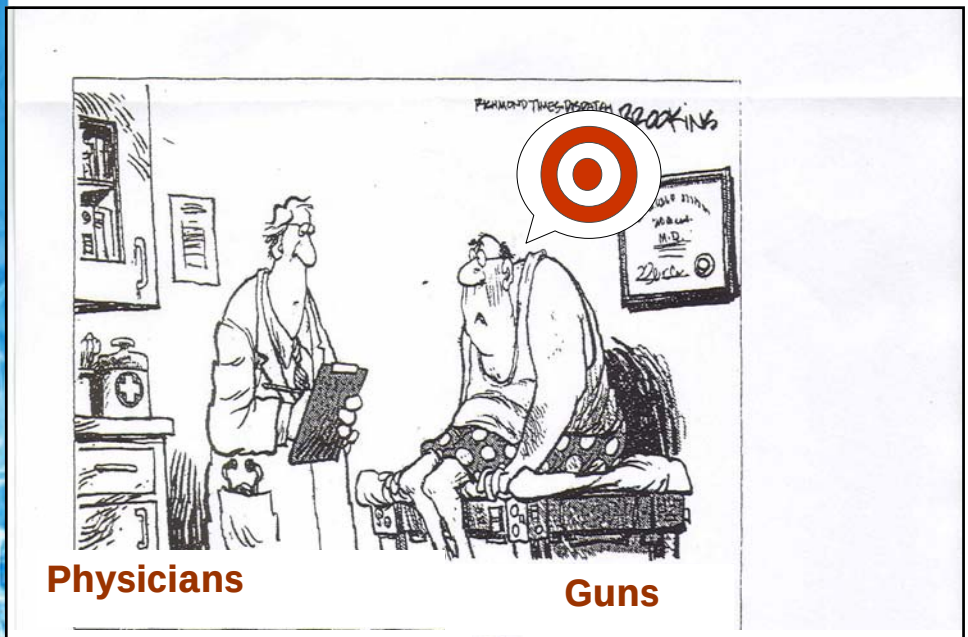
Making Personalized Predictive Medicine A Bedside Reality

PCAST Meeting
September 11, 2007



Physicians

700,000 US Physicians
Accidental Annual Deaths > 120,000
Accidental Deaths/Physician = 0.171

Guns

80,000,000 Owners
Accidental Gun Deaths/Year~1500
Accidents/Gun Owner=0.000188

Since the Mid-1970's

- Explosion in Research Capability, Medical Technology and Allied Industry
- The Biotechnology Revolution
  - Genomics, proteomics, molecular imaging, nanotechnology, information technology
- Despite The Above
  - Health care and the training of physicians remains focused on disease not health
  - And Medical Practice Remains Reactive

Disease and Probability

- Unless both the physician and patient seek to better understand the individual patient's probability of disease and therapeutic response, they are both condemned to this reactivity.

Toward a probabilistic future health prediction for each individual

- "The medicine of today is reactive, with a focus on developing therapies for pre-existing diseases, typically late in their progression. Over the next 10 to 20 years medicine will move toward predictive and preventative modes."

Hood, L. Science, 2004

Contributors to the Reactivity of Healthcare

- Current Health Care emphasizes acute care rather than … wellness, early detection, and prevention.
- It focuses on Third Party payments, thus the patient has little responsibility
- It relies on paper

Gingrich, N. Managed Care 2/05

The Value of Personalized Predictive Medicine

- The more predictive medicine becomes, the more responsible and proactive both the physician and the patient can become
- Understanding disease and the ability to predict outcome facilitates **deliberation, decision and responsibility for both parties**

Personalized Predictive Medicine

- Oriented to detection and reduction of risks from disease, in addition to diagnosis and treatment of disease
- Different time-scheme vs. symptom related medicine. It is related to symptoms and illnesses that could manifest themselves far into the future.
- Assumes a statistical style of reasoning and the concomitant practices in the application of knowledge.

Drivers of Mortality and Cost

- **Complexity of Health Care**
- **Lack of Integration of Healthcare Data**
  - **Lack of EMR**
  - **Lack of Portability**
- **Lack of Predictability of Intervention Outcome**
  - **Diagnosis, Medications, Procedures, Devices**
- **Lack of Predictability of Individual Prognosis and Possibility of Hospitalization/Complication**
- **Predictive Capacity at the Population Level**

Enhancing Medical Decision Making

- **Evidence Based Medicine**
  - Meta Analysis Approach
  - Selective Rules
  - At Best Population Based Prediction
- **Personalized Medicine**
  - Individual Based Prediction
  - Arguably Clinically More Relevant
  - Eliminates Selection Bias

How to Get to Personalized Predictive Medicine

- Integrated Portable EMR
- Ability to mine EMR for Personal Predictive Value
  - Diagnosis, Co-Morbidities, FMH, Medications, Lab
- Application of Machine Learning to Medicine
- Outcome-Driven Biomarkers that Augment Individualized Prediction
  - Genetic, Proteins, Metabolites, “Routine Labs”

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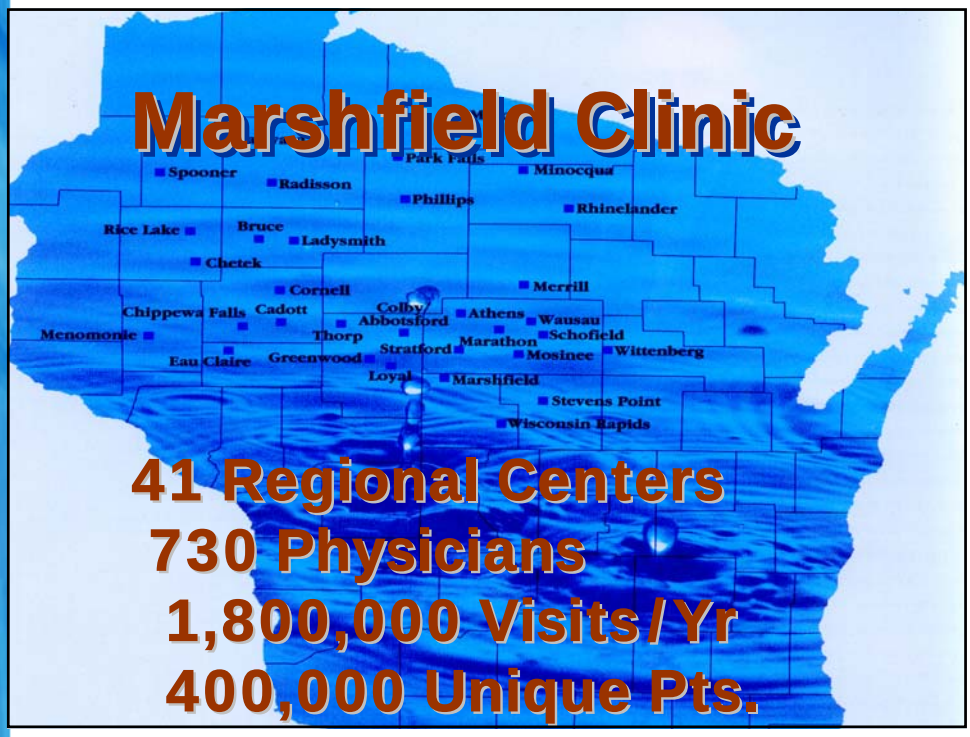
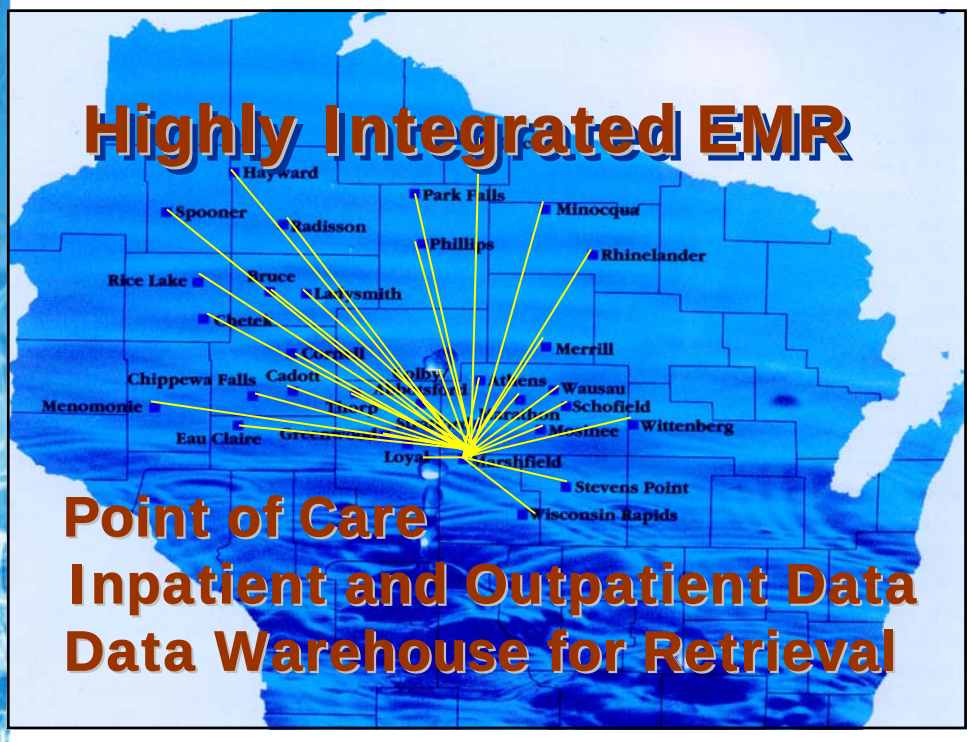

Marshfield Clinic
Spooner
Radisson
Park Falls
Minocqua
Phillips
Rhinelander
Rice Lake
Bruce
Ladysmith
Chetek
Cornell
Merrill
Chippewa Falls
Cadott
Colby
Abbotsford
Athens
Wausau
Menomonie
Thorp
Schofield
Marathon
Eau Claire
Greenwood
Stratford
Mosinee
Wittenberg
Loyal
Marshfield
Stevens Point
Wisconsin Rapids
41 Regional Centers
730 Physicians
1,800,000 Visits/Yr
400,000 Unique Pts.


Highly Integrated EMR
Hayward
Spooner
Radisson
Park Falls
Minocqua
Phillips
Rhinelander
Rice Lake
Bruce
Ladysmith
Merrill
Chippewa Falls
Cadott
Wausau
Menomonie
Schofield
Eau Claire
Wittenberg
Stevens Point
Wisconsin Rapids
Point of Care
Inpatient and Outpatient Data
Data Warehouse for Retrieval

EMR Status

- 1,623 total users system wide
- 2,376 procedure terms with 29,838 code rules
- 18,729 diagnoses with 44,920 code rules
- Over 1,800,000 visits in 2006
- 1,200,000 total electronic records
- 48 departmental lexicons

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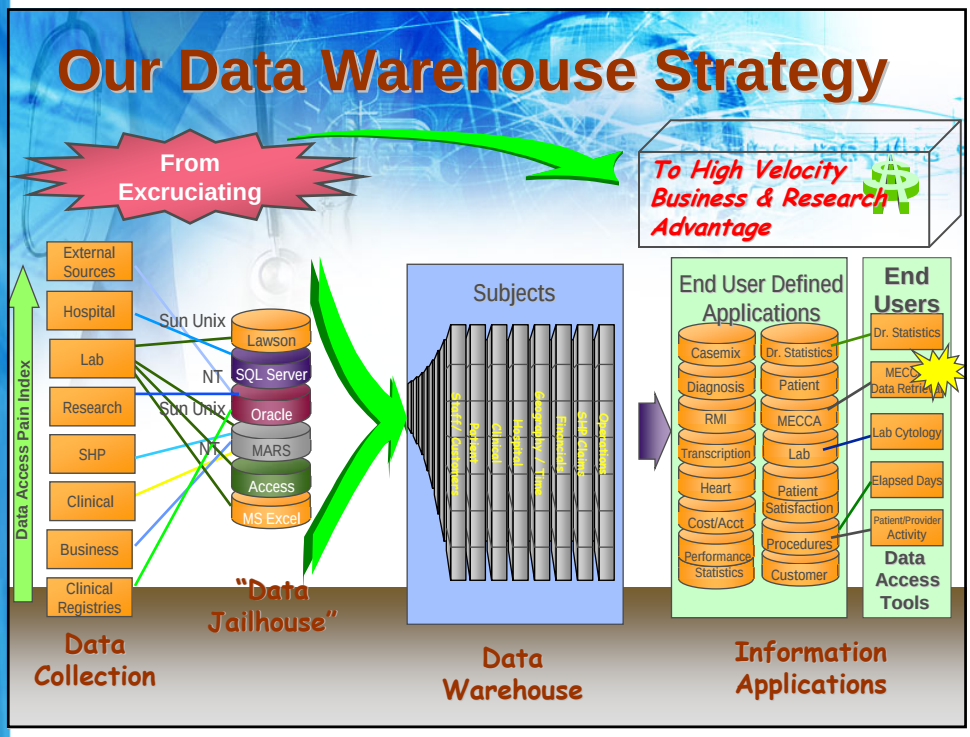

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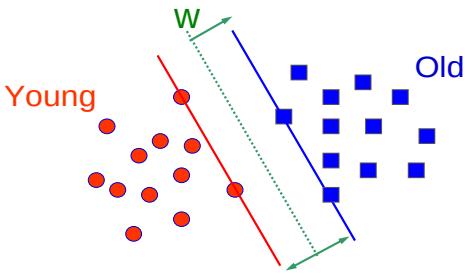
Machine Learning

- The same class of tools that recognize spoken words, detect fraudulent use of credit cards, drive autonomous vehicles on public highways, and play games such as backgammon at levels approaching the performance of human world champions - **can predict the recovery rates of pneumonia patients.**

Support Vector Machines
Maximizing the Margin between Bounding Planes (Mangasarian & Fung)



Machine Learning and EMR

Using Clinically Available Electronic Data
Dx, FMH, Co-morbidities, Labs,etc

COX-2 +/- MI

Can predict MI in COX-2 Population with 74% Accuracy

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NEWS FOCUS

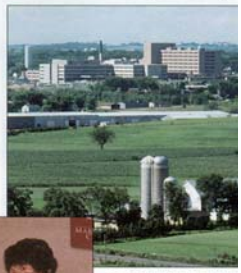
ountries and health providers are following Iceland's path and combining health and genetic data large populations. They promise to deliver "personalized" medicine, but will they?

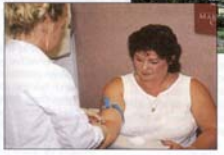
Population Databases Boom From Iceland to the U.S.

, residents of the dairy country of isconsin received an unusual invita- their local health care provider: an y to donate their DNA for research. gn up, they will give blood and talk nic staffer about their family disease et, and exercise habits. The projected participants will also give re- extraordinary freedom to use this on—including details of their genet- o—to probe the complex interplay enes, environment, and disease. researchers have amassed a bank of mples, they will scan each subject's elltale markers of increased risk for iseases. Ultimately, these data will ned with the participants' electronic cords in a powerful new type of With a touch of a few keys, says Caldwell, director of the Marshfield Research Foundation, which will udy, researchers will be able to mine dential data for links between genes, actors, and illness. Caldwell's team find disease t have so far usive and to tricky epi- c questions, ow much a combination and expo- unlight, say, g alcohol— to raise the ncer or heart The consen- t such databases will be the key to

involved, requires huge DNA collections, bigger than any gathered to date—some projects aim to sample a million people—plus long-term health data on each person who donates his or her DNA.

That's a dangerous combination, say some ethicists. They worry that data won't remain confidential and suggest that compa-





Heartland biobank. This teer's DNA will go into a to be probed by the Marshfield Clinic, which plans to study gene-environment interactions among residents of central Wisconsin.

nies, whi role in some projects, should not be allowed

find it. To compensate, need to study genetic prof more people and also incor mation on phenotype, or he

ago made the startling announce

Study Population

Over 19,000 patients

Approximately 50% participation

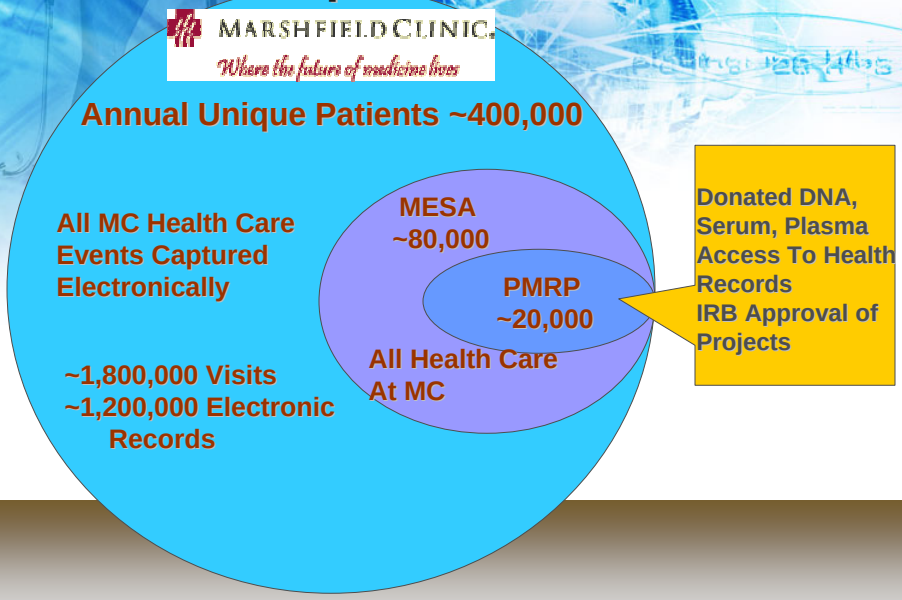
Study activated 9/18/02

DNA, serum and plasma

Permission to use healthcare data

Science 298: 1158-61, Nov. 2002

PMRP Population Construct



Perioperative Genotyping for Safety

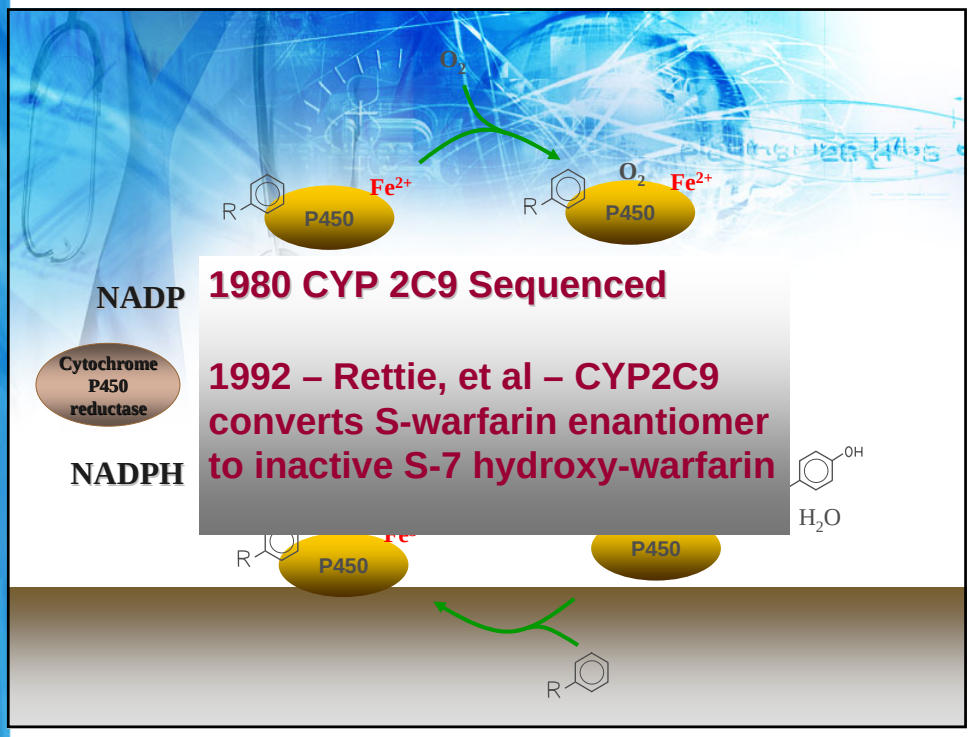
- 450 patients undergoing general anesthesia and surgery
- Tested for 48 polymorphisms in 22 genes including *ABC, BChE, ACE, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, b2AR, TPMT, FII, FV, FVII, MTHFR, TNFa, TNFb, CCR5, ApoE, HBB, MYH7, ABO* and *Gender*
- 391 of 450 patients were found to be homozygous for mutant alleles at 1 or more loci in pathogenic genes, with a mean of 2 mutant homozygous loci per patient.
- Significant genetic heterogeneity is present in advance of surgery and anesthesia in most patients, and is not accounted for using contemporary methods of detection, for example, by taking a family medical history.

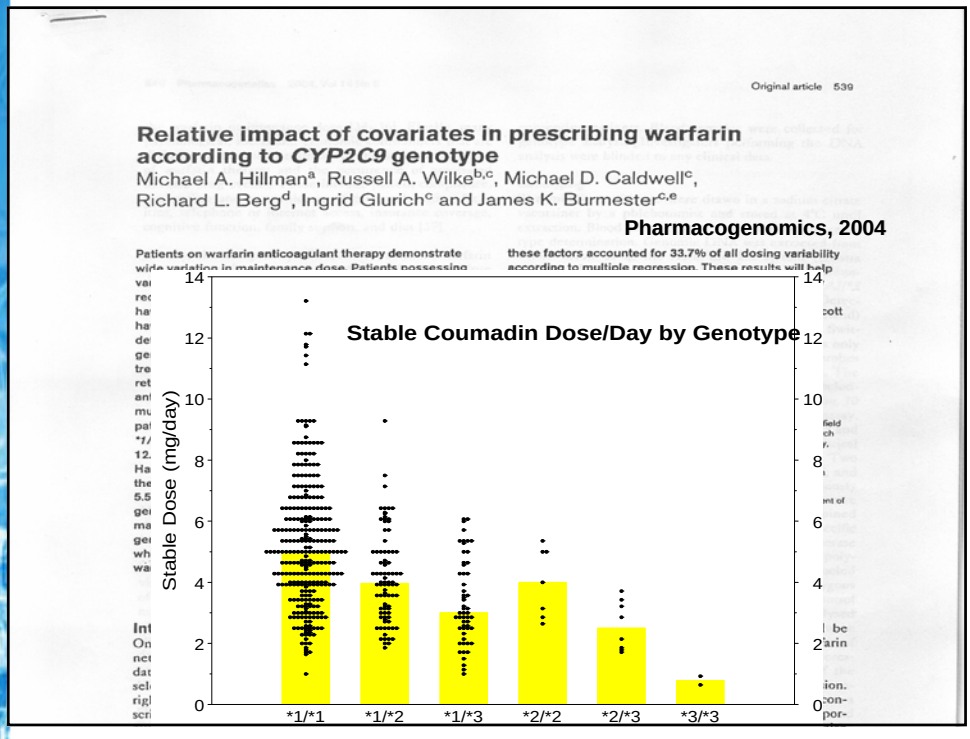
Warfarin as the Icon for Personalized Medicine

- “Warfarin, sold under the brand name Coumadin and in generic forms, yesterday became the first widely used drug to include genetic testing information on its label.”Associated Press 8/17/07
- "This means personalized medicine is no longer an abstract concept but has moved into the mainstream," the Food and Drug Administration's clinical pharmacology chief, Larry Lesko, said in disclosing the label change.
- The updated label for warfarin suggests that lower doses may be best for patients with variations in two specific genes.

Historical Approach to Warfarin Dosing

- Marked Individual Dose Variability
- Narrow Therapeutic Index
- No tests available for dosing guidelines
- Dose Adjusted Based on:
  - Age
  - BMI
  - Co-morbidities
  - Medications
- Using this approach account ~20-25% variability





Original article 539

Relative impact of covariates in prescribing warfarin according to *CYP2C9* genotype

Michael A. Hillman[a], Russell A. Wilke[b,c], Michael D. Caldwell[c], Richard L. Berg[d], Ingrid Glurich[c] and James K. Burmester[c,e]

Pharmacogenomics, 2004

Patients on warfarin anticoagulant therapy demonstrate wide variation in maintenance dose. Patients possessing

these factors accounted for 33.7% of all dosing variability according to multiple regression. These results will help

Stable Coumadin Dose/Day by Genotype

Stable Dose (mg/day)

0 2 4 6 8 10 12 14

*1/*1 *1/*2 *1/*3 *2/*2 *2/*3 *3/*3

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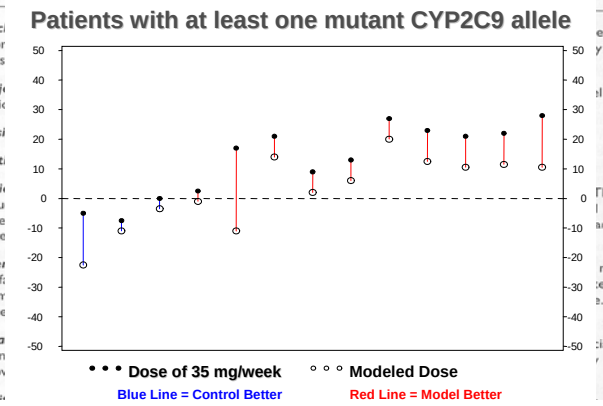
http://www.clinmedres.org

Original Research

A Prospective, Randomized Pilot Trial of Model-Based Warfarin Dose Initiation using CYP2C9 Genotype and Clinical Data

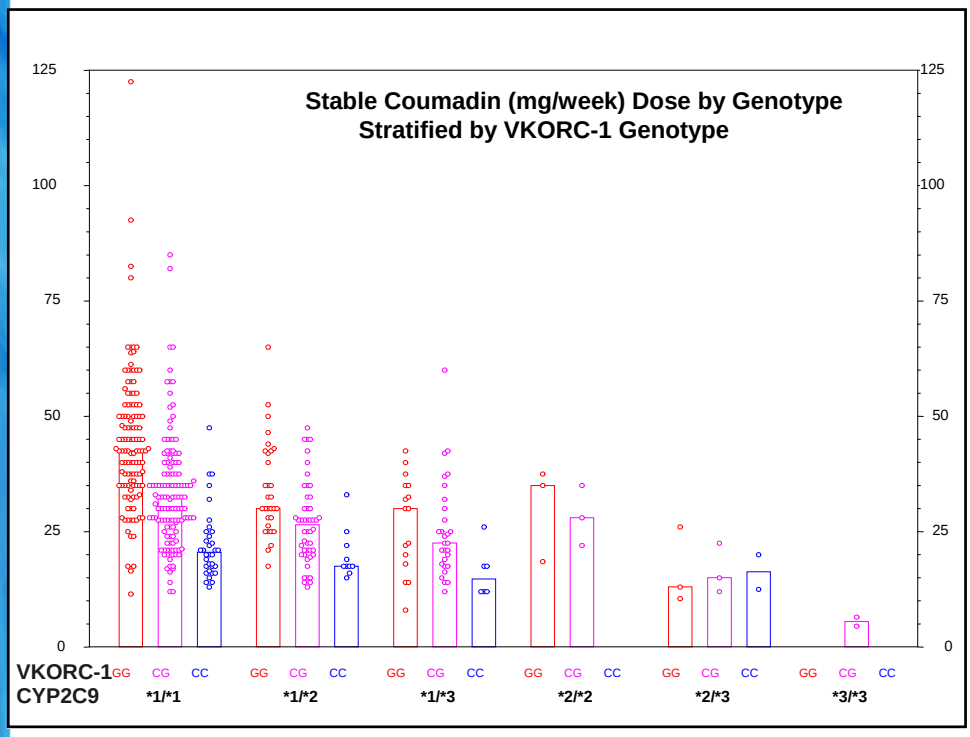
Michael A. Hillman, MD, MBA; Russell A. Wilke, MD, PhD; Steven H. Yale, MD; Humberto J. Vidaillet, MD; Michael D. Caldwell, MD, PhD; Ingrid Glurich, PhD; Richard L. Berg, MS; John Schmelzer, PhD; and James K. Burmester, PhD

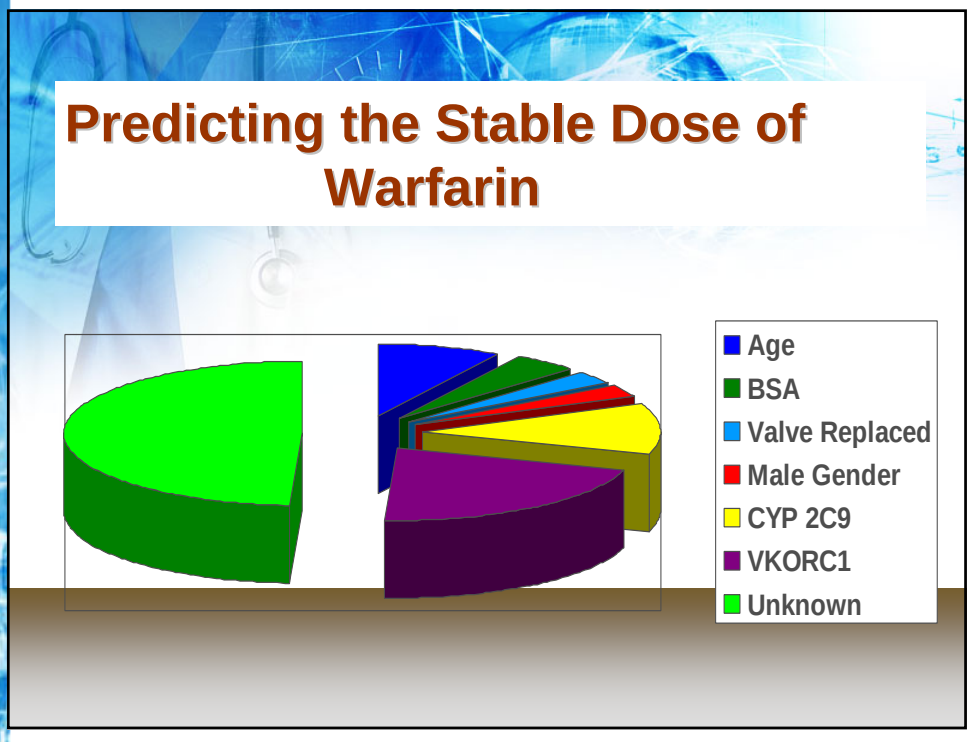


Model-based dosing was better predictor in 54% of subjects (77% with abnormal allele)

VKORC1: Modeled Variance

	Model with VKORC1	Model without VKORC1
N=	354	354
Adjusted R^2	.5594	.3346

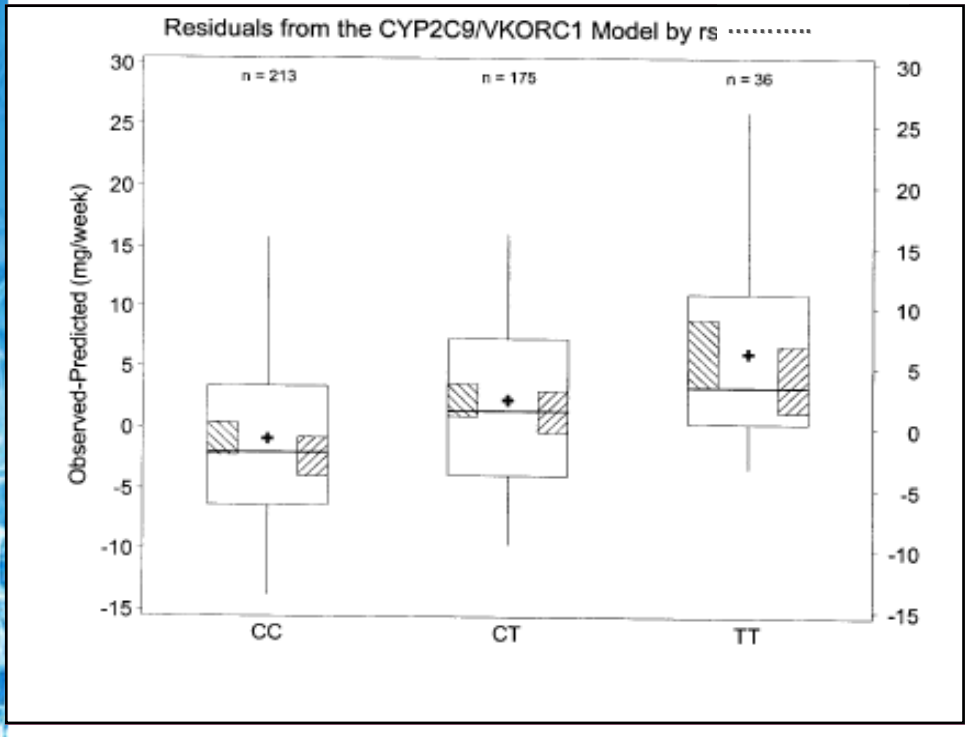

Stable Coumadin (mg/week) Dose by Genotype
Stratified by VKORC-1 Genotype
125
100
75
50
25
0
VKORC-1 GG CG CC GG CG CC GG CG CC GG CG CC GG CG CC GG CG CC
CYP2C9 *1/*1 *1/*2 *1/*3 *2/*2 *2/*3 *3/*3


Predicting the Stable Dose of Warfarin
Age
BSA
Valve Replaced
Male Gender
CYP 2C9
VKORC1
Unknown

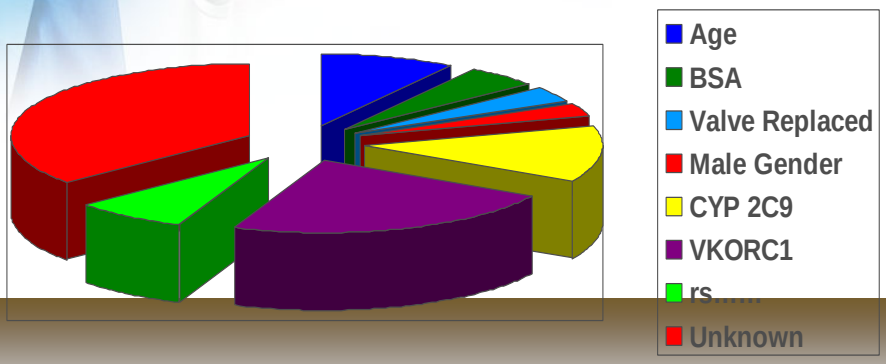
Analysis of residuals from the CYP2C9/VKORC1 model by rs----------

	N	Mean	Std Dev	Lower 95% CL for Mean	Upper 95% CL for Mean
CC	213	-0.9	9.7	-2.2	0.4
CT	175	2.3	8.9	1.0	3.6
TT	36	6.1	8.4	3.3	9.0

Kruskal-Wallis p-value = 0.0000004



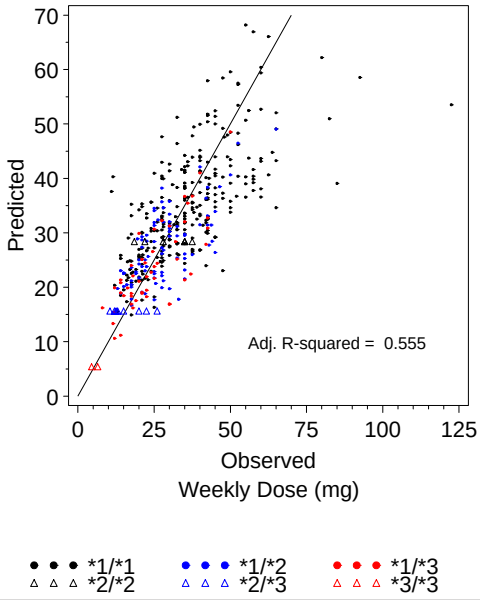
Predicting the Stable Dose of Warfarin



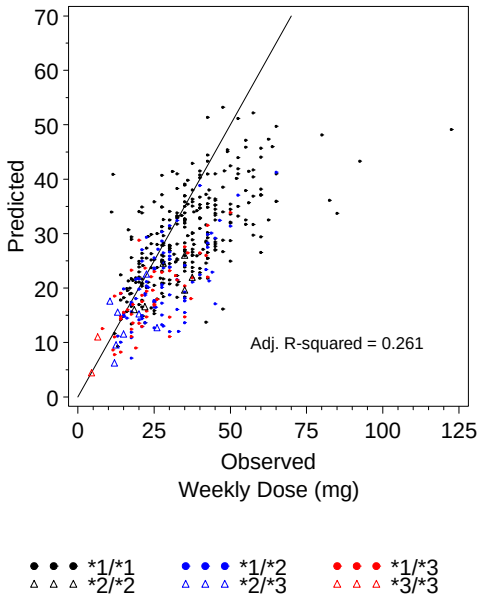
Current Pharmacogenetic Approach to Warfarin Dosing

- **Using Phenotypic Data including age, body surface area, co-morbidities, genotypes for three genes can now explain ~ 64% of the variance in individual warfarin dosing versus ~ 25% with phenotypic data alone**

CYP2C9 + VKORC1 Composite Model



Sconce et al Model Applied to MCRF Data



Warfarin Dosing Algorithms

- Not transportable from population to population
- Most cohorts too small to properly assess the effects of medications, ethnic origin, co-morbidities, etc
- Led to the development of the International Warfarin Pharmacogenetic Consortium

International Warfarin Pharmacogenetic Consortium

- Voluntary Consortium of Investigators from 21 Institutions with cohorts of patients with known phenotypic data regarding warfarin response and data regarding CYP 2C9 and VKORC-1 genotypes
- Agreement to aggregate de-identified primary data to enable analysis for warfarin pharmacogenetics
- Aggregated Data curated by and placed on PharmGKB secure web site
- After analysis by consortium data will be made public

IWPC Attributes

- Clearly Unique Data Set
- Currently over 5000 patient's data collected
- Encompassing diverse ethnicity
- Substantial data on other medication exposure
- Analysis in process

Next Steps

- Based on Existing Data, FDA Considered Changing the Label for Warfarin to Require Varying Dose Based on Genetic Information. They took an intermediate step last month.
- Initial Concerns Were the Absence of a Prospective Clinical Trial and The Ability of Most Clinical Labs to Genotype in Real (Clinically Relevant) Time
- NHLBI Multicenter Trial

Model Based Warfarin Dosing vs. Standard of Care to Predict Stable Warfarin Dosing

A Prospective Randomized Study
Sponsored By The
Agency for Healthcare Policy and Research

Study Design

Randomized, prospective, controlled trial on 260 subjects requiring warfarin therapy

Patients randomized at point of diagnosis to:

- Standard of Care vs. Model based dosing based on genotype (Dosing calculator)
- After Initial Dose Subsequent Doses per Anticoagulation Clinic guidelines
- Inpatient Orders written by study nurse and countersigned by study MD

Eligibility Criteria

- Eligibility for warfarin therapy based on diagnoses
- No contraindications to warfarin
- Age greater than 40 years
- No previous exposure to warfarin
- Caucasian male or female
- Target INR 2 to 3.5
- Women of childbearing potential must use effective method of contraceptive

Outcome Measurements

- Time in therapeutic range
- Absolute deviation from clinically optimal dose
- Time to stable INR in therapeutic range
- Warfarin related thromboembolic or hemorrhagic adverse drug events
- Time to first INR above 4

Getting to Personalized Predictive Medicine

1. Make It Comfortable and Safe for a Patient's Genetic Sequence to be a part of Their EMR
2. Affordable Full Length Genomic Sequencing
3. Sequence the US Population
4. Bring Powerful Tools of Machine Learning to the EMR
5. Ask the right questions with our tools
    1. Predict Untoward Outcomes (Hospitalization, Complications, ADRs)
    2. Make diagnoses more precise
    3. Therapeutic Efficacy
6. Bring the answers to these questions back to the individual patient

For Patient Genetic Sequencing

- One Time Testing
- Eliminates the Need for Subsequent Genetic Tests
- As New Associations Develop the Data Are Already Available in the Patient's Record
- Cost Effective

Against Patient Genetic Sequencing

- More Data for Discrimination in Employment and Insurance
- Uniquely Identifying Data Available
- Fear of Genetic Tests

“ The Discrepancy Between Current Medical Practice and the Capabilities for Improvement Is Greater Now Than At Any Time Since the Early Part of the 20th Century”

R Snyderman, JAMA, 2004:291,882-883