Personalized Medicine: Genetic Testing 101 - Costs, Benefits and Effectiveness

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Challenges to Health care in 2011

- Economic Downturn with a no employment recovery
- The inevitable cost of Health Care Reform
- Coverage of millions of uninsured
- Flat to reduced NIH funding

- More efficient, effective health care
- More Prevention, more Personalized Medicine

Challenges for Personalized Medicine

- Genomics has not delivered
- Proteomics has not delivered
- Bioinformatics has not delivered
- Empty Pharmaceutical Pipelines
- Effective Electronic Medical Records are Rare Events

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Mission Statement

BRATER FELLOWSHIP

RESEARCH IN PERSONALIZED MEDICINE

CLINICAL TESTING IN PERSONALIZED MEDICINE

IU RESOURCES FOR PERSONALIZED MEDICINE

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Indiana Institute for Personalized Medicine

The Indiana Institute for Personalized Medicine explores how genetic information and environmental exposure affect each person's risk to develop certain diseases and response to medication.

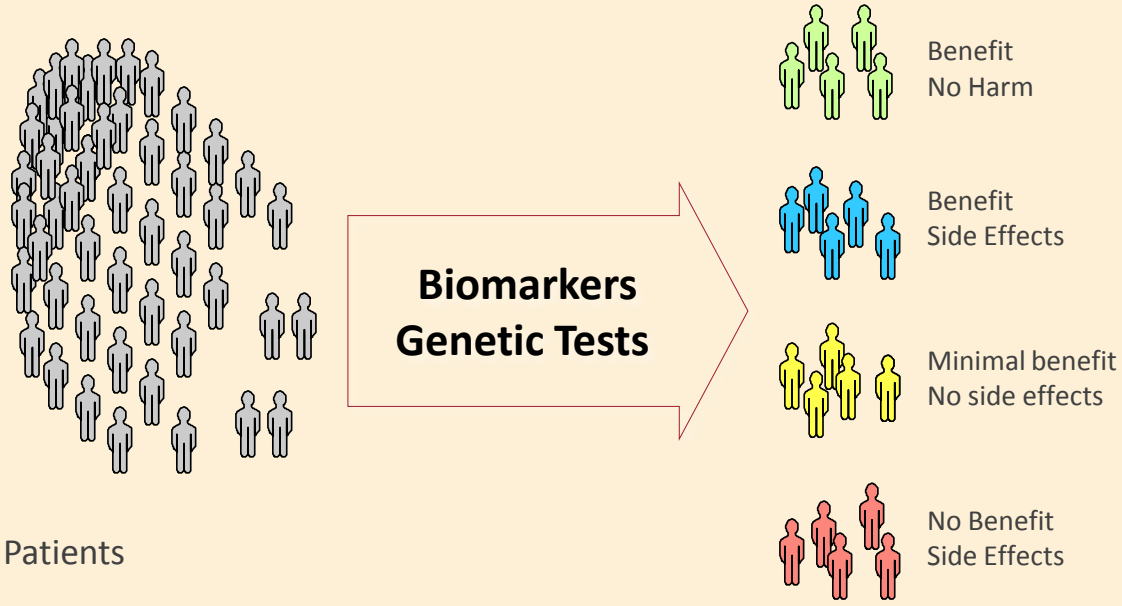
The Institute examines how this new model of genome-informed personalized healthcare may be translated in clinical settings to advance the practice, delivery and economics of health care.

While personalized medicine is transforming the health system as we know it, we are bridging the gap between genomics research and patient care.

When Medicine Gets Personal

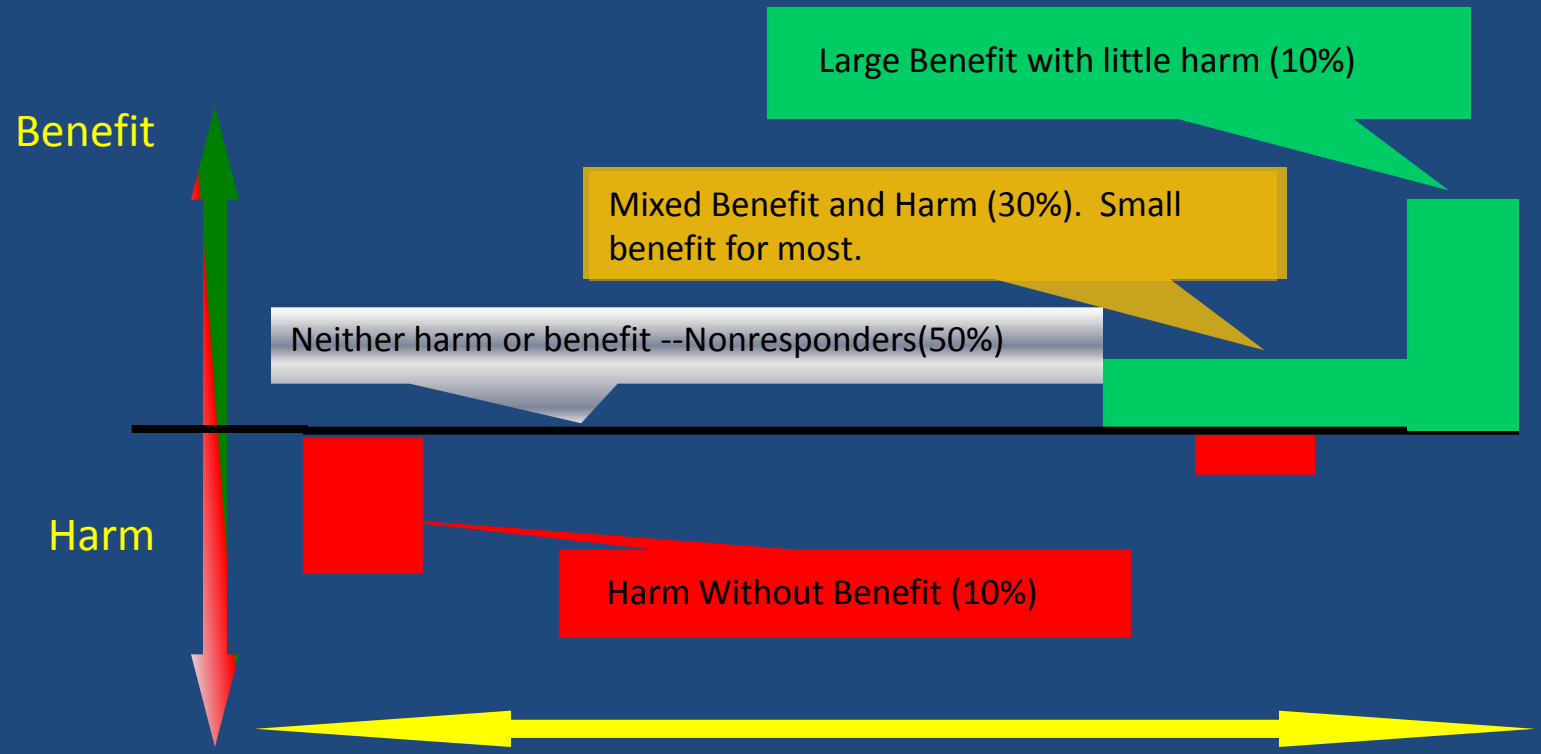
Pharmacogenomic Personalization of Therapy for Heart Failure

GOAL: To develop pharmacogenetic biomarkers that constitute a predictive panel to guide the stratification of heart failure therapy, and therefore to improve treatment outcomes and quality of life of individual patients.



- **The right drug**
- **To the right disease**
- **At the right time**
- **With the right dosage**

The Problem with Mean Response Data : Heterogeneity in Response to Medicines In Clinical Trials



Evans B, Flockhart DA et al. (2010)

Factors Influencing Response to Heart Failure Therapy

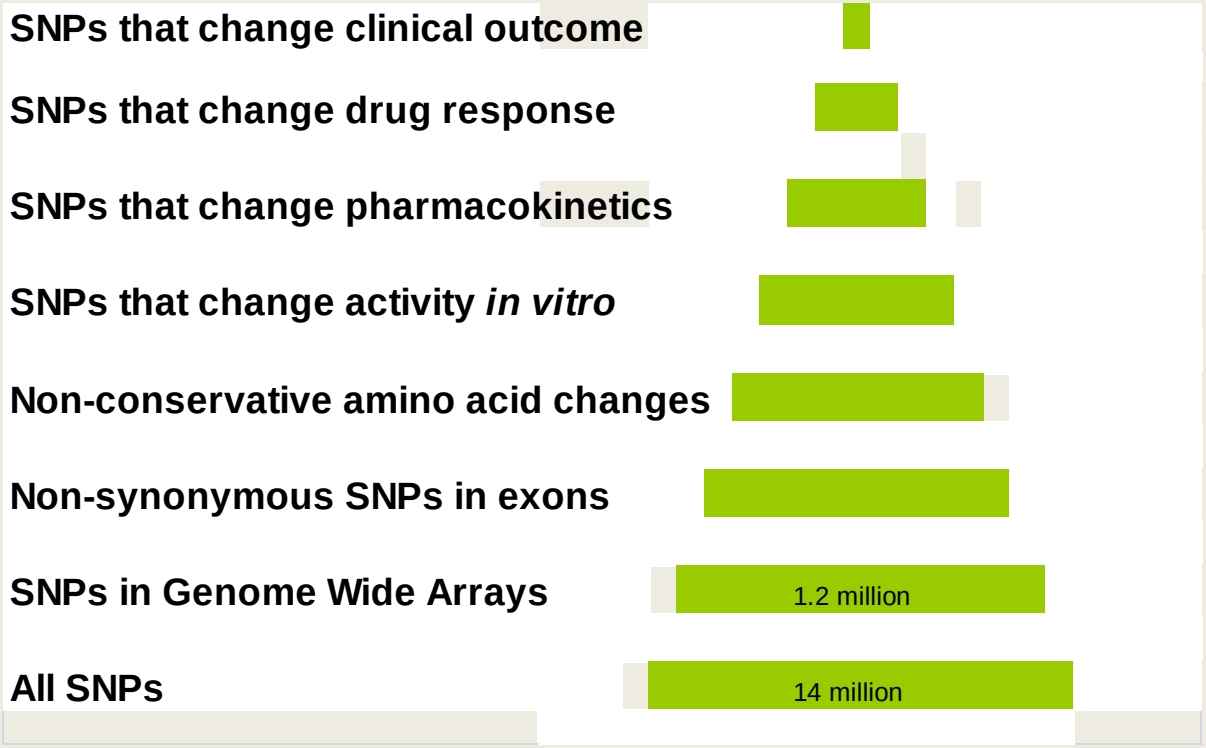
Genetic Polymorphisms

Candidate Variants:

β blockade signaling pathways
ACE - inhibitor signaling pathways
Renal diuretic signalling
Therapeutic ADME genes

Clinical Factors

NYH 1-IV
Diabetes
Demographic factors
Co-morbidity



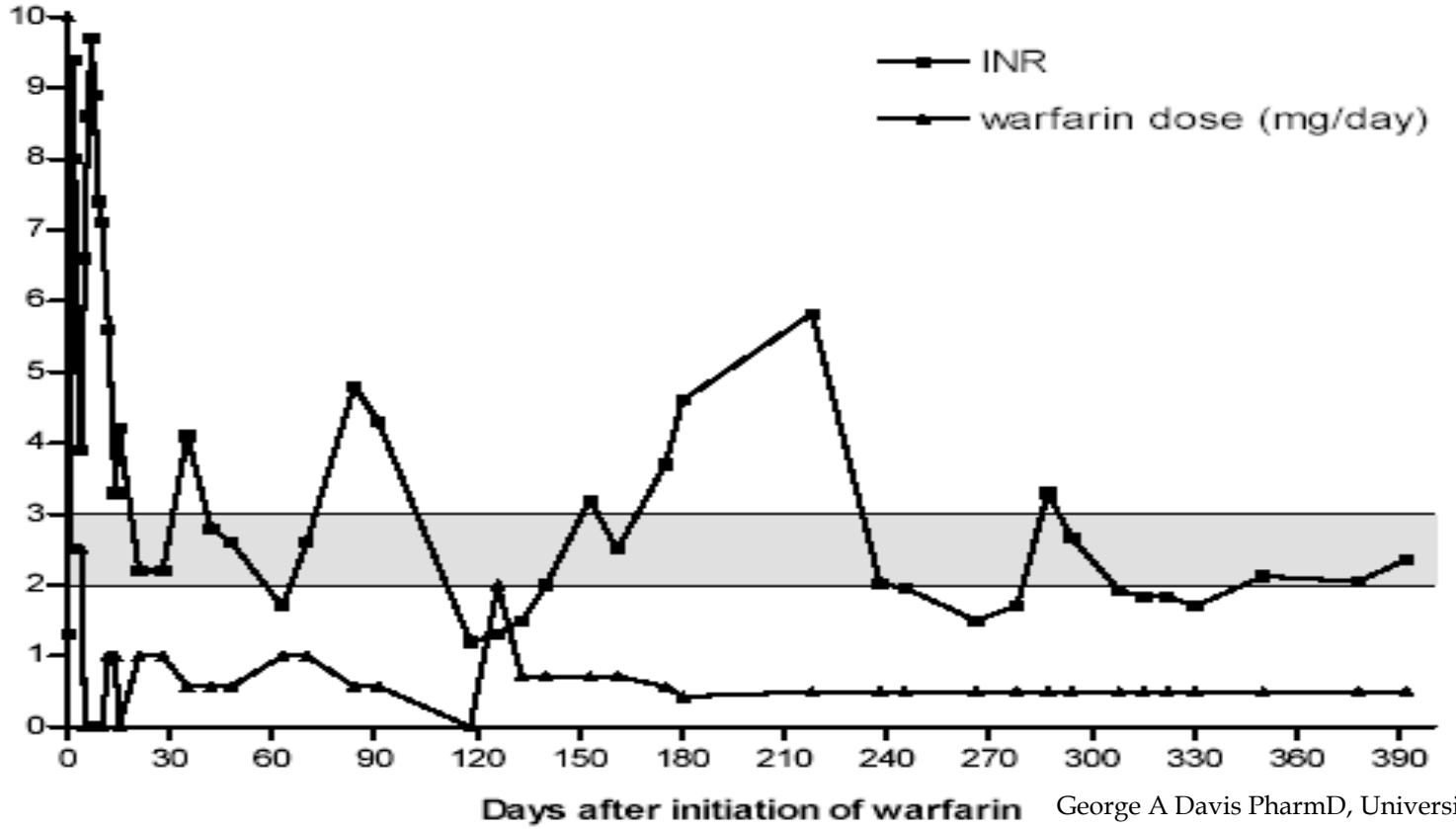
Fourteen Drugs and Their Available Pharmacogenetic Tests October 2011

- **Abacavir**
- Clopidogrel
- **Tamoxifen**
- metformin
- **Imatinib**
- 5-Fluorouracil
- **Clozapine**
- QT-prolonging Drugs
- **Irinotecan**
- Azathioprine and Mercaptopurine
- **Warfarin**
- Carbamazepine
- **Interferon**

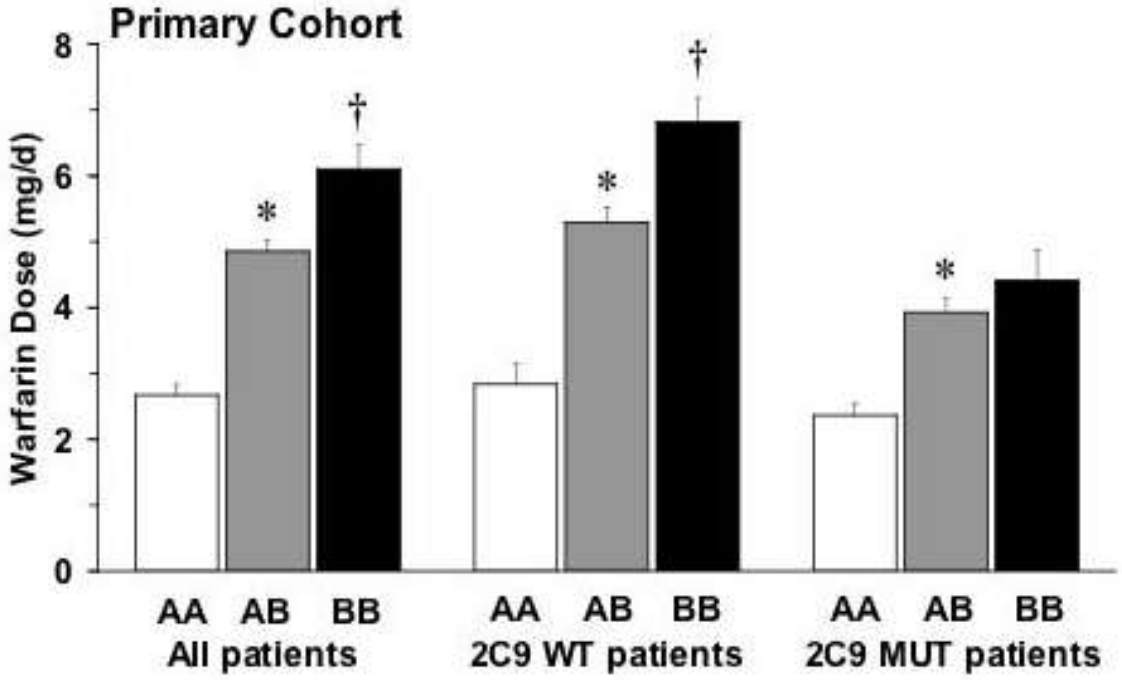
- **HLA *B5701**
- CYP2C19
- **CYP2D6**
- OATP3
- **BCR-ABL**
- DPYD-TYMS
- **2 SNPs in HLA-DQB1**
- Familion™
- **UGT1A1**
- TPMT
- **CYP2C9 and VKCoR**
- HLA-B* 1502
- **IL 28b**

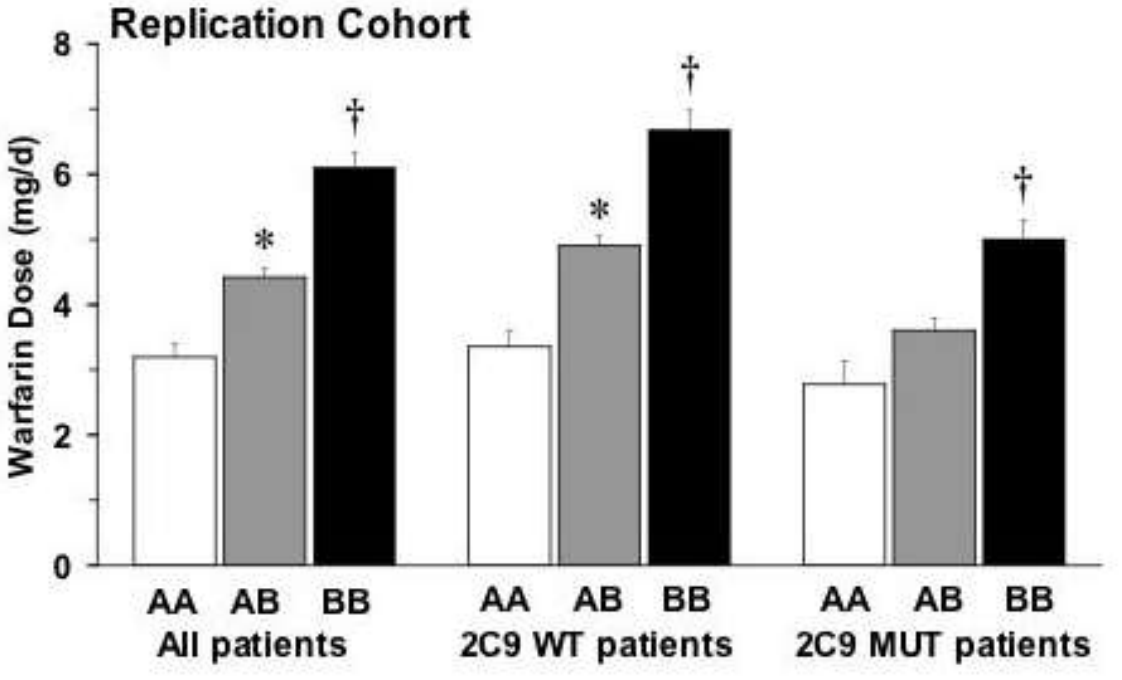
The potential difficulty in dosing a CYP 2C9 poor metabolizer with warfarin

Figure 1. INR values and warfarin doses of a patient with CYP2C9*3 allelic variant requiring over 1 year to maintain a therapeutic INR.



George A Davis PharmD, University of Kentucky, 2002





VKORC1 Haplotype and CYP2C9 Genotype changed Warfarin Dose

Primary cohort: UW (N=185);

Replication cohort: Wash U (N=368).

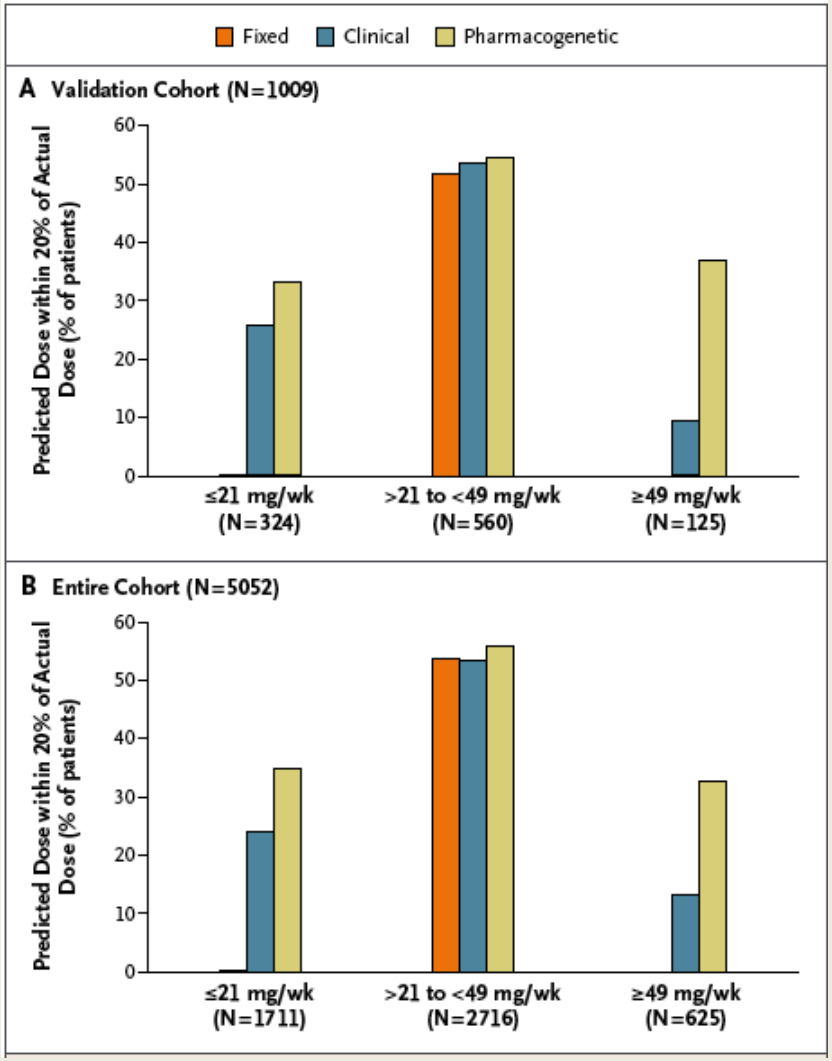
All participants were Caucasian.

Rieder et al. N. Eng J. Med 2005;352: 2285-2293[

Warfarin Pharmacogenomic Testing has Clinical Validity

Pharmacogenetic Prediction worked better for the 46% of patients who require less than 21, or more than 49 mg per week.

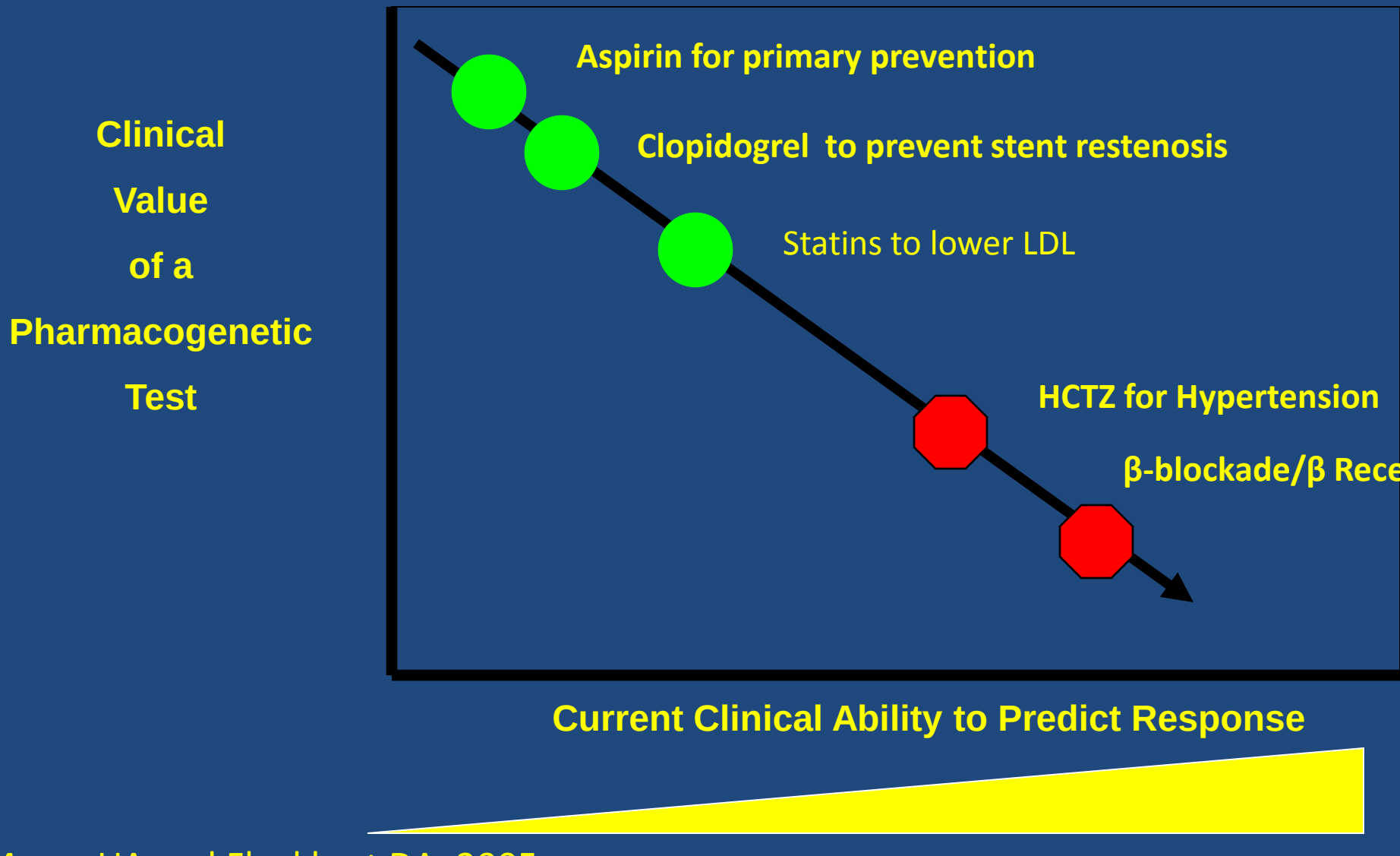
None of the Fixed and INR-guided estimates for low and high dose groups were within 20% of actual dose



Klein T et al, 2009.

Pharmacogenetic Principle 1:

Value Decreases when Current Predictive Ability is High



Meyer UA and Flockhart DA, 2005

Reality in Warfarin Pharmacogenomics

INR is of most value in warfarin clinics and academic settings

Most warfarin is given outside these

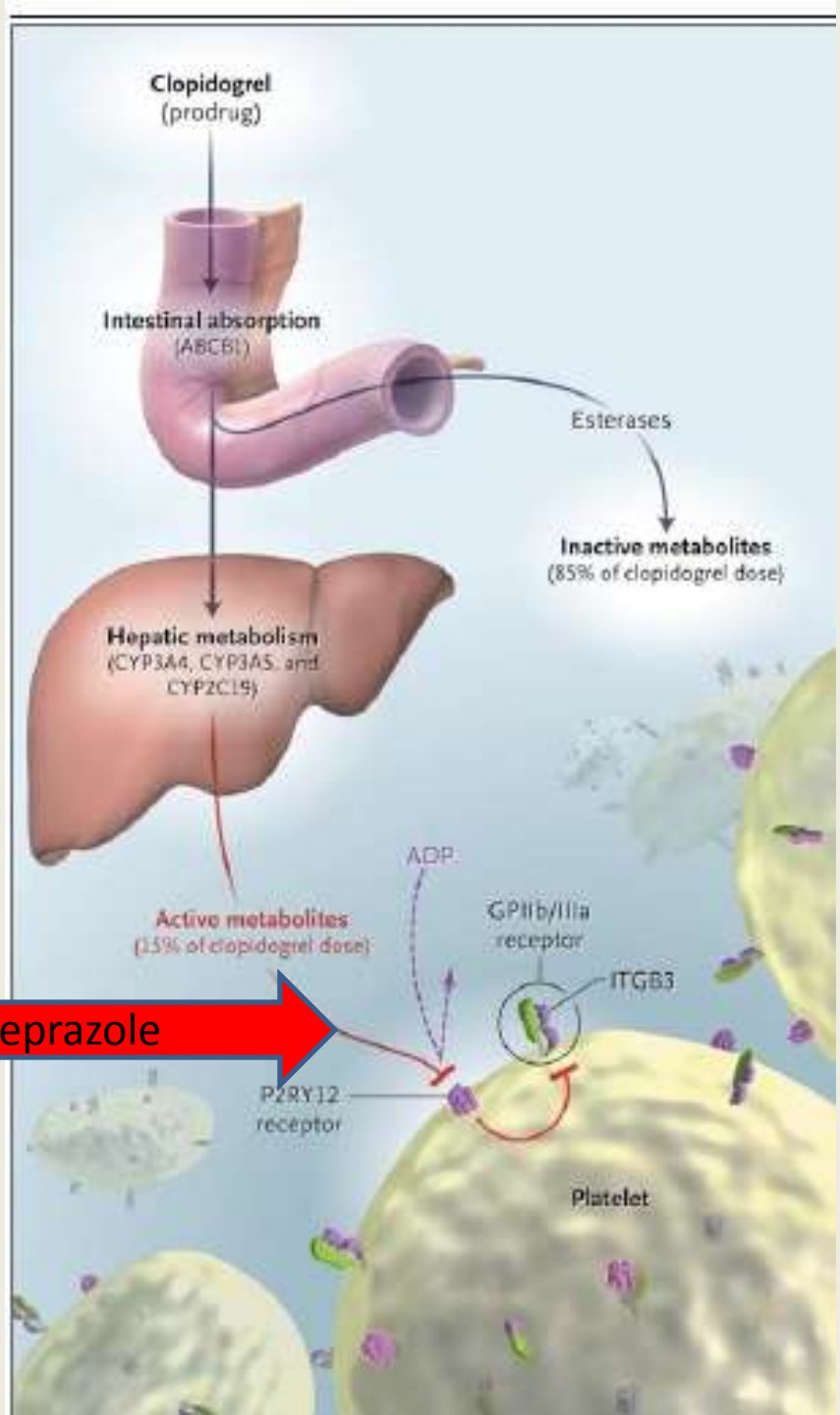
Pharmacogenomic testing of most value in non-academic enironments

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

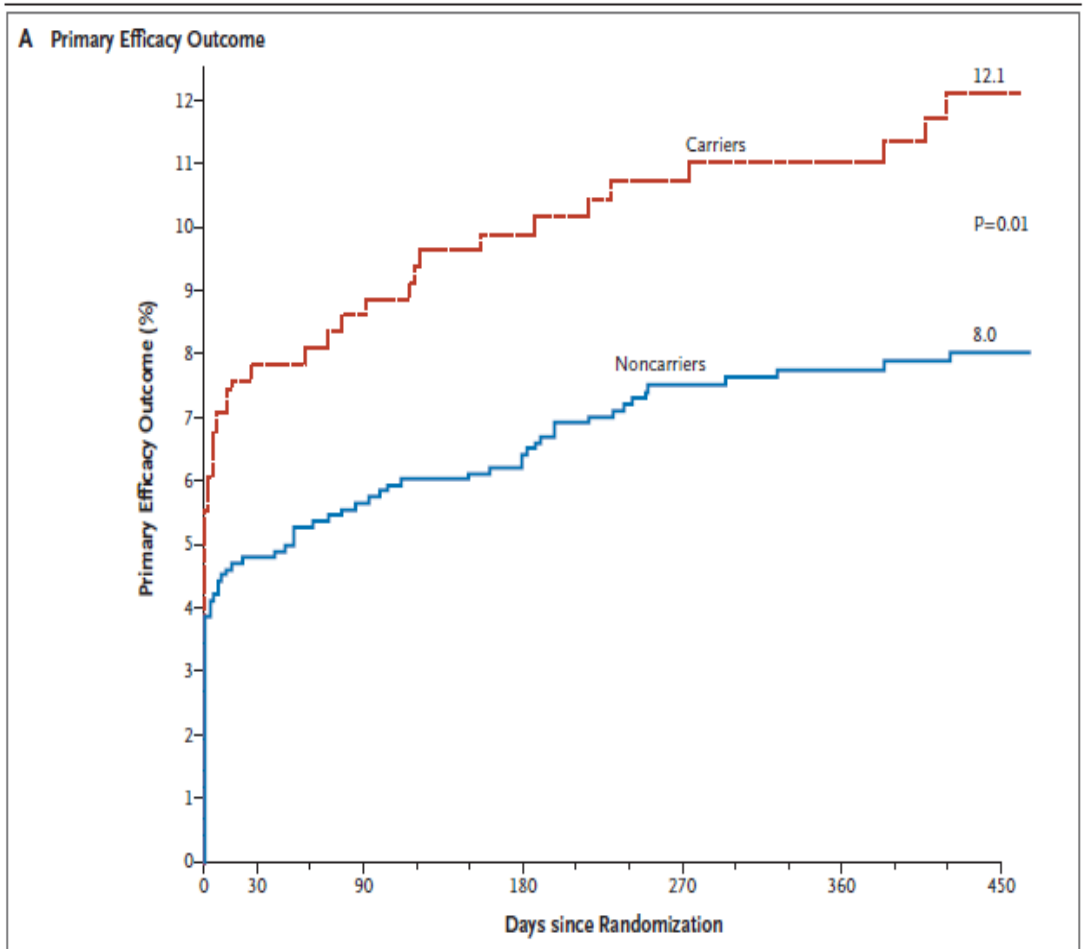
Tabassome Simon, M.D., Ph.D., Céline Verstuyft, Pharm.D., Ph.D., Murielle Mary-Krause, Ph.D., Lina Quteineh, M.D., Elodie Drouet, M.Sc., Nicolas Méneveau, M.D., P. Gabriel Steg, M.D., Ph.D., Jean Ferrières, M.D., Nicolas Danchin, M.D., Ph.D., and Laurent Becquemont, M.D., Ph.D., for the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators



Omeprazole

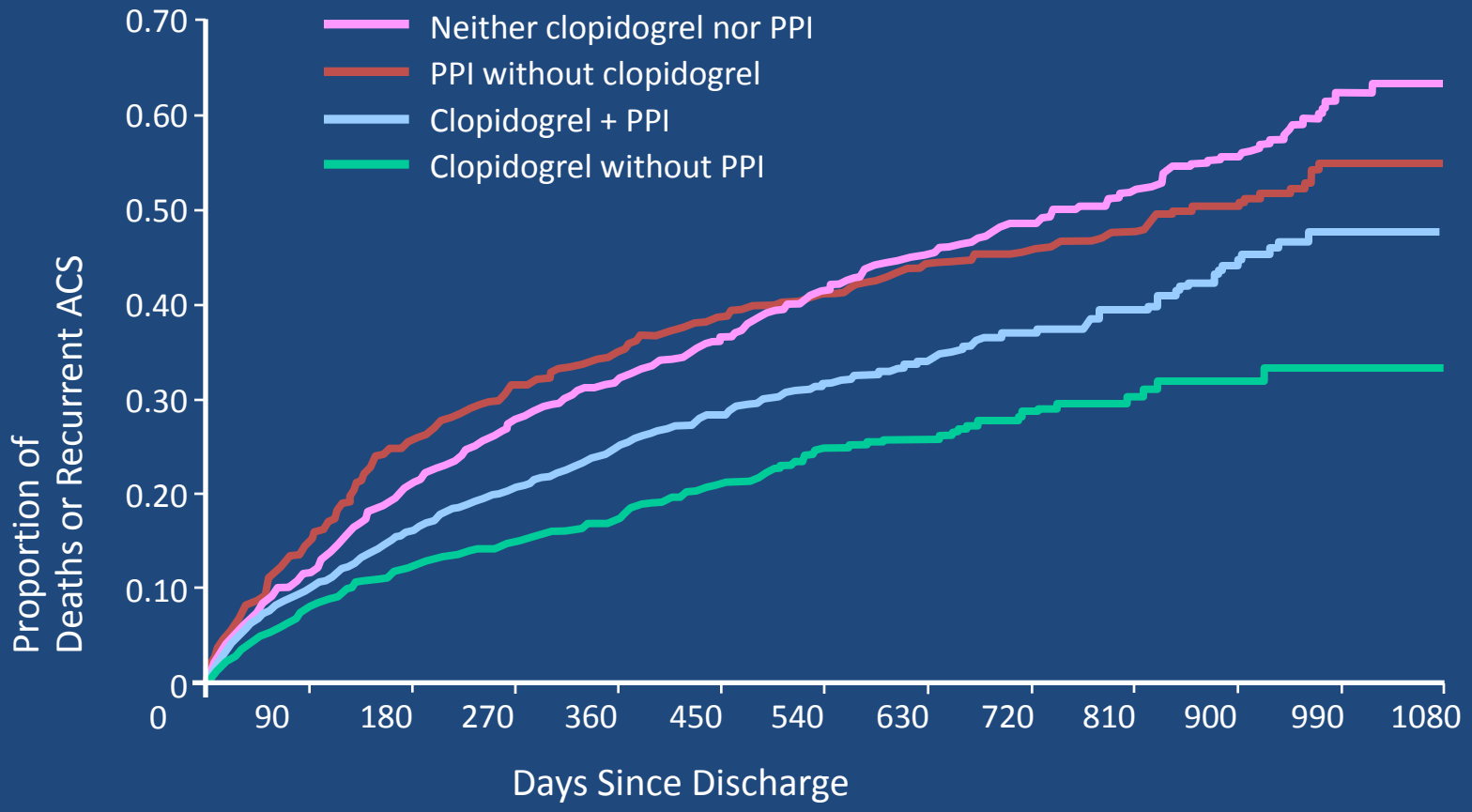
Carriers of a CYP2C19 Genetic Variant Experienced More Cardiovascular Events

(NEJM 360;4 January 22, 2009)



Simon et al, NEJM, April, 2009

Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI



Ho PM, Maddox TM, Wang L, et al. JAMA. 2009;301(9):937-944.

Summary

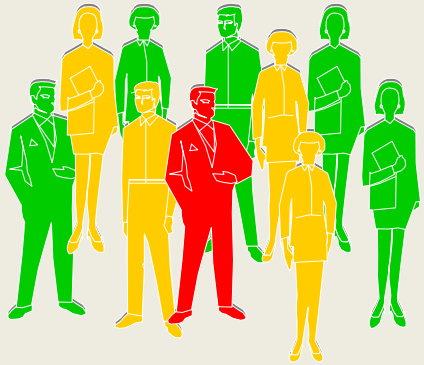
- Pharmacogenomic testing is now being widely applied to some of the most widely prescribed drugs
- Pharmacogenomic biomarkers require demonstration of clinical utility before widespread implementation
  - This has happened in very few cases to date
- Clinical pharmacogenomic predictive tests must provide real value over existing predictors
- Economic utility is often as important as clinical utility

Tools for Personalized Medicine at the Indiana University School of Medicine

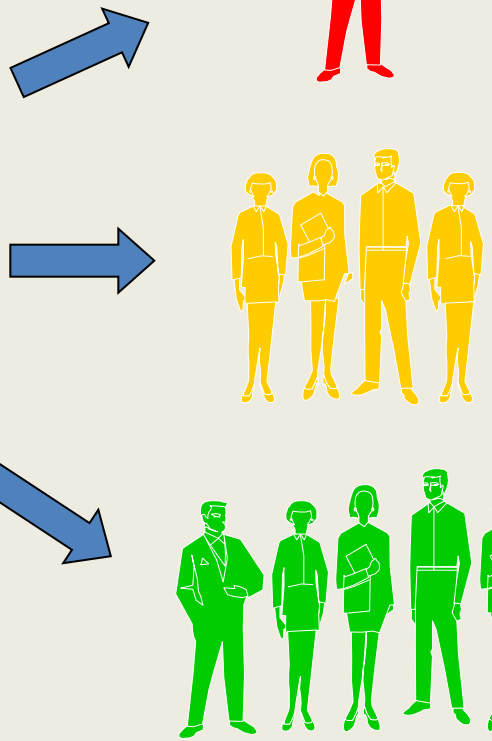
- A Robust Electronic Medical Record with Long Follow Up
- A Biobank of Samples that Links to the EMR
- Genomic and Pharmacogenomics Expertise
- Imaging Expertise
- Informatic Expertise
  - Center for Computational Biology
- Modeling Expertise
  - CTSI Disease and Therapeutics Modeling Program
- Trained Professionals
- Strategic Partnerships with Implementers

Pharmacogenomics Testing to Guide Treatment

All Patients with Same Diagnosis (10% risk)



PGx testing



high risk: treat with alternative drug or dose

moderate risk: treat with alternative drug or dose

low risk: treat with conventional dose