Should Genetic Testing Be Used to Guide Warfarin Therapy? A Cost-Utility Analysis Based on Current Evidence

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Introduction

- Warfarin is an effective and commonly prescribed anticoagulant, but is also one of the most common causes of serious adverse drug events.[1]
- Warfarin has highly variable dosing requirements that are influenced by the *CYP2C9* and *VKORC1* genes.[2-3]
- The FDA recently added this information to the warfarin label.
- A recently completed RCT of dose initiation with genetic testing vs. standard of care (COUMAGEN) provides an initial evidence base for evaluating the potential utility and costs of warfarin pharmacogenomic testing.[4]

Methods

- We developed a Markov model to project the incidence of bleeds and thromboembolic (TE) events, quality-adjusted life-years (QALYs), direct medical care costs, and incremental cost effectiveness ratios.
- The hypothetical patient cohort consisted of 65-year old patients newly initiated on warfarin for therapy of at least one year and cared for by anticoagulation clinic specialists.
- We used a lifetime horizon and payer perspective in 2007 US dollars. Costs and outcomes were discounted 3% per year.
- Data were derived from the COUMAGEN trial[4] (N=200), Intermountain Health Care, the University of Washington Anticoagulation Clinic, and the published literature. Trial data from the first month of follow-up were most complete and thus utilized.
- Although currently available warfarin genetic testing is available for about $550, we used $250 (range $100-$550) to reflect likely decreases within the year.
- The probability of a bleeding or thromboembolic event was based on the percent of time spent above, below and within therapeutic range using the International Normalized Ratio (INR) measure of anticoagulation status.[5]
- In the model, these relationships were based on longitudinal data published originally by Fihn et al[6] and expanded upon by Lafata et al[7] (See Table 1). Additionally, patients with *CYP2C9* variants had an increased risk of bleeds compared to wild type (RR = 2.3).[3,8]
- Patients were stratified by genotype into three groups: 1) wild-type for both genes, 2) variant *VKORC1*/wild type *CYP2C9*, and 3) variant *CYP2C9* regardless of *VKORC1* status.
- Quality-adjusted life-years were calculated by multiplying the amount of time in each health state by the utility of the state (Table 2)

References:
1. Ansell et al, Chest;126:204S (2004)
2. Rieder et al, NEJM;352:2285 (2005)
3. Higashi et al, JAMA;287:1690 (2002)
4. Anderson et al, Circulation;116:2563 (2007)
5. Samsa and Matchar, J Thromb Thrombolysis;9:283 (2000)
6. Fihn et al, Ann Int Med;124:970 (1996)
7. Lafata et al, J Gen Intern Med.;15:31 (2000)
8. Limdi et al, Clin Pharmacol Ther. 2007 Jul 25; [Epub ahead of print]

Decision Model
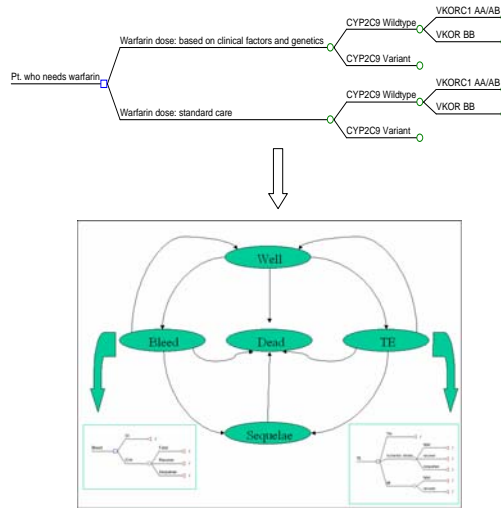
Stratified Trial Results

% of Time In, Above and Below Therapeutic Range in 1st Month
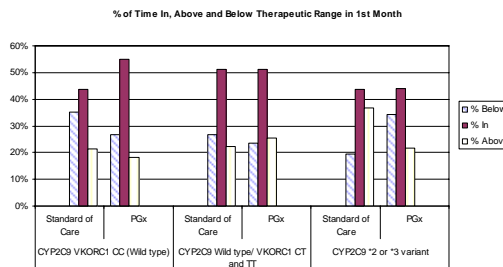
Model Parameters

Table 1	Parameter
Warfarin Initiation	
Hospital initiation	20%
Additional days to therapeutic dose for standard of care (days)	1.9
PGx test (cost)	$250
Hospital cost/ day	$459
LMWH/ day	$31
Genotype variant prevalence	Probability
CYP2C9 *2 or *3 (variant/low-dose)	30%
VKORC1 1173 CC [haplotype BB] (wild type/high-dose)	43%
Adverse Events	Risk
Bleed (above range)	0.1569
Bleed (within range)	0.0565
Bleed (below range)	0.0653
TE (above range)	0.024
TE (within range)	0.0299
TE (below range)	0.1626
	Probability
Intracranial bleeds (ICH)| Bleed	17%
Death prob.	38%
Sequelae	19%
	Probability
TIA| TE	29%
Ischemic strokes| TE	41%
Dead	9%
Sequelae	47%

Table 2. Health state/event utilities and costs

Event	Base Case Utility	Lower Limit	Upper Limit	Base Case Cost	Lower Limit	Upper Limit
Warfarin, no event	0.987			$63	47	79
TIA	0.90	0.86	0.95	$7,080	5,310	8,850
Ischemic stroke (1st month)	0.39	0.29	0.49	$12,371	9,278	15,463
MI (1st month)	0.87	0.78	0.96	$23,907	17,930	29,884
Extracranial Bleed	0.84	0.76	0.92	$9,127	6,845	11,409
ICH Bleed (1st month)	0.39	0.29	0.49	$28,255	21,191	35,319
Sequelae	0.39	0.29	0.49	$3,858	2,893	4,822

Abbreviations: TE, thromboembolic event (clot); TIA, transient ischemic attack; ICH, intracranial hemorrhage; MI, myocardial infarction

Results: Base Case

- Testing increased quality-adjusted life-years (QALYs) by 0.0033 (~1 day) and increased costs by $101 compared to standard of care.
- There was a 63% probability that testing was cost effective at a $50,000/QALY threshold, and a 26% probability that QALYs were decreased.
- In a population of 1,000 people, testing reduced the number of bleeds by 1.6, and increased the number of thromboembolic events by 0.5.

Results: Sensitivity Analyses
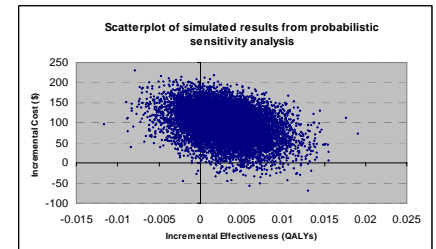
Discussion & Limitations

- Our results suggest that testing may result in a small improvement in quality-adjusted life years with a modest increase in cost.
- These results are based on preliminary data, and specific to patients cared for in an experienced anticoagulation clinic.
- The risk-benefit profile varied across strata:
  - Patients wild-type for both genes had a decrease in clotting risk
  - Patients with a *VKORC1* variant had little change
  - Patients with a *CYP2C9* variant had a decrease in bleeding risk, but an increase in clotting risk
- In order to establish that warfarin pharmacogenomics improves patient outcomes in a clinically meaningful and cost-effective manner, there will need to be:
  1. improvements in the effectiveness of using genetic information to guide warfarin therapy,
  2. decreases in the cost of genotyping, and
  3. larger clinical studies that are powered to assess differences in INR across genetic strata.
- In summary, currently there is not sufficient evidence to recommend genetic testing for warfarin patients on a widespread basis.