

# AYUSCREEN WARFARIN

AyuGen for prevention and better treatment

## AyuScreen Warfarin Sensitivity Test

### Warfarin Is Under-Prescribed Because Of Its Associated Risk

Warfarin (Coumadin) is one of the most effective anticlotting agents, but is under-prescribed due to serious, life threatening side effects associated with it. It is one of the commonly implicated drugs in emergency department visits for adverse drug events.

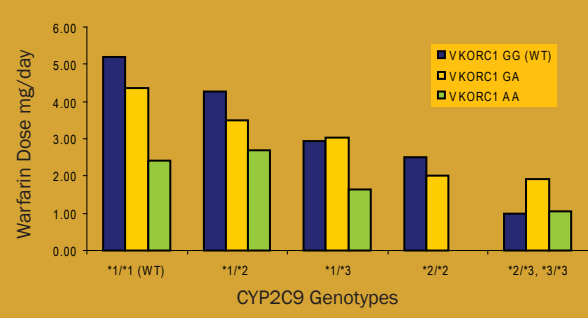
- A major risk associated with warfarin is frequent and severe bleeding with approximately 2 to 24 bleeding episodes per 100 patients – of these 1 to 7 are actually major bleeding events (Schulman, 2003).
- Incorrect dosing, especially during the induction phase, carries a high risk of either severe bleeding (warfarin dose too high) or failure to prevent thromboembolisms (warfarin dose too low).
- Significant inter-patient variability in warfarin's response is observed.
- Majority of warfarin-related adverse events are preventable with optimal dosing.

### Genetic Testing For Safer Treatment And Monitoring Of Warfarin

By integrating warfarin sensitivity testing into routine warfarin therapy, the US alone would avoid 85,000 serious bleeding events and 17,000 strokes annually. It is estimated that the reduced health care spending from integrating genetic testing into warfarin therapy would be \$1.1 billion annually (McWilliam et al., 2006).

- Studies reveal that genetic variants in 2 genes, CYP2C9 and VKORC1, can explain up to 50% of the variation in dose and drug response.

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- Higashi et al (2002) have shown that the CYP2C9\*2 and CYP2C9\*3 genetic variants are associated with an increased risk of over-anticoagulation and bleeding events among patients receiving warfarin for anticoagulation.
- This simple blood test will identify patients who are sensitive to warfarin and therefore may need careful dose optimization.

### Effect Of Genetic Variations On Warfarin Dosing

- Cytochrome P450 isoenzyme 2C9 (CYP2C9) is the main enzyme that metabolizes warfarin into its inactive form involved in the metabolism and clearance of S-warfarin (the main active form of warfarin).

CYP2C9 *1/*1	Extensive metabolizer
CYP2C9 *1/*2 or *1/*3	Intermediate metabolizer
CYP2C9 *2/*2 or *2/*3 or *3/*3	Poor metabolizer

- Warfarin inhibits VKORC1 (Vitamin K epoxide reductase subunit 1) which is involved in making vitamin K available in a form that activates vitamin K-dependent clotting factors. The presence of a genetic variation in VKORC1 increases the person's sensitivity towards warfarin (Reider et al., 2005).

GG	Lower sensitivity to Warfarin
GA or AA	Higher sensitivity to Warfarin

### How Can This Be Put Into Practice?

- **If a patient is a poor metabolizer or highly sensitive to warfarin, then he / she may be recommended a lower dose of Warfarin, based on this test.**

- Along with the genetic information, other factors like age, weight and concomitant medication (eg. statins) should also be considered while deciding the dose.

US FDA has approved the use of genetic information while prescribing the dose of warfarin. In November of 2005, the clinical Pharmacology Subcommittee of FDA agreed sufficient evidence exists to support the use of lower doses of warfarin for patients with genetic variations in CYP2C9 and VKORC1.

#### Sample Requirements

- This test requires 3ml of peripheral blood collected in EDTA or citrate tubes / Vacutainer tubes.
- Please contact our collection center in your city or alternatively you can call 020- 2553 8990 or 094231 18990 for further information.

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 2. McWilliam A., Lurie R., Scuderi C. (2006) Health care savings from personalizing medicine using genetic testing: the case of warfarin. *American Enterprise Institute-Bookings Joint Center*, November 2006. Available from <http://www-bookings.org/publications/abstract.php?paper=1127>.  
 3. Reider M.J., Reider A.P., Dager B.F., Nickerson D.A., Eby C.S., McLeod H.L., Blough D.K., Thummel K.E., Venstra D.L., Rettig A.E. (2005) Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *NEJM*, 352: 2289-91.  
 4. Schulman S. (2003) Care of Patients Receiving Long-Term Anticoagulant Therapy. *NEJM*, 349: 675-683.  
 5. Science E. R., Khan S.I., Wynne H.A., Avery D., Mackintosh L., King B.P., Ward R., Fritcheva P., Dohi A.K., Kamali F. (2005) The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood*, 105 (7): 2329-2333.  
 6. <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01701.html>

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