The WARFARIN Study: Genetic Testing and Systems Reengineering to Support Personalized Medicine

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Can Pharmacogenetics Deliver on Personalized Healthcare?

• Has the US healthcare reform accelerated or decelerated the move to a more personalized medicine?

• Can Comparative effectiveness Research (CER) serve as a catalyst for personalized medicine?

• How will the Patient-Centered Outcomes Research Institute (PCORI), created by the US Health Reform and Affordable Care Act affect the adoption of personalized Medicine?

Ofili E. and Sproles D.
Conference Scene: The healthcare reform act, comparative effectiveness research and personalized medicine

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Genetic Testing and Personalized Medicine: Challenges and Opportunities

• Despite slow progress, genetic variations that are associated with beneficial or harmful drug responses continue to hold promise for individualized or personalized approaches to treatment

• The greatest obstacle to the adoption of personalized approaches such as genetic testing is the lack of adequately designed studies with clinical outcomes

• Systems limitations impact the timely reporting of test results for real time treatment decisions
Warfarin Study: Genetic Testing and Personalized Medicine

Francis Collins, Director of NIH, predicts in his book that Coumadin™ (Warfarin) will be the first drug for which the so-called Dx–Rx paradigm [a genetic test (Dx) followed by a prescription (Rx)] will enter mainstream medical practice.

- FDA economists have estimated that by formally integrating genetic testing into routine Warfarin therapy, the US alone would avoid 85,000 serious bleeding events and 17,000 strokes annually
- 9 out of 10 cardiologists surveyed believe that personalized medicine will have a larger role in cardiovascular patient treatment within the next 10 years
Warfarin: A Case Study on the Challenges and Potential Benefits of Genetic Testing

GI absorption
93±8% Absorbed

CYP1A2
CYP3A4
CYP2C19
CYP2C9

R, S-warfarin

S-7-OH warfarin
S-6-OH warfarin
R-4-OH warfarin
R-7-OH warfarin
R-6-OH warfarin

VKOR

Vitamin K
γ-Glutamyl-carboxylase
Calumenin

Vitamin K (H2)

O2+ CO2

Active factors II, VII, IX, and X
Inactive factors II, VII, IX, and X

Mean warfarin dose (mg/kg/wk) by week of therapy in patients differentiated by allelic type

Mean observed (INR) by week of therapy in all patients, differentiated by allelic type

Maximum observed (INR) by week of therapy in all patients, differentiated by allelic type

Mean ± SEM warfarin dose (mg/kg/wk) in the second week of therapy in all patients, differentiated by allelic type
Mean ± SEM warfarin dose (mg/kg/wk) in the tenth week of therapy in all patients, differentiated by allelic type
WARFARIN Study Rationale

2006
FDA issued black box warning on warfarin highlighting the risks of bleeding.

2007
FDA updated warfarin prescribing information to explain that genetics may influence the patient’s response to the drug.

2007 – 2009
FDA cleared 4 platforms for the determination of warfarin-related gene variants.

2009 May
CMS considers suspending Medicare payment for warfarin genetic testing.

2009 Aug
Decision not to cover costs of warfarin pharmacogenetic tests unless more clinical data is generated on patient health outcomes.

Today
Iverson™ Genetic Diagnostics sponsoring a clinical study to obtain data on health outcomes for warfarin patients.
Reimbursement Code Granted by CMS

Only CED for general coverage
- Initially to be used with patients enrolled in the WARFARIN Study

Study objective...
- Compare number of warfarin-related adverse events (bleeding & clotting) in 2 randomized groups at 30, 60, and 90 days post initiation

If Successful Study will...
- Expand government reimbursement beyond the Study and make genetic testing a standard of care
- Participating Health Systems and providers already engaged
Iverson Process: Focus on Medical Provider and Systems Reengineering

**Step 1:** Patient blood/buccal specimen collected using Iverson “Go Genetic” kit

**Step 2:** Specimen shipped prepaid FEDEX overnight

**Step 3:** Patient specimen received at Iverson Lab and DNA analyzed

**Step 4:** Patient reports generated

**Step 5:** Patient reports transmitted to patients' Medical Provider

**Step 6:** Genetic interpretation services offered by Iverson Ph.D. personnel
The WARFARIN Study

• The purpose of the WARFARIN study is to determine the utility of genetic testing in reducing the incidence of adverse events, both bleeding and thromboembolism, associated with the initiation of warfarin therapy.

• Patient inclusion criteria
  - ≥ 65 years old
  - New start on warfarin treatment for at least 1 month, target INR > 2.0
  - Subject and medical record will be examined for previous testing. Prior testing will eliminate subject.

• All participants will be screened using genetic testing
  - 2,300 eligible to continue randomized portion of study
  - 1,500 additional will receive standard of care and short follow up (Registry)
Study Objectives and Design

- This study is designed to assess if genotype testing of CYP2C9, VKORC1, and the collection of patient demographic and medical information, can reduce the number of bleeding and clotting related adverse events related to warfarin in subjects receiving anticoagulation therapy.

- **Study design**
  - Multi-center
  - Randomized
  - Blinded
  - Parallel-group
  - Information provided by the Warfarin GenoSTAT assay from Iverson Genetic Diagnostics to modify the warfarin dosing protocol
Primary and Secondary End Points

• **Primary End Point**

  To determine if the utilization of warfarin-related pharmacogenetic testing will have lower rates of hemorrhagic or thromboembolic adverse events at 30 days after initial dose when compared to standard (clinical) warfarin initiation

• **Secondary End Points**

  • Reduction in the number of INR tests required for warfarin dose stabilization
  • Reduction in the time to stable INR
  • Reduction in cumulative warfarin dose necessary to reach and maintain warfarin therapeutic range
  • Improvement in the quality of life for subjects who receive the Warfarin GenoSTAT test
  • Rates of hemorrhagic or thromboembolic adverse events 60 and 90 days after initial dose
Study Flow Diagram

FOLLOWING PATIENT INFORMED CONSENT

Perform Warfarin Dosing Panel

Randomization to obtain dose recommendation

Standard Group (clinical algorithm) 1650
- Dose adjusted as directed by clinician
  - 30, 60, 90 day AE follow up

Genetic Group (clinical and genetic algorithm) 1650
- Dose adjusted as directed by clinician
  - 30, 60, 90 day AE follow up

Final data analysis and study conclusions and publication

MSM/ACTSI enabled Biorepository of 7,000 plus patients: LIMS

Fail to meet genetic criteria: no further participation

Iverson Genetic Diagnostics, Inc.

Subject Identification

Clinical Site Activity
Interventions and Duration

• Subjects given an initial dose of 5 mg warfarin
• Blood sample taken
• Subject’s genetics will be determined and information entered in www.WarfarinDosing.org to calculate recommended dose

Dosing algorithm developed by Dr. Brian Gage of Barnes-Jewish Hospital at Washington University Medical Center.
Interventions and Duration

RANDOMIZED SUBJECTS

- **ARM A** – receives a warfarin dose calculated with the algorithm at WarfarinDosing.org using only clinical data *(standard arm)*

- **ARM B** – receives a warfarin dose calculated with the algorithm at WarfarinDosing.org using clinical data and genotype information provided by the Warfarin GenoSTAT test *(genetic arm)*

- Investigators will be blind to Arm and genotype

- Subjects will be given recommended dose on the second day

- Subject’s dose adjusted as needed under physician’s direction and recorded

- Randomized subjects followed up after 30, 60, and 90 days to record any hemorrhagic or thromboembolic adverse events related to warfarin
Interventions and Duration

REGISTRY SUBJECTS

• Registry subjects will receive genotype and warfarin dose calculated with the algorithm at www.WarfarinDosing.org using clinical data and genotype information provided by the warfarin sensitivity test.

• Registry subjects will receive a brief warfarin-related events follow up at 30 days.
Warfarin Study Sponsorship

Sponsor
Iverson Genetic Diagnostics
Bothell, WA, Study lab in Atlanta, GA

Principal Investigator
Elizabeth Ofili, MD
Chief of Cardiology
Morehouse School of Medicine

Reimbursement
Sponsor will receive reimbursement from CMS for those patients enrolled in WARFARIN

CMS
Approved study for warfarin responsiveness under protocol #CAG00400N-02
Patient-Centered Outcomes Research Institute

• Independent institute created by the US Health Reform Act

• Will examine the utility and effectiveness of medical products and services in "various subpopulations" differentiated by race, ethnicity, sex, age, co-morbidities, as well as genetic and molecular subtypes
Future Directions

• For personalized medicine to be widely adopted in clinical practice, payors need evidence of effectiveness and financial viability

• The adoption of genome medicine to diagnostic and therapeutic approaches in healthcare must rely on well designed prospective studies with clinical outcomes
Atlanta Clinical & Translational Science Institute (ACTSI)

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Thank you!!!!

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