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Scott and White Warfarin Dosing and Genetic Testing Program

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Scott and White Hospital

- 110-year-old Central Texas healthcare organization
 - Academic Medical Center affiliated with The Texas A&M University System Health Science Center College of Medicine
 - 800 + -bed system of 4(+2) hospitals with 40,000 admissions
 - 30 satellite locations throughout central Texas
 - More than 200,000 Scott & White Health Plan members
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S&W Path to Warfarin PGx

- • Which test to choose
 - • Understand groups involved in Warfarin dosing
 - When to test and which group to test
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CHALLENGES

- Different groups of healthcare personnel involved
 - Pathologists, pharmacists, hematologists, hematopathologists, hospitalists, geneticists, genetic counselors, nurses, payors
 - Education, awareness and demystifying of pharmacogenomics
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Warfarin

- • Widely prescribed drug (**2 million** patients on warfarin, **30 million** Rx /yr)
 - 3.6% of all drug induced adverse events, 2nd highest severe adverse events
 - – **87,000** major bleeding a year
 - – **43,000** ER visits a year
 - – **17,000** strokes a year
 - – **10,000** deaths a year
 - Joint Commission safety initiatives (anticoagulants)
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All of This Is Summarized in the Black Box Warning in Warfarin Label

WARNING: BLEEDING RISK

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥ 65 , highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see **PRECAUTIONS**), and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see **PRECAUTIONS: Information for Patients**).



Updated Label 2007

Meta-analysis of 9 studies involving 2775 patients (99% caucasian)

- – Increased bleeding risk 2C9 *2 or *3 alleles
- – Decreased dose requirements
- • *2, **17% reduction** dose compared to wild type *1/*1
- • *3, **37% reduction** dose compared to wild type *1*1



219 Swedish patients grouped retrospectively

- – Number patients INR>3 first 2 weeks doubled if *2 or *3 allele

201 Caucasians treated with stable warfarin doses

- – 30% variability dosing VKORC1 alone
- – 40% variability dosing VKORC1 and 2C9
- – 55% variability dosing genes, age, height, wt, drug interactions, indications
- **Precautions**
- – Numerous factors alone or in combination may influence the response of the patient
- • Diet, medications, botanicals
- • 2C9 and VKORC1 variants

Summary of relationships for warfarin therapy: Demystifying role of genetics

- **•CYP2C9 sets the rate: accumulation and elimination**
 - –influences warfarin clearance and is associated with need for decreased maintenance dosages

 - **•VKORC1 sets the amount: effective concentration**
 - –influences warfarin pharmacodynamic response and is also associated with specific warfarin maintenance dose
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Warfarin Dose & CYP2C9

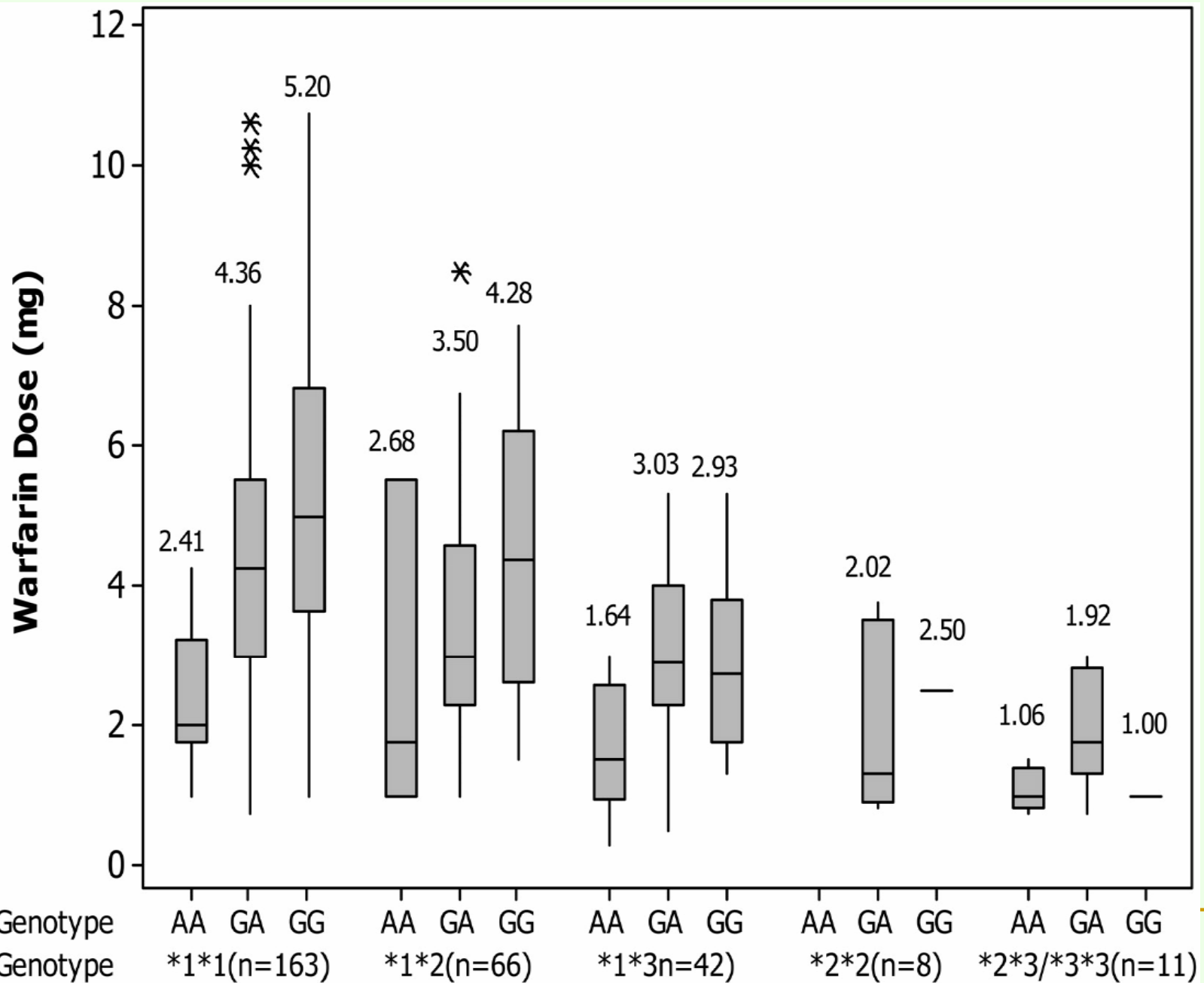
Allele CYP2C9	Frequency	Metabolizer	Daily Dose (mg)
*1*1 (wild-type)	56%	Rapid or extensive	5 mg
*1*2 (variant)	22%	Intermediate	2.50-2.70 mg
*1*3 (variant)	14%		
*2*2 (variant)	3%	Poor	1.50-1.70 mg
*2*3 (variant)	4%		
*3*3 (variant)	1%		



Warfarin Dosage & VKORC1

Allele VKORC1	Frequency	Sensitivity	Daily Dose
GG (wild-type)	25%	Low 100%	6.7 mg
GA (variant)	56%	Intermediate 50-70%	4.2 mg
AA (variant)	19%	High 10-15%	2.7 mg

*Sconce et al, Blood 2005, Rieder MJ et al NEJM 2005
Wadelius M et al Pharmacogenomics 2005*





Existing Coagulation protocol

- • Hospital based patients are dosed in on age- based algorithm by pharmacy.
- • Empirically adjust dose daily by trial and error based on INR, other medication

New guidelines are being established to suggest a initial starting dose of 2.5 mg instead of 5 mg as was done previously.



Anticoagulation Forum Panel

(Newsletter vol. 11, no.2, summer 2007)

- 1. Practitioners could acquire a false sense of complacency about the need for rigorous monitoring by assuming that genotyping will lead to accurate dosing
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Talking points

Genetic testing is not substitute for monitoring of INR values.

By combining initial dosing based on genotype with algorithm-based adjustment of dose using the first 3 INR values, one can account for 79% of individual variation.

The web-based algorithm will even remind you (by e-mail) to add the INR values within 3 days of entering the initial clinical and genetic data!



Concerns



- Wait time for genotyping results may delay initiation of therapy leading to adverse events
 - Talking points:
 - Tests can be run on the Osmetech on an individual batch mode so test results can be issued about 4 hours after being sent to the lab, so no delay.
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Concerns



- Patients who appear (based on gene testing) to be extremely sensitive to warfarin could get systematically under-dosed and thus be at higher risk for thrombosis.
 - Talking points: 3 studies undertaken as a committee
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Initial Study



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- 20 random patients
 - Results presented to Director of Pharmacy and Director of Anticoagulation/Coumadin Clinic.
 - 3 patients with polymorphisms identified
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Initial results

- **Warfarin Dose Study (20)**
 - 3 patients with polymorphisms identified.
 - Up to 12 weeks to attain target, stable dose.
 - These patients could be shown to be initially on target using Gage PGx dosing recommendations

 - -Problem: Patients with wild type genotype
 - Could not satisfactorily establish relationship because of complex history, incomplete history etc.
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Subsequent study 2

Samples retrospectively collected

100 randomized patients selected by Director of Anticoagulation Clinic

Wild-type genotypes identified and time to achieve therapeutic INR compared to those with polymorphisms (Gage Pgx used)



Study 3

- Initial dose should be closer to final therapeutic dose based on INR
 - Time to final stable dose should be shorter
 - 100 patients dosed prospectively by Gage PGx
Use INR as surrogate endpoint to bleeding

 - – Time to reach therapeutic INR (2 to 3)
 - – Time stays within therapeutic INR (2 to 3)
 - • **If INR > Predicted Goal at any time**
 - – Change to pharmacy protocol for dose adjustment
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Conclusions

- Ongoing educational process.
 - Lab: Advantages: Ease of use, cost and footprint.
 - Clinicians: Additional tool to help workflow

 - Absence of strict guidelines and prevalence of empiric treatment regimens makes this to difficult to implement without a lot of interaction between healthcare personnel.
 - Advantages: Each lab can customize workflow and meet challenges of best practices guidelines (Joint Commission)

 - By demystifying and standardizing protocol, optimizes patient care.
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References

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 2. Regulatory Perspective on Warfarin Relabeling with Genetic Information: Lawrence J. Lesko, Ph.D., FCP Director, Office of Clinical Pharmacology Center for Drug Evaluation and Research Food and Drug Administration Silver Spring, Maryland, USA
 3. Gage et al. (2008) Use of Pharmacogenetic and Clinical Factors to Predict the Therapeutic Dose of Warfarin. Clin Pharmacol Ther.84: 326-331.
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