# Pharmacogenomics - A Powerful and Challenging Approach to Personalized Medicine

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National Institute of General Medical Sciences

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# Pharmacogenomics

- Genetic variation is a significant contributor to individual differences in responses to drugs including effectiveness and adverse reactions
- Clear definitions of both genotype and **phenotype** are crucial to progress in understanding pharmacogenomic effects
- The challenges of translating high-quality scientific findings to clinical settings should not be underestimated

# PGRN Overview

- **PGRN is comprised of 12 Groups,** individually awarded, with >200 Investigators at ~40 sites
- **It is trans-NIH,** funded by NIGMS, NHLBI, NIDA, NCI, NIEHS, NIMH, NHGRI, NLM, and ORWH
- **~$28 M total costs/year,** funded for 5 years
- **First goal is highest quality research** - this is where the research groups will have an impact
- **Knowledge Base PharmGKB** collects data and knowledge for PG, including drug pathways and VIP genes, and is a hypothesis-generating resource open to all investigators

# PGRN as a Network

- **Different approaches to the field**, including:

  "phenotype-to-genotype" (*collect the patients, categorize the responses, and do genetic analysis*)

  "genotype-to-phenotype" (*consider known genes/ pathways of interest, determine variants, study for functional impact*)

- **Although PGRN groups work in different diseases,** together they can consider common study design issues, evaluate statistical models, highlight unique issues

- **PGRN External Advisory Panel** recommends ways to become "more than sum of the parts", and stimulate collaborations, influence others (FDA, industry, clinicians)

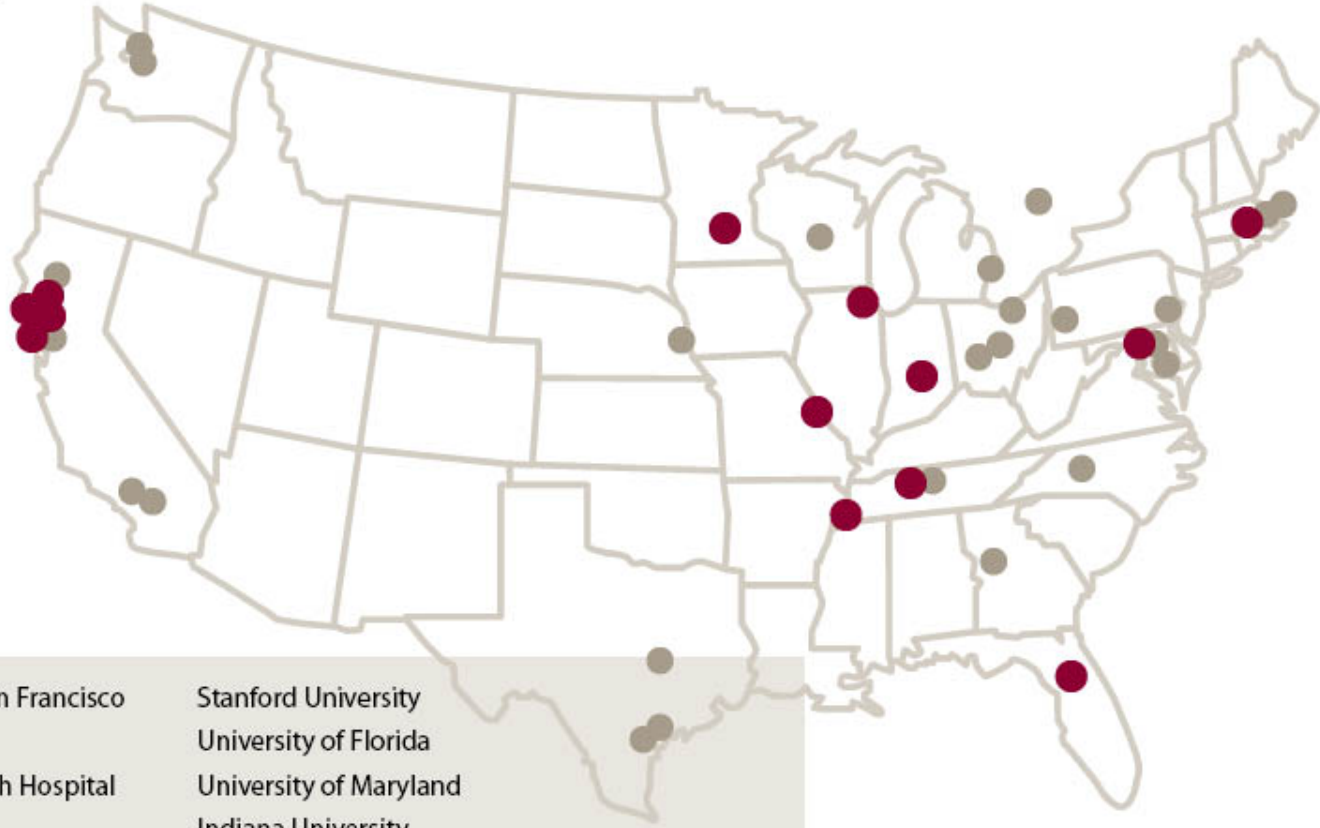
# Pharmacogenetics Research Network

National Institutes of Health
U.S. Department of Health & Human Services

## Research Sites

NIH Funding Institutes

**NIGMS**
**NHLBI**
**NIDA**
**NCI**
**NIEHS**
**NIMH**
**NHGRI**
**NLM**
**ORWH**



University of California, San Francisco
University of Chicago
St. Jude Children's Research Hospital
Mayo Clinic
Vanderbilt University
Washington University
SRI International
Stanford University
University of Florida
University of Maryland
Indiana University
Brigham and Women's Hospital
Children's Hospital of Oakland Research Institute

● Primary Investigator Site
● Co-Investigator Site

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## Areas of Research

### Cardiovascular

**Pharmacogenomic Evaluation of the Antihypertensive Response (PEAR)**
Julie A. Johnson, Pharm.D., University of Florida

**Pharmacogenomics and Risk of Cardiovascular Disease (PARC)**
Ronald M. Krauss, M.D., Children's Hospital Oakland Research Institute

**Pharmacogenomics of Arrhythmia Therapy (PAT)**
Dan M. Roden, M.D., Vanderbilt University

**Amish Pharmacogenomics of Antiplatelet Intervention Study (PAPI)**
Alan R. Shuldiner, M.D., University of Maryland

### Pulmonary

**Pharmacogenetics of Asthma Treatment (PHAT)**
Scott T. Weiss, M.D., Brigham and Women's Hospital

### Addiction

**Pharmacogenetics of Nicotine Addiction and Treatment (PNAT)**
Neal L. Benowitz, M.D., University of California at San Francisco
Huijun Ring, Ph.D., SRI International

### Cancer

**Consortium on Breast Cancer Pharmacogenomics (COBRA)**
David A. Flockhart, M.D., Ph.D., Indiana University

**Comprehensive Research on Expressed Alleles in Therapeutic Intervention (CREATE)**
Howard L. McLeod, Pharm.D., Washington University

**Pharmacogenetics of Anticancer Agents Research Group (PAAR)**
Mark J. Ratain, M.D., University of Chicago
Mary V. Relling, Pharm.D., St. Jude Children's Hospital

### Metabolism/Transport

**Pharmacogenetics of Membrane Transporters (PMT)**
Kathleen M. Giacomini, Ph.D., University of California, San Francisco

**Pharmacogenetics of Phase II Drug Metabolizing Enzymes (PPII)**
Richard M. Weinshilboum, M.D., Mayo Clinic

### Informatics

**PharmGKB: Catalyzing Research in Pharmacogenetics**
Russ B. Altman, M.D., Ph.D., Stanford University

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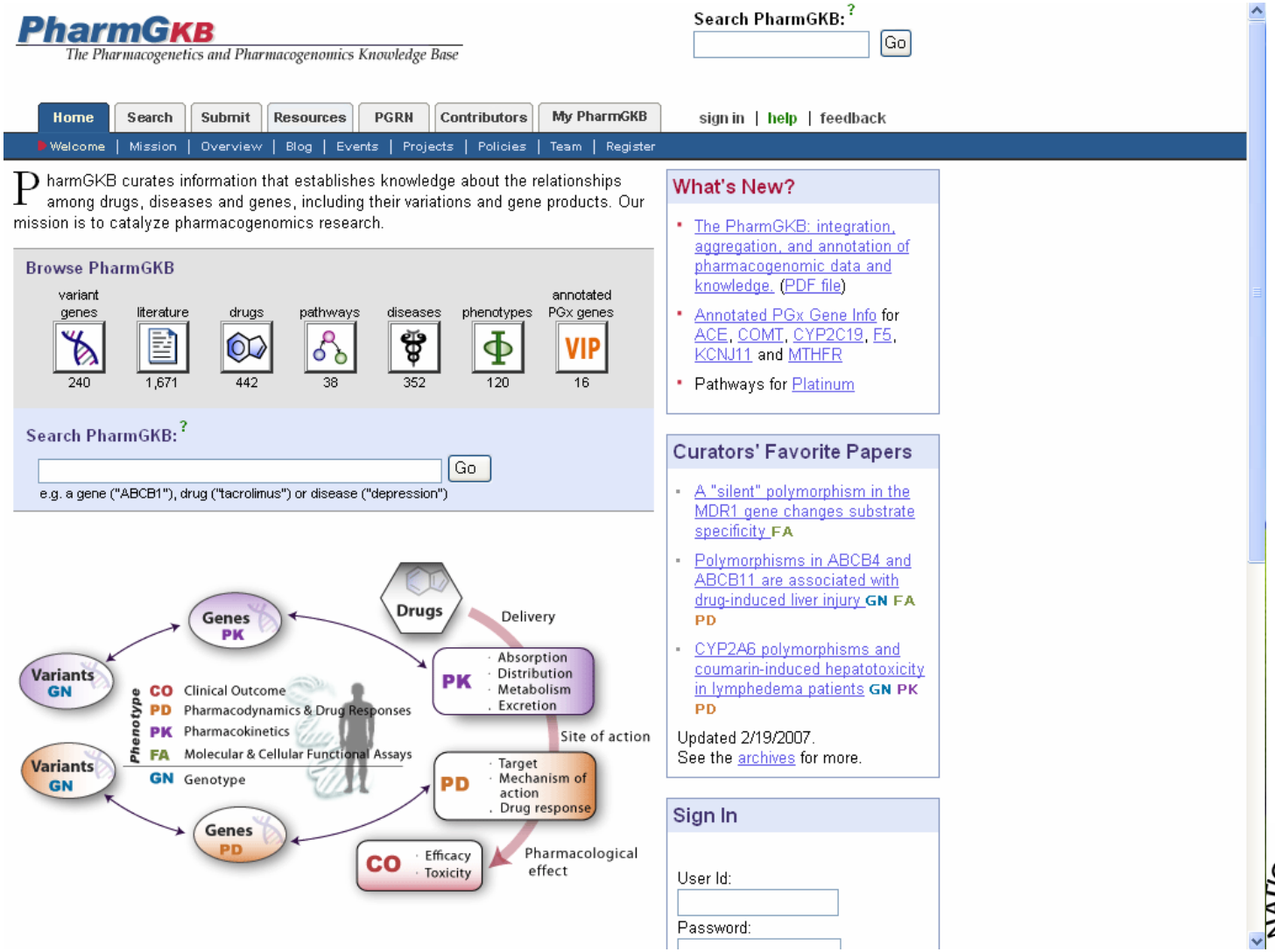
PharmGKB



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## PharmGKB

**The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB)** is an integrated knowledge base for pharmacogenetics, linking phenotypes and genotypes.

**Features:**

- A web-based format for pharmacogenetics knowledge
- Curated, linked genotypes and phenotypes
- Genomic, molecular and cellular, and clinical datasets
- Annotated, interactive, consensus drug pathways
- Automated methods for identifying relationships
- Community-based literature submissions
- Access to the entire research community

**www.pharmgkb.org**

# For More Information

- www.nigms.nih.gov/pharmacogenetics
- www.pharmgkb.org
- **PGRN Affiliate Membership** program
- Specialized workshops (next statistics workshop planned in conjunction with GAW 2008)
- Presentations at national scientific meetings (being planned for AHA and others)
- Announcements at PharmGKB

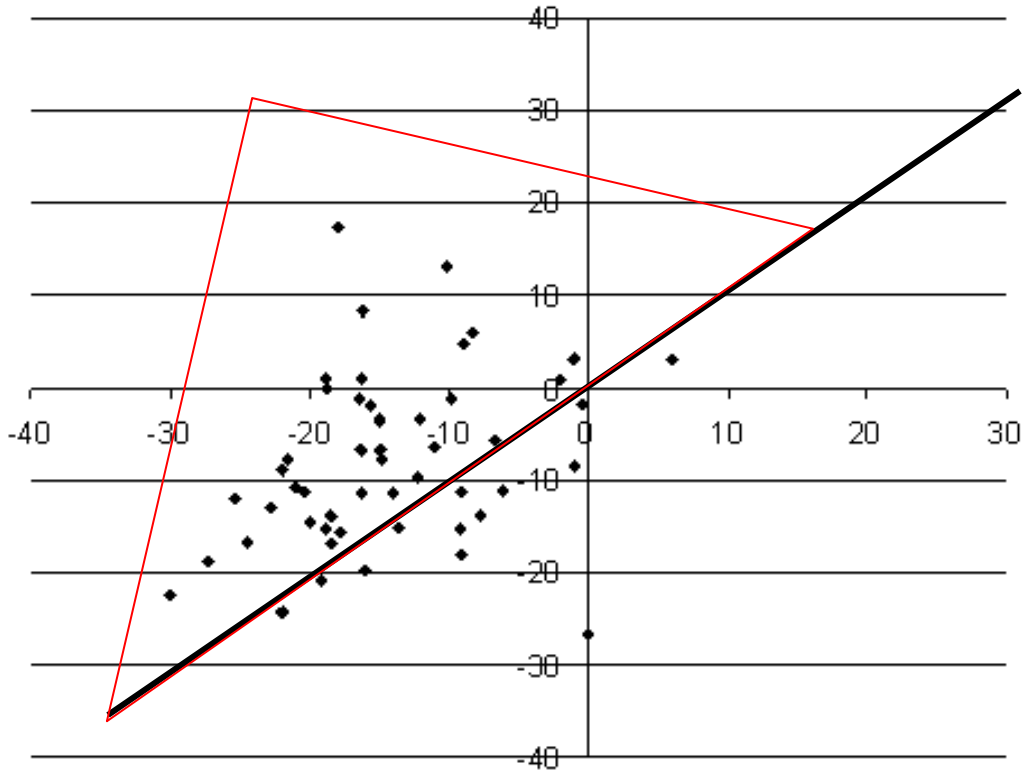
# Example: Warfarin (coumadin) dosing

- Variations in gene CYP2C9 encoding a drug metabolizing enzyme are responsible for 6% of the variation in warfarin response
- Variations in gene encoding warfarin target, vitamin K epoxide reductase, (VKORC1) are responsible for 27% of variation
- Studies underway and planned to analyze the paths and benefits to move these discoveries to general clinical settings

# Example: β-Blockers and hypertension

- β-Blockers have many applications including the treatment of a hypertension
- Drug responses measured by changes in blood pressure
- Blood pressure can be measured in a number of ways
  - Clinical
  - Home
  - Ambulatory

# What is the best measure of BP for assessing antihypertensive response?



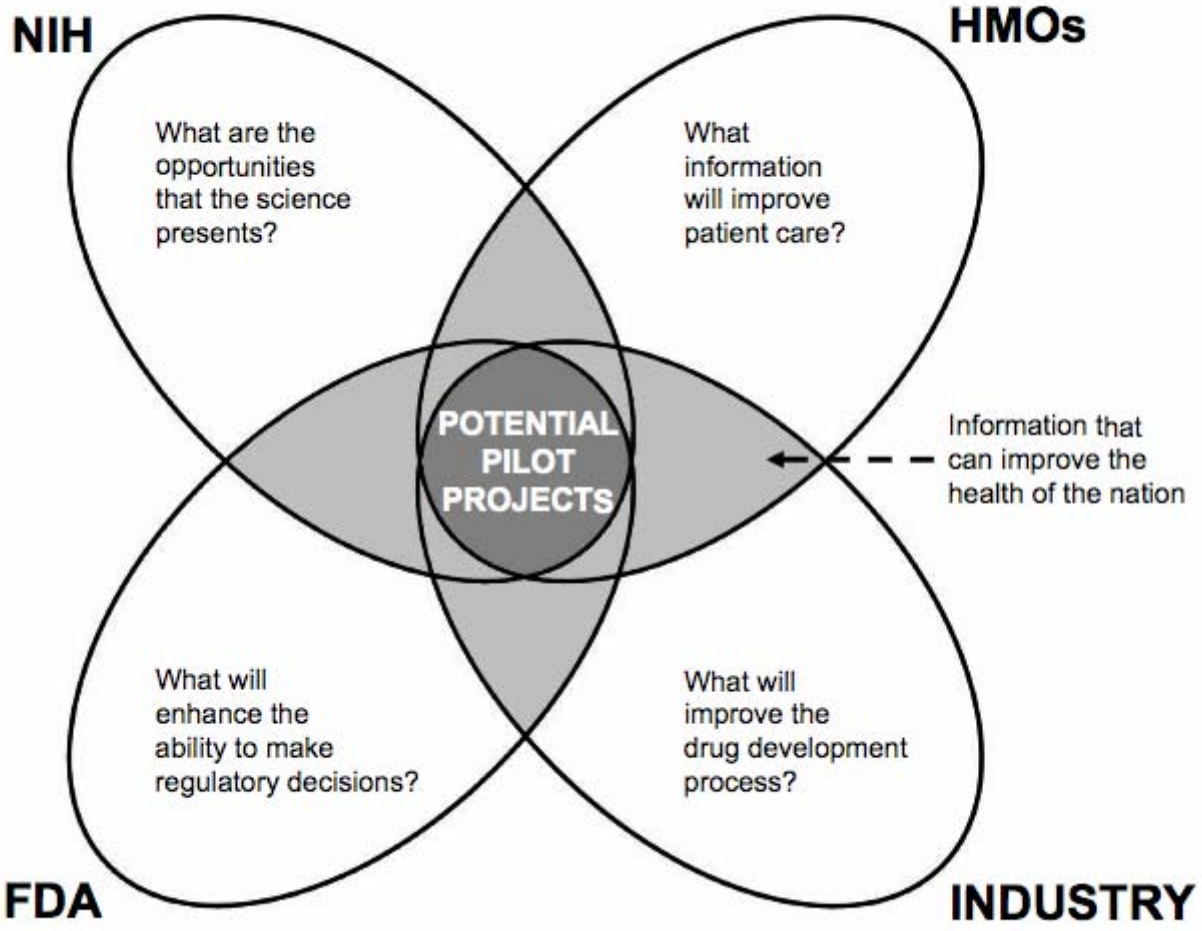

% Responders (defined as 10% ↓ in BP):

Clinic BP – 71%
Amb BP – 47%

From Julie Johnson, (Pharm D Pharmacotherapy 2006;26:1247)

# Understanding the Genetic Basis of Medication Safety: A Workshop

Jointly organized by NIH and FDA December 11-12, 2006



**Annals of Internal Medicine –** Review

# Pharmacogenomics: Challenges and Opportunities

**Dan M. Roden, MD; Russ B. Altman, MD, PhD; Neal L. Benowitz, MD; David A. Flockhart, MD, PhD; Kathleen M. Giacomini, PhD; Julie A. Johnson, PharmD; Ronald M. Krauss, MD; Howard L. McLeod, PharmD; Mark J. Ratain, MD; Mary V. Relling, PharmD; Huijun Z. Ring, PhD; Alan R. Shuldiner, MD; Richard M. Weinshilboum, MD; and Scott T. Weiss, MD, for the Pharmacogenetics Research Network**

***Ann Intern Med.*** **2006;145:749-757.**

**www.annals.org**