Tan 2010).

Warfarin dosing is influenced by a variety of factors such as sex, age, smoking status, medications, diet, height, and weight. Another factor that may be associated with the optimal dose of warfarin is the presence of certain genetic variants (Jonas 2009). The more active S-enantiomer of warfarin is metabolized to inactive forms by the liver enzyme cytochrome P450 (CYP450) 2C9 (Rettie 1992; Kaminsky 1997). A number of single-nucleotide polymorphisms (SNPs) in the CYP450 2C9 gene have been demonstrated to reduce enzyme activity (Rettie;1994; Yamazaki 1998); the most common are 430C>T (R144C) and 1075A>C (I359L). These polymorphisms, which have been observed at frequencies of approximately 12% and 7%, respectively in Caucasian populations, have been designated as 2C9*2 and *3 alleles, respectively, by the Human Cytochrome P450 Allele Nomenclature Committee ([http://www.cypalleles.ki.se/cyp2c9.htm](http://www.cypalleles.ki.se/cyp2c9.htm)). The *2 and *3 alleles of these polymorphisms have been correlated in retrospective studies with impaired warfarin metabolism (Rettie 1994) and reduced maintenance dose requirements (Margaglione 2000; Aithal 1999).

The Vitamin K Epoxide Reductase Complex, Subunit I (VKORC1) enzyme is in the pathway that activates clotting factors via gamma-carboxylation of several blood clotting factors (Stenflo 1974), and is the target of warfarin action (Suttie 1987). Certain variations in the VKORC1 gene have been associated in retrospective studies with warfarin sensitivity.15,16 A warfarin-sensitive haplotype has been identified (Rieder 2005), and the promoter polymorphism -1639G>A can be used to identify patients with a warfarin-sensitive genotype (-1639AA) (Sconce 2005). The distribution of the -1639G>A allele is highly population-dependent, being found at approximately 40% in Caucasian populations, and as high as 90% in Asians (Rieder 2005; Yuan 2005).

The polymorphisms genotyped by the CMGDL Warfarin Sensitivity test via the eSensor® Warfarin Sensitivity Test are listed below:

<table>
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<th>Polymorphism</th>
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<tr>
<td>CYP450 2C9 430 C&gt;T</td>
<td>*2</td>
</tr>
<tr>
<td>CYP450 2C9 1075A&gt;C</td>
<td>*3</td>
</tr>
<tr>
<td>VKORC1 -1639G&gt;A</td>
<td>GG, GA, or AA</td>
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The CYP450 2C9 allele designations as established by the Human Cytochrome P450 (CYP) Allele Nomenclature Committee ([http://www.cypalleles.ki.se/cyp2c9.htm](http://www.cypalleles.ki.se/cyp2c9.htm)). The major alleles of these polymorphisms are designated as *1.
Clinical Significance and Test Indications

Warfarin (Coumadin®) is one of the most widely adopted anticoagulants. Warfarin use has potentially severe hemorrhagic or thrombotic consequences if dosage is incorrect. The labeling of warfarin includes information about CYP2C9*2, CYP2C9*3, and VKORC1 -1639G>A indicating that these mutations, highly prevalent among Caucasians, affect dose requirements.

Test Indications:

- This test is indicated to determine the genotype affecting warfarin metabolism
- Although widespread adoption of genotyping for warfarin sensitivity is not recommended, this test is useful in warfarin-naïve patients.
- In addition this test may help management of patients with previous history of difficulty with anticoagulation or are on warfarin prophylactically after surgery.

Related Tests (visit our website at www.medgen.med.miami.edu )

References:

- eSensor® Trombophilia Risk Test Product Insert , P10205REV:A
- http://www.cypalleles.ki.se/cyp2c9.htm
