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Diagnostic Technology: Genotyping polymorphisms affecting warfarin metabolism

Clinical Questions:

1. Does genotyping polymorphisms affecting warfarin metabolism improve clinical outcomes for patients in primary care?
2. What is the cost-effectiveness of genotyping polymorphisms affecting warfarin metabolism in primary care?

Background, Current Practice and Advantages over Existing Technology:

Currently warfarin is initiated with a loading dose, which is usually reduced in the elderly or those with specific comorbidities. Subsequent dosing will depend on the patient's INR, which is monitored regularly until it is in the therapeutic range. The use of dosing algorithms, computer-assisted dosing, and self-management improve anticoagulant control [1].

There is wide inter-individual variation in dose requirements. It has been estimated that up to 40% of the dose variability can be attributed to common polymorphisms in enzymes responsible for the metabolism of warfarin [2 3 4]. The commonest polymorphisms are the CYP2C9*2 and *3 variants of the cytochrome P450 enzyme CYP2C9, and the -1639 single nucleotide polymorphism of the VKORC1 gene which codes for the Vitamin K epoxide reductase enzyme [4]. There are many other genes that have been identified, but these have not been consistently shown to have a significant clinical effect on dose requirements [4].

Knowledge of the genotype of an individual with respect to enzymes involved in warfarin metabolism could facilitate more accurate titration of anticoagulation, and fewer adverse events.

Details of Technology:

There are a number of lab-based commercial platforms available. These include: Third Wave Invader Plus, Paragon Dx SmartCycler, Idaho Technology LightCycler, Autogenomics INFINITI™, Luminex Tag-It, Biotage Pyrosequencing, Osmetech eSensor® and the Smart Amplification Process version 2 (SMAP-2)[5,2,6, 7]. Their specific methodology varies, but, with the exception of SMAP-2 which does not require DNA purification, all amplify and label extracted DNA. Turnaround time varies between 1.5 to 10.6 hours [5,2]. Once the patient's genotype has been determined algorithms that combine genetic and clinical information are used to determine the dose of warfarin required.

Patient Group and Use:

Individuals who are being started on warfarin in primary or secondary care who could potentially have genotyping performed to detect polymorphisms associated with warfarin metabolism, prior to commencing therapy in order to titrate anticoagulation more accurately.

Importance:

Warfarin is widely used for a number of different conditions, most commonly atrial fibrillation, venous thromboembolism and prosthetic valve replacement. NICE estimates that the numbers of people requiring anti-coagulation per year is 1.4% [8]. Warfarin has a narrow therapeutic window outside of which there is a risk of bleeding events, or thromboembolism [9]. The risk of bleeding events is highest during initiation of anticoagulation. One study estimated that the risk of bleeding was ten times greater in the first month, than after one year of therapy [10]. It has been estimated that up to 40% of the dose variability between individuals can be attributed to common polymorphisms in enzymes responsible for the metabolism of warfarin [2 3 4] and as such genotyping might offer a means of more accurate anticoagulant control, and thus fewer adverse events especially during the initiation of anticoagulation.

Previous Research:

Accuracy compared to existing technology

A Health Technology Assessment (HTA) report in 2010 found all genotype assays were accurate (99-100%) for CYP2C9*2/*3 and VKORC1 (1639)[11]. Another study found 4 assays had >95% accuracy for the same polymorphisms [2].

The accuracy with which algorithms employing genetic data predict dose requirements has also been assessed. A number of studies have compared the ability of different pharmacogenetic algorithms to predict dose requirements, and have found them to be broadly similar [2],[12]. Current pharmacogenetic algorithms may not be as accurate in an ethnically diverse populations [12]. A randomised trial was recently performed comparing two pharmacogenetic algorithms with standard dosing and found fewer out of range INRs. Percentage out of range INRs for the pharmacogenetic group and standard dosing were 31% versus 42% at 1 month, and 30% versus 42% at 3 months. [13].

Impact compared to existing technology

A systematic review in 2010 assessing the impact of genotyping included only three studies of mixed inpatient and outpatient populations. All studies used different regimens for standard dosing and pharmacogenetic groups. Two of three studies assessed the proportion of patients in the therapeutic range on day five. Both demonstrated a higher proportion in range in the pharmacogenetic group (70% versus 68% and 49% versus 11%). However, only one of the three studies found the time spent in therapeutic range to be higher in the pharmacogenetic group, and in this study the proportion of patients in therapeutic range on day five in the standard dosing arm was much lower than in the other two studies. There was no significant difference in bleeding between pharmacogenetic and standard dosing groups, but no assessment was made of clinical adverse events of bleeding or thromboembolism [14].

A different systematic review including the same three studies attempted to perform a meta-analysis, which, though limited by different methodology and quality between the studies, showed no difference in bleeding rates or time in therapeutic range. It was noted that the highest quality study showed a trend towards more rapid achievement of a stable dose [15]. A prospective, comparative effectiveness study in an outpatient setting in the USA (896 patients receiving warfarin genotyping; 2688 matched control group) comparing 6-month incidence of hospitalization reported that the genotyped cohort had 31% fewer hospitalizations overall (hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.58 to 0.82, $p < 0.001$) and 28% fewer hospitalizations for bleeding or thromboembolism (HR: 0.72, 95% CI: 0.53 to 0.97, $p = 0.029$)[16].

Guidelines and Recommendations:

An HTA report in 2010 concluded that large clinical trials were required to assess clinical utility of genotyping. As a short period of testing a patient's INR is usually sufficient to establish a stable dose, and in light of the introduction of new oral anticoagulants, they did not recommend a further review of evidence [11].

British Committee for Standards in Haematology Guidelines from 2011 state that there is insufficient evidence for genotyping prior to initiation of warfarin therapy [1]. They highlight research which suggests that response to the previous dose of warfarin rapidly becomes more important than genotype in predicting the required dose [17], and that standard dosing algorithms can accurately predict maintenance dose [18].

In 2007 the FDA approved a change in labelling of warfarin to suggest that genotype may affect choice of initial dose [19].

Cost-effectiveness and economic impact:

A systematic review in 2010 stated that more reliable cost-effectiveness estimates are required [20]. A further review examined two cost-effectiveness models, neither of which demonstrated a cost-benefit from genotyping [21].

Research Questions:

1. Does genotyping improve control of anticoagulation and reduce the frequency of adverse events?
2. In light of the prospective clinical data, will genotyping be cost-effective?
3. What is the clinical utility and cost-effectiveness of these tests when used in the primary care setting?
4. Are existing algorithms accurate in populations other than Caucasians?
5. Do polymorphisms influence the metabolism of new oral anticoagulants such as dabigatran and rivaroxaban?

Suggested next step:

1. Studies of clinical utility to date are small. Most use surrogate outcome measures (e.g. time spent in therapeutic range) as they are underpowered to assess bleeding and thrombotic risks due to low frequency of these events. However, high INRs do not correlate directly with risk of haemorrhage, and may therefore not be appropriate as a surrogate marker. Large scale clinical trials are required to assess the clinical utility of genotyping. Several such studies are underway, for example COAG (http://coagstudy.org/), GIFT [22]and EU-PACT [23].

2. Systematic reviews to date are inconclusive. Cost-effectiveness assessments will be informed by the data from large scale clinical studies that are currently underway. The EU-PACT study will assess cost-effectiveness as a secondary outcome measure.

3. It is unclear to what extent warfarin will remain in use given the introduction of new oral anticoagulants. There is little pharmacogenetic data for dabigatran or rivaroxaban. Such data may be particularly important given the lack of monitoring parameters for these drugs.

4. The accuracy of pharmacogenetic algorithms can be reduced when they are applied to populations that are more ethnically diverse than those on which they were derived [12 24,25]. The International Warfarin Pharmacogenetic Consortium is working towards a universally applicable algorithm, and will investigate the effect of racial and ethnic differences in genetic polymorphisms on warfarin dosing [25].

Expected outcomes:

Currently there is insufficient evidence to draw firm conclusions regarding the clinical benefit of genotyping prior to initiation of anticoagulation, and cost-effectiveness studies thus far are discouraging. The benefits of genotyping are likely to be greatest in the first few days of anticoagulation when there are no INR results to indicate how the patient will respond to warfarin. In order to become clinically useful and demonstrate cost-effectiveness future studies would need to demonstrate a large reduction in adverse events in the first few days. It is also likely that genotyping would need to become cheaper and the results more rapidly available, in order that they could be used routinely in the initiation of therapy.[21]

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