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AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology

Prioritising Summary

**Cytochrome P450 gene test to establish
the correct warfarin dose in patients
requiring oral anti-coagulant therapy**

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PRIORITISING SUMMARY

REGISTER ID: 000439

NAME OF TECHNOLOGY: CYTOCHROME P450 GENE TEST

PURPOSE AND TARGET GROUP: TO ESTABLISH THE CORRECT WARFARIN DOSE IN PATIENTS REQUIRING ORAL ANTI-COAGULANT THERAPY

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes ARTG number
- No
- Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Japan	✓		
United States	✓		

IMPACT SUMMARY:

Aomori et al (2009) have developed an in-house rapid, single-nucleotide polymorphism assay for the detection of genotypes involved in warfarin metabolism. This technology would be made available through specialist pathology laboratories for the screening of patients who require oral anti-coagulant therapy. This summary will examine the use of this assay in addition to the need for CYP2C9 genotyping for all patients commencing anti-coagulant therapy.

BACKGROUND

In Australia, warfarin is the most commonly prescribed anti-coagulant and is indicated in patients who have undergone prosthetic valve replacement, have experienced a pulmonary embolism or deep vein thrombosis within the past three or six months, respectively, have experienced a recurrent deep vein thrombosis or pulmonary embolism, patients with atrial fibrillation, embolic stroke, congestive heart

failure or dilated cardiomyopathy. Warfarin has a narrow therapeutic window with a given dose having a variable inter-individual effect. Warfarin under-dosing of a patient may lead to a thromboembolism and conversely over-dosing may lead to a severe bleeding event. Therefore patients need to undergo regular monitoring with the regular testing of the patient's prothrombin time using the international normalised ratio (INR) (Wu 2009; Yin & Miyata 2007). The INR is a standardised ratio of the patient's prothrombin time (PT) versus a normal sample. The effectiveness of an anti-coagulant drug such as warfarin can be determined by how much it *prolongs* the PT, measured in seconds, or *increases* the INR. Patients on warfarin usually have a target INR of 2.0 to 3.0, that is the time taken to form a clot or a prothrombin time is 2-3 times as long as in a normal patient (Australasian Association of Clinical Biochemists 2007). The appropriate warfarin dose for a patient is determined by measuring the INR and altering the dose if the INR is too high or too low but must also take into account the patient's age, body mass index, sex and medical history.

Warfarin action

Warfarin is a vitamin K antagonist and is a specific inhibitor of the vitamin K epoxide reductase, which is encoded by the VKORC1 gene. This enzyme is responsible for the recycling of reduced vitamin K, which is required for the activation of clotting factors II, VII, IX and X. By inhibiting the action of the reductase, warfarin decreases the available level of reduced vitamin K and in so doing, reduces the level of functional clotting factors and hence reduces clotting. Polymorphisms in the VKORC1 gene have been identified, with some mutations resulting in an increase or decrease in reductase activity and as a consequence affecting the dose requirement of warfarin (Singh 2007; Yin & Miyata 2007). Two common mutations have been identified: the substitution of cysteine for threonine at position 1173 (C1173T) and the substitution of glycine for alanine at position 1639 (G1639A) (Kamali & Wynne 2009).

Warfarin metabolism

The cytochrome P450 (CYP450) enzymes are members of an isoenzyme super-family that catalyse the oxidation of a range of drugs including warfarin. Some of the CYP450 genes are highly polymorphic¹, which are phenotypically expressed by either an increase or a decrease in enzyme activity. This in turn may lead to altered rates of drug metabolism, resulting in either toxicity from an excess of drug, or at the other end of the metabolism spectrum, a lack of drug efficacy (Matchar et al 2007).

Warfarin is comprised of two forms, the S and R-form, with the S-form having the greatest anticoagulant effect. The CYP2C9 gene is important in the metabolism and inactivation of S-warfarin. Polymorphisms in the gene based on single base substitutions give rise to enzymes with reduced metabolic activity, resulting in the slow clearance of warfarin from the blood and an increased risk of bleeding. The two

¹ Polymorphism: The occurrence in a population of several phenotypic forms associated with alleles of one gene or homologs of one chromosome.

most common gene variants are CYP2C9*2 and CYP2C9*3, with the wild-type or normal gene designated CYP2C9*1. Patients homozygous or heterozygous for these polymorphisms may require a significantly lower dose of warfarin to achieve a therapeutic dose of anti-coagulation (Kamali & Wynne 2009; Singh 2007).

The identification of polymorphisms in the CYP2C9 and VKORC1 genes may assist in determining the appropriate dose regimen for patients about to commence anti-coagulant therapy.

In 2007, the United States' Food and Drug Administration approved an update of labelling for warfarin, highlighting the influence that patients' genotypes may have on the way they respond to the drug and advising that genetic testing may assist to identify an appropriate initial dose and lower the risk of complications from taking warfarin. In the US, warfarin is the second most common drug, after insulin, implicated in emergency room visits for adverse drug events (FDA 2007).

CLINICAL NEED AND BURDEN OF DISEASE

Several studies have reported on the prevalence and frequency of polymorphisms in the CYP2C9 and VKORC1 genes. The paper by Kamali and Wynne (2009) from the United Kingdom reported that approximately 20 per cent of Caucasians are heterozygous CYP2C9*1/*2 and two per cent are homozygous CYP2C9*2/*2. There are fewer CYP2C9*3/*3 homozygotes or CYP2C9*1/*3 or CYP2C9*2/*3 heterozygotes. Reductase activity is reduced by 30 and 80 per cent in patients with the *2 or *3 genotype, respectively, with *3/*3 homozygotes having the least amount of enzyme activity. Frequencies of VKORC1 AA, AG and GG in Caucasians are reported to be 14, 47 and 39 per cent respectively. The prevalence of CYP2C9 and VKORC1 alleles varies greatly amongst different ethnic groups (Kamali & Wynne 2009).

An Australian group have reported (unpublished data) from a study of 120 patients attending a anti-coagulation clinic that the frequencies of allelic variants of the CYP2C9 and VKORC1 genes responsible for altered warfarin metabolism were 31 and 59 per cent, respectively (Byron & Dear 2007).

There are two brands of warfarin currently on the market in Australia, Coumadin (offered as 1, 2 or 5 mg tablets) and Mavaran (offered as 1, 3 or 5 mg tablets). Dosage will depend on the patient's INR. Once an ideal dose is established patients usually require one tablet per day, with each prescription containing 50 tablets. In the calendar year January 2009 to December 2009, there were 962,521 prescriptions for warfarin (1 mg), 857,438 for warfarin (2 mg), 268,740 for warfarin (3 mg) and 522,087 for warfarin (5 mg), for a total of 2,610,786 warfarin prescriptions (Medicare Australia 2010).

As in Australia, two brands of warfarin are offered to New Zealand patients. In the period from January 1st to October 31st 2009, the number of unique warfarin

prescriptions was approximately 240,000. A unique prescription is considered to be the number of actual prescriptions written, excluding repeat dispensing/refills, with a prescription with three refills being only counted once. The number of dispensings for the same period was approximately 330,000, meaning the number of times a patient is dispensed a medicine including refills (personal communication PHARMAC).

The number of prescriptions may give an indication as to the upper limit of patient numbers that may require genotyping at initiation of anti-coagulant therapy.

DIFFUSION

The rapid single-nucleotide polymorphism assay is not currently in use in Australia but established and NATA² accredited pathology laboratories would have the necessary skills to perform this assay.

Gribbles Pathology in Victoria currently offer warfarin dose genotyping as a combined single base extension assay which identifies the commonly described mutations in both CYP2C9 (*1,*2 & *3) and VKORC1 (G1639A). Gribbles currently receive approximately 300 referrals from around Australia per year. Most of these referrals come from clinicians with patients who have experienced difficulty during the warfarin induction period. Clinicians have reported that they have more confidence when prescribing warfarin when the genotype is normal, or to significantly reducing the maintenance dose at an earlier point in treatment when an abnormal genotype is found (personal communication Gribbles Pathology). One laboratory in South Australia is accredited to perform this test, however this laboratory only tested one patient in 2007 (Suthers 2008).

The [Diversity Health Institute](#) Laboratory, which is funded from a variety of sources including NSW Health and the Commonwealth Department of Health and Ageing, has recently commenced testing for the CYP2C9*2 and *3 polymorphisms. Genotyping is based on the restriction fragment length polymorphism (RFLP) –PCR based method. In 2009 DHI genotyped 270 patients using this method (personal communication Diversity Health Institute).

The Australian Gene Survey noted that in 2006 the laboratory in Victoria performed a total of 95 pharmacogenetic tests, of which 60 (63%) originated from patients living in Victoria. The number of pharmacogenetic tests performed doubled in 2007 to 190, with the same proportion being performed on patients from the region (63%) (Suthers 2008).

COMPARATORS

The Medicare Benefits Schedule lists item number 66812 as the item number currently used for therapeutic drug monitoring to measure the amount of warfarin

² NATA = National Association of Testing Authorities, Australia

currently in the blood. Item number 66812: “Quantitation by any method or methods, in blood, urine or other body fluid, of a drug being used therapeutically by the patient from whom the specimen was taken”, fee \$35.45.

To identify patients who may metabolise warfarin poorly, a molecular assay must be used to identify patients with genetic variants of the P450 CYP2C9 drug metabolising enzyme. Currently no MBS item number exists for this purpose but a number of similar tests are listed. For example item number 73317 for the detection of the C282Y genetic mutation of the HFE gene for haemochromatosis, fee \$37.10.

SAFETY AND EFFECTIVENESS ISSUES

Several commercial platforms and in-house assays are available for the genotyping of polymorphisms which affect warfarin metabolism and dosing. There are many studies which identify the types of variants and their frequencies, however there is a lack of data describing the clinical utility of genotype-guided dosing. That is, by identifying a patient’s genotype, is the amount of time taken to reach optimal warfarin dose significantly reduced and are the number of adverse drug events associated with warfarin reduced? Two large randomised controlled trials are currently being conducted in the United States that attempting to clarify these questions (see Other Issues) (Jonas & McLeod 2009; Sheffield & Phillimore 2009).

Aomori et al (2009) reported on the use of an in-house developed rapid SNP detection assay using the Smart-amplification process (SMAP-2). SMAP-2 is a unique genotyping technique which uses a number of specific primers: a turn-back primer, a folding primer, a boost primer (accelerates the speed of amplification), two outer primers and a competitive probe. Accurate amplification occurs due to the presence of asymmetric primers which minimises misamplification pathways and the use of *Taq* MutS, a DNA mismatch binding protein which binds to mismatched DNA, preventing amplification. The SMAP-2, unlike all assays described previously, *does not require* DNA purification from blood samples and requires minimal sample preparation (5 minutes). In addition, only a small amount of sample is required. Prepared samples are added directly to the SMAP-2 reaction mixture, which are assembled on ice then incubated for 60 minutes at 60°C.

Blood samples from 125 patients were obtained from several sources: healthy Japanese volunteers, unrelated Japanese patients currently being treated with warfarin and patients being treated at a Swedish anti-coagulation clinic. All samples were assayed with the SMAP-2 assay and compared to the results obtained by PCR-RFLP (level III-2 diagnostic evidence). Results showed perfect concordance. Of the 125 samples, one sample was heterozygous CYP2C9*1*2 and one was homozygous CYP2C9*2*2. For the CYP2C9*3 SNP, eight samples were heterozygous CYP2C9*1*3 and one was homozygous CYP2C9*3*3. For the VKORC1 (G1639A) mutation, only one sample was homozygous for the wild type (AA), with 25 heterozygous (GA) and 99 homozygous for the mutation (GG).

King et al (2008) reported on the use of four commercially available systems for the genotyping of polymorphisms associated with warfarin metabolism: the INFINITI Analyser (AutoGenomics, USA), Invader Assay (Third Wave Technologies, USA), Tag-It Mutation Detection Assay (Luminex Molecular Diagnostics, Canada) and Pyrosequencing (Biotage, Sweden). All systems were capable of determining the two common single nucleotide polymorphisms (SNPs) in CYP2C9 (*2 and *3) and the common VKORC1 (G1639A) SNP. The INFINITI and Tag-It assays could also detect several other SNPs in the VKORC1 gene. The INFINITI, Invader and Tag-It assays all use allele-specific primer extension but different methods of signal amplification and detection. The INFINITI is a microarray and requires no manual steps after loading reagents and amplified DNA onto the instrument. The INFINITI was 100 per cent accurate for all SNPs, however the assay time required was eight hours. The Invader is considered to be a moderately complex assay and substantially more (5-50 times more) DNA is required to ensure successful genotyping. The Invader system was 100 per cent accurate for the CYP2Cp SNPs and 99 per cent accurate for the VKORC1 SNP, however the Invader was relatively fast compared to other assays with a turnaround time of only three hours. The Tag-it assay required several manual steps, and therefore an opportunity of error, between automated steps and was considered a complex assay to perform. The Tag-It was also 100 and 99 per cent accurate for the CYP2C9 and VKORC1 SNPs, respectively, however the assay took approximately eight hours to complete. The Pyrosequencing assay was considered to be moderately complex as it uses specific SNP primers and requires a separate plate for each genotype. DNA samples were sourced from blood samples provided by 112 patients enrolled in several other studies. The majority of patients were Caucasian (75%) or African American (22%). Samples were processed by all four assays and any discrepancies were resolved with bidirectional sequencing (level IV diagnostic evidence). Assay results are summarised in Table 1. All commercial platforms provided an accurate means of genotyping for polymorphisms which affect warfarin dosing (King et al 2008).

Table 1 Accuracy results on 112 DNA samples [95% CI]

Platform	CYP2C9*2	CYP2C9*3	VKORC1 (1639)
INFINITI	100 [97, 100]	100 [97, 100]	100 [97, 100]
Invader	100 [97, 100]	100 [97, 100]	99 [96, 100]
Tag-It	100 [97, 100]	100 [97, 100]	99 [96, 100]
Pyrosequencing	99 [96, 100]	100 [97, 100]	100 [97, 100]

Rai et al (2009) reported on an in-house developed multiplexed assay to identify four SNPs in a single sample: CYP2C9*2*3, VKORC1 (G1639A) and a SNP in a gene not previously discussed, GGCX (T1181G). This assay was described as minimally hands-on with a PCR amplification step, inactivation and hybridisation steps followed by capillary electrophoresis separation and identification of fragments. Assay time was approximately five hours. Samples with known and unknown genotypes were

assayed and compared to sequencing results with 100 per cent concordance (level III-2 diagnostic evidence).

The initial focus of this summary was to describe a new, rapid single-nucleotide polymorphism assay for the detection of genotypes involved in warfarin metabolism. However, it has become apparent during the writing of this summary, that a thorough examination of the need for warfarin testing in Australia and New Zealand is required. This is beyond the scope of the current summary and would require a Horizon Scanning Report to explore all the available techniques and clinical need for such testing.

COST IMPACT

The single base extension assay offered by Gribbles Pathology, which identifies mutations in both the CYP2C9 and VKORC1 genes, currently costs \$90 on a user-pays basis (personal communication Gribbles Pathology).

The RFLP-PCR based genotyping method offered by the Diversity Health Institute for the CYP2C9*2 and *3 polymorphisms costs \$50 on a user-pays basis (personal communication Diversity Health Institute).

Patients placed on anti-coagulation therapy may be required to have several INR readings performed before an ideal dose is established. The cost of genotyping all patients for CYP2C9 and VKORC1 polymorphisms would be countered by the cost of conducted several prothrombin time assays, including INR (MBS item number 65120, fee \$14.05).

Two economic studies, both conducted in the United States, were identified which examined the health benefits and health care savings or costs of warfarin pharmacogenetic testing. Conflicting results were reported by these studies. As both of these studies were conducted from an economic point of view of health care in the United States their findings may not be applicable to the Australasian health scene.

McWilliam et al (2006) estimated that genotyping for polymorphisms of only the CYP2C9 gene would avoid 85,000 serious bleeding events and 17,000 strokes annually in the estimated two million users of warfarin. Integrating genetic testing was estimated to reduce health care spending from warfarin therapy by US\$1.1 billion annually, with a range of about US\$100 million to US\$2 billion. These costs are based on the estimated price of US\$250 for CYP2C9 genotyping, however this price would be reduced if large scale testing was conducted (McWilliam et al 2006). A recent study developed a Markov model in a hypothetical population to assess the addition of genotyping to standard care for patients attending an anti-coagulation clinic, based on data from a RCT (n=200). The perspective of the study was that of a US third party payer. Using the model a reduction in the incidence of bleeding events was decreased, however there was a small absolute increase in the incidence of thrombotic events. Genotyping increased QALYs by 0.0027 or one day and

increased costs by US\$162. Compared with standard care, the incremental cost-effectiveness ratio was US\$60,750 per QALY. The cost of genotyping varied but was based on a base case of US\$175. The largest influence of the ICER in a sensitivity analysis was the basic cost of genotyping. If genotyping cost less than US\$13 then genotyping would be a cost-saving strategy. The authors of this study concluded that pharmacogenetic testing may provide a small clinical benefit, with significant uncertainty in economic value (Meckley et al 2010).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

A randomised trial of genotype-guided dosing of warfarin therapy, conducted by the University of North Carolina, commenced in August 2008 and expected to be completed in December 2009. The trial recruited patients beginning warfarin for a variety of diseases or conditions, requiring long-term oral anticoagulation with target INR > 2.0 for at least three months (ClinicalTrials.gov 2010b).

A multi-centre randomised trial of genotype-guided dosing of warfarin therapy, conducted by the National Heart, Lung, and Blood Institute, commenced in September 2009. The trial is aiming to enrol 1,200 patients and is expected to be completed in March 2012. The primary outcome measure is the percentage of time patients spend within the therapeutic INR range. Secondary measures include the occurrence of a serious clinical event (bleed or thromboembolism) or a INR >4.0 (ClinicalTrials.gov 2010a).

In 2006, the United States' Centres for Disease Control awarded seed funding to an evidence-based cost-utility analysis examining the use of genotyping for variants in the CYP2C9 and VKORC1 genes to influence the warfarin dose requirements of patients (CDC 2009).

SUMMARY OF FINDINGS

Polymerase chain reaction is an accurate means of identifying genetic mutations. All techniques discussed in this summary use PCR and other molecular techniques as the basis of their methodology. All commercial platforms and in-house assays assessed proved to be accurate for identifying the specific polymorphisms of the CYP2C9 and VKORC1 genes that are considered to be important in warfarin metabolism. Of the assays assessed, the single-nucleotide polymorphism SMart-amplification assay was the most rapid whilst still maintaining 100 per cent accuracy. However, large clinical trials are needed to determine the clinical utility of genotyping all patients prior to commencing warfarin therapy before pharmacogenomics enters routine clinical practice.

HEALTHPACT ACTION:

It is likely that in five-years all patients currently on warfarin therapy will be placed on alternative pharmaceutical options. In addition, a two-week period of testing a patient's international normalised ratio is usually deemed sufficient to ascertain the correct warfarin dose. Therefore no further review on behalf of HealthPACT is required.

NUMBER OF INCLUDED STUDIES

Total number of studies	3
Level III-2 diagnostic evidence	2
Level IV diagnostic evidence	1

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SEARCH CRITERIA TO BE USED:

Base Sequence

Dose-Response Relationship, Drug

Molecular Sequence Data

Nucleic Acid Amplification Techniques/*methods

Polymorphism, Single Nucleotide/*genetics

Warfarin/*pharmacology

Anticoagulants/pharmacokinetics/*therapeutic use

DNA Mutational Analysis