candidate modifier truly plays a role in disease penetrance.

Finally, what should we do with the information gained from studies that have unequivocally identified a modifier gene? Recently, a polymorphism in the RAD51 gene has been associated with a protective effect in women harbouring BRCA1 mutations.[13] It is to be expected that in the near future similar data will appear that has a significant effect on the risk of developing malignancy in persons harbouring germline MMR gene mutations. At this stage clinical decision making is relatively comfortable about providing information concerning monogenetic disease risk; however, this may be tempered by the use of additional information which is less precise in its ability to predict disease likelihood. It is to be expected that there will be more than one modifier gene and that some may well cancel each other out. For this information to be incorporated into clinical practise all modifier genes will need to be identified and appropriate decision algorithms developed for the correct implementation and interpretation of this information ■

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Warfarin Pharmacogenomics

A big step forward for individualized medicine: enlightened dosing of warfarin

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Using genetic testing, a potential new face has been put on one of medicine's oldest, most commonly used and dreaded medications. Warfarin is an anticoagulant medication prescribed worldwide to prevent stroke and venous thromboembolism. Its use is complex due to a narrow therapeutic window, variability in dose–response, interactions with drugs and diet and risk of serious bleeding.[1] The optimal dose of warfarin is titrated to prolongation of the patient's blood test, the protime and international normalized ratio (PT/INR). Achieving and maintaining the target PT/INR and dose of warfarin is labor intensive and challenging. The importance of INR within the target range is critically important due to the risk of clinical bleeding with excessive prolongation and risk of thrombosis with inadequate prolongation. Many factors affect the metabolism of warfarin making adjustment of the drug dosage common. The traditionally understood clinical factors such as drug–drug interactions, dietary interactions, age and body surface area account for a significant portion of the variability in warfarin dosing.[1]

Genetic variants can affect warfarin metabolism and two genes in particular have been intensively studied: vitamin K epoxide reductase complex 1 (VKORC1) and a cytochrome P450 gene CYP2C9.[2–5] In addition to an effect on warfarin dose, observational clinical studies have looked at anticoagulation-related outcomes and have found increased risk of over-anticoagulation and bleeding events associated with certain CYP2C9 polymorphisms.[6] It is currently accepted that these two genes, VKORC1 and CYP2C9 explain a significant portion, albeit incomplete, of the unpredictability of warfarin management.

These two genes are the focus in a meticulously designed prospective genetic-based cohort study by Millican *et al* recently published in Blood. These investigators studied warfarin induction treatment in orthopedic patients undergoing joint replacement. CYP2C9 and VKORC1 genotyping was determined pre-operatively and used in a complex nomogram-dosing regimen. The warfarin-dosing nomograms were tailored to include clinical factors and genetic factors for two cohort groups; the first group was dosed based upon the CYP2C9 genotype and the second group was dosed based upon both VKORC1 and CYP2C9 genotype. The study end point was therapeutic warfarin dose. The investigators found strong correlation between the warfarin dose predicted by their nomogram and the therapeutic warfarin dose that was required to achieve the therapeutic target INR. Some clinical factors such as smoking, liver disease and blood loss were found to affect the warfarin dose. The investigators are careful to note that their study was in a carefully selected cohort of orthopedic patients but it is reasonable to think these findings could potentially extend to other patient populations.

The scientific and clinical evidence that supports lower warfarin doses for patients with certain genetic variations in CYP2C9 and in the VKORC1 has recently moved the US Food and Drug Administration (FDA) to change the labeling of warfarin (marketed as Coumadin®) recommending genetic testing to guide warfarin dosing. Dosing must still be individualized and based upon a patients PT/INR value.[8] The new warfarin label is not a mandatory or a 'black box' warning and does not require the genetic testing prior to or during warfarin treatment. But to educate the medical community, FDA has taken a big step forward to assert that certain variations in the two genes may increase the need for more frequent INR monitoring and require lower warfarin doses.

Some will argue that there has not yet been a randomized trial to definitively prove that genotyping for warfarin dosing improves efficacy or safety. But such a trial is soon to be underway, supported by the National Institutes of Health. A randomized trial of genotype-guided dosing of warfarin therapy is planned for 2000 patients randomized to three groups: standard of care (trial and error dosing), a clinical-dosing algorithm, and a clinical-dosing algorithm plus genetic-dosing algorithm. Cost-effectiveness will also be assessed. If safety and efficacy can be taken to a higher level, an end to the trial and error warfarin-dosing era will be a true paradigm shift into the realm of individualized medicine and pharmacogenomics.

Upwards of 30 genes have been reported to possibly relate to warfarin metabolism but the CYP2C9 and VKORC1 have been shown to be most important and have been studied most intensively.[5] Whether other, yet undiscovered genetic and non-genetic influences on warfarin metabolism will be uncovered remains to be seen. Certainly not all of the genomically related dose variability of warfarin is yet explained.

In the meantime, however, a real dilemma exists for treating physicians and patients taking warfarin. Who to test and how to manage? What dosing nomogram to use? The clinical availability of the genetic testing is limited but presumed soon to be expanding. How or will the genotyping be reimbursed, given these commercially available tests are quite expensive for both CYP2C9 and VKORC1. And should all this be coordinated centrally, since studies have shown that warfarin monitoring can be improved and INR is more frequently in range with the adverse event rates lower when a centralized anticoagulation service is used compared to usual individual physician care.[9]

All of this potential to improve warfarin dosing by recognizing individual genetic variability is coming at a time when new oral anticoagulants are undergoing intensive study to try and displace or supplant warfarin. Although there are many unanswered questions, there is likely the persistence of warfarin for many years going forward with over 30 million Americans currently on chronic administration (Figure 1). It seems that research efforts that would further determine the genomic and non-genomic basis of warfarin-individualized response would be well worth it. The ability to take a medicine that has been disliked and feared so intensely by both physicians and patients to a level of heightened safety, by virtue of utilizing individual markers, is exciting. The paper by Millican *et al*,[7] along with the FDA new guidance,[8] represents substantive progress to transform therapeutics from the 'one size fits all' to a more enlightened approach. Hopefully, this will serve as an example for the future direction of medicine■

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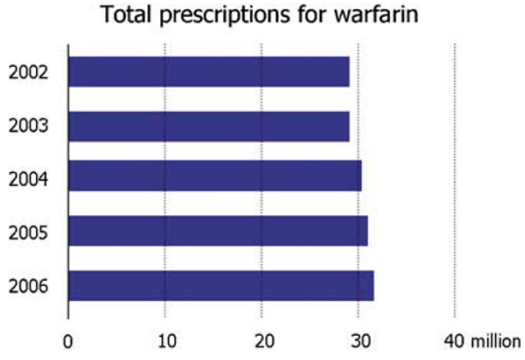

Figure 1 US prescriptions for Warfarin.

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