Advancing the pharmacogenomics agenda with i2b2 tools

Russ B. Altman, MD, PhD
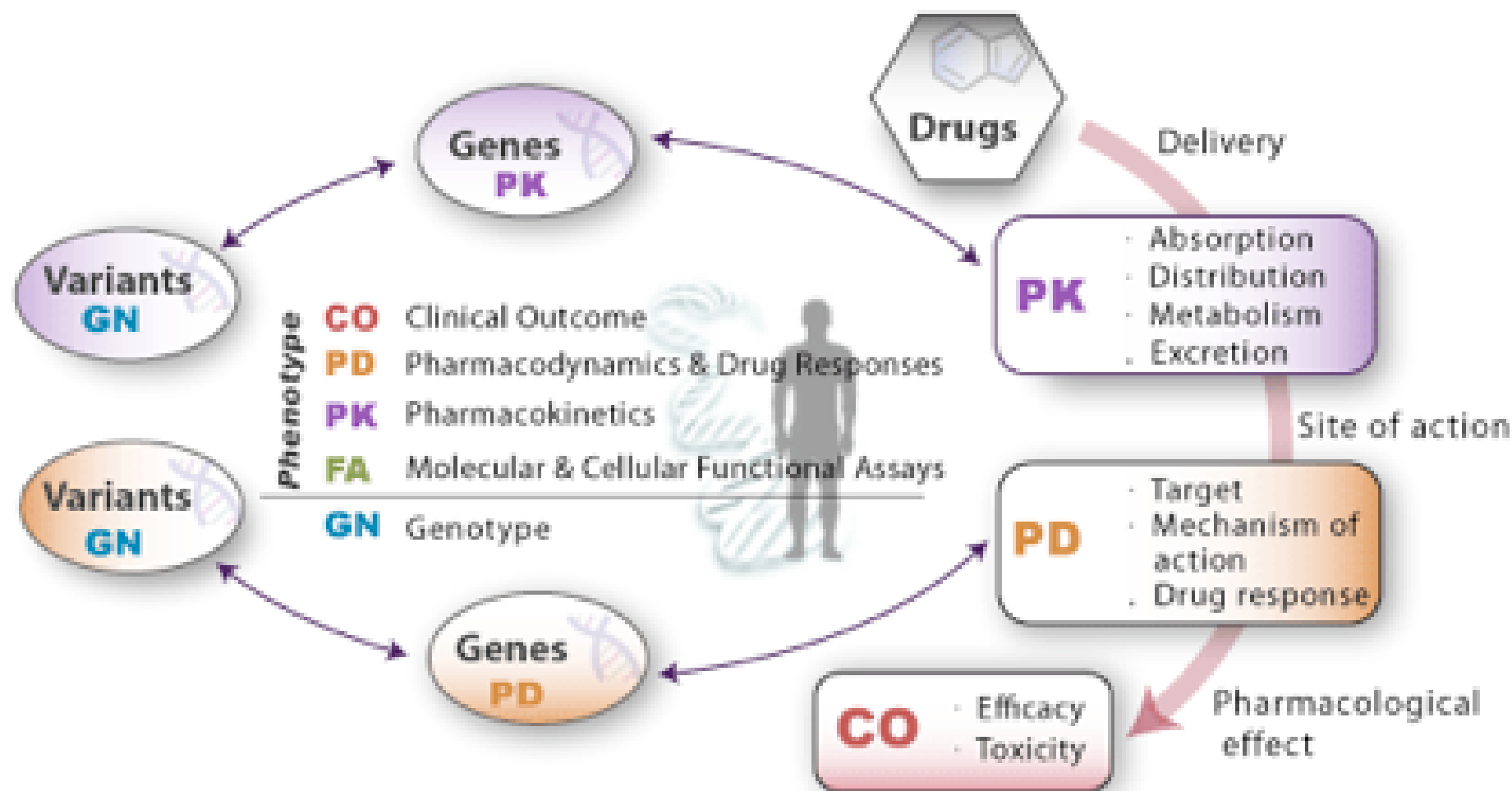
Stanford University
Stanford, Califonia

Pharmacogenetics & Pharmacogenomics

- **Understand how genetic variation leads to variation in the responses to drugs**

- **One of the promises of the genome project**

Instructions from Zak

"I would like you to consider what we could be doing, if we are capable of producing high-throughput phenotypes/genotypes/samples that would best serve pharmacogenomics agenda?"

Drugs

Delivery

PK
· Absorption
· Distribution
· Metabolism
· Excretion

Site of action

PD
· Target
· Mechanism of action
· Drug response

Pharmacological effect

CO
· Efficacy
· Toxicity

Genes PK

Variants GN

Variants GN

Genes PD

Phenotype
CO Clinical Outcome
PD Pharmacodynamics & Drug Responses
PK Pharmacokinetics
FA Molecular & Cellular Functional Assays
GN Genotype

Example: Warfarin (Coumadin)

- Anticoagulant, prevent clots/strokes/MI

- Very difficult to dose--can't predict well based on clinical variables

- Overdose & underdose both dangerous

- Two genes explain much of variability (CYP2C9 and VKORC1). [New gene CYP4F2]

- Trials ongoing to see if dose can be set using demographics + genetics, reduce side effects, improve outcomes.

PharmGKB

The Pharmacogenetics and Pharmacogenomics Knowledge Base

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PharmGKB curates information that establishes knowledge about the relationships among drugs, diseases and genes, including their variations and gene products. Our mission is to catalyze pharmacogenomics research.

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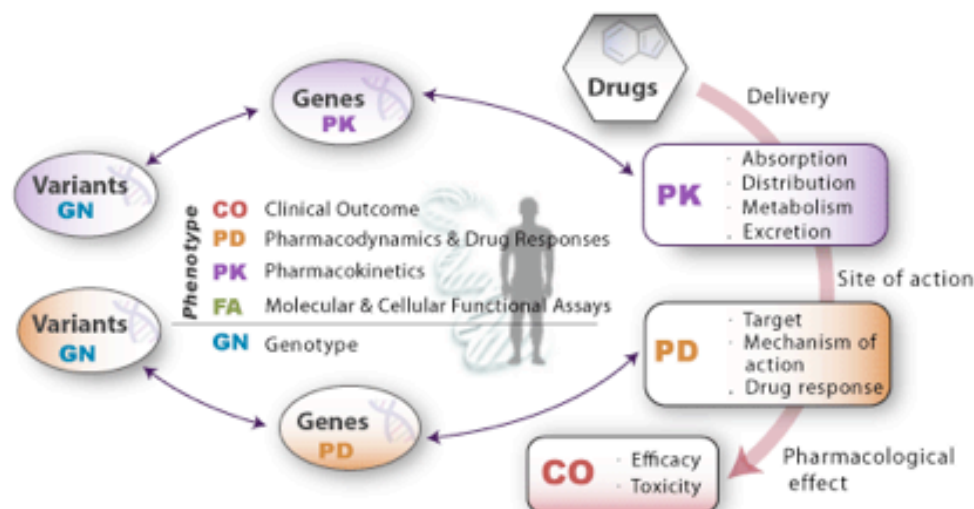| variant genes	literature	drugs	pathways	diseases	phenotypes	annotated PGx genes
608	2,352	545	52	545	129	27

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e.g. a gene ("NOS3"), drug ("ace inhibitors") or disease ("ALL")

CO Clinical Outcome
PD Pharmacodynamics & Drug Responses
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GN Genotype

What's New?

- NIH Request for Info on PGx Research
- Genetic Variants Associated with Expression Differences between Populations

Curators' Favorite Papers

- Lopinavir-ritonavir combination affects pharmacokinetics of irinotecan **PK**
- Prasugrel versus clopidogrel in patients with acute coronary syndromes **CO**
- Genetic variation in human OATP family members **PD PK GN**

Updated 4/7/08. See the archives for more.

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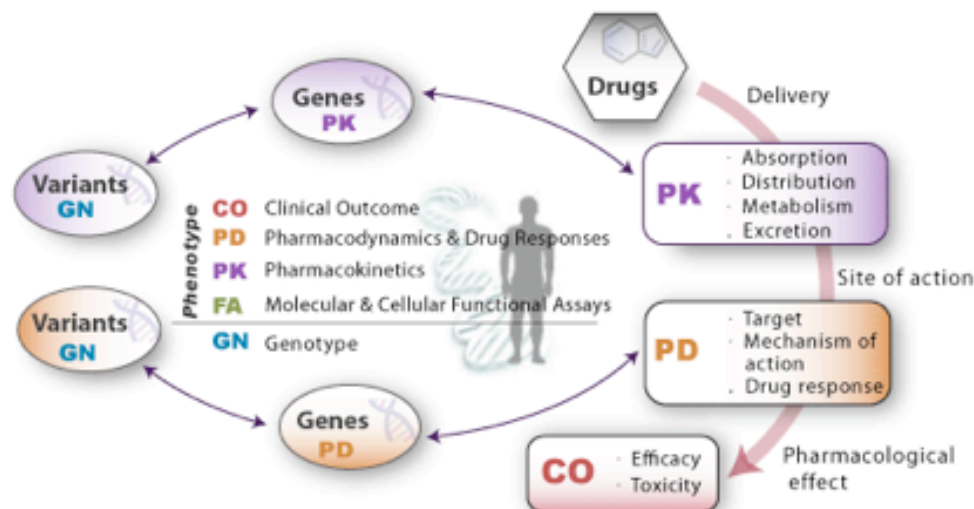
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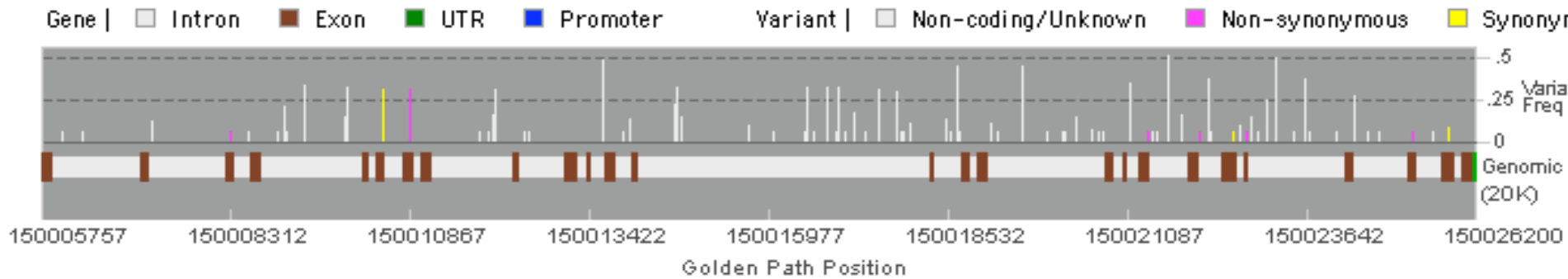
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Variant Positions on [NOS3](#)

Gene | ☐ Intron ■ Exon ■ UTR ■ Promoter   Variant | ☐ Non-coding/Unknown ■ Non-synonymous ■ Synonym

Click To: ◯ Move ⦿ Magnify

Current Position: [150015978]   **Move:** [<] [50 ⬍] [>]   **Magnify:** ▪▮▮▮ ❓

Legend

- deletion

* feature derived from NCBI RefSeq

Number of variant positions: 121

Golden Path Position	Variant	Strand	Feature	AA Translation	Frequency (%)	Sample Size	Ph
[chr7:150004282](#) [T/A](#)		plus			[52.13/ 47.87](#)	94	
[chr7:150004311](#) [A/T](#)		plus			[98.94/ 1.06](#)	94	
[chr7:150004375](#) [G/T](#)		plus			[97.87/ 2.13](#)	94	

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β-agonist and β-blocker Pathway

Simplified pharmacodynamic pathway of drug action on beta 2 adrenergic receptor in a stylized airway cell.

Legend
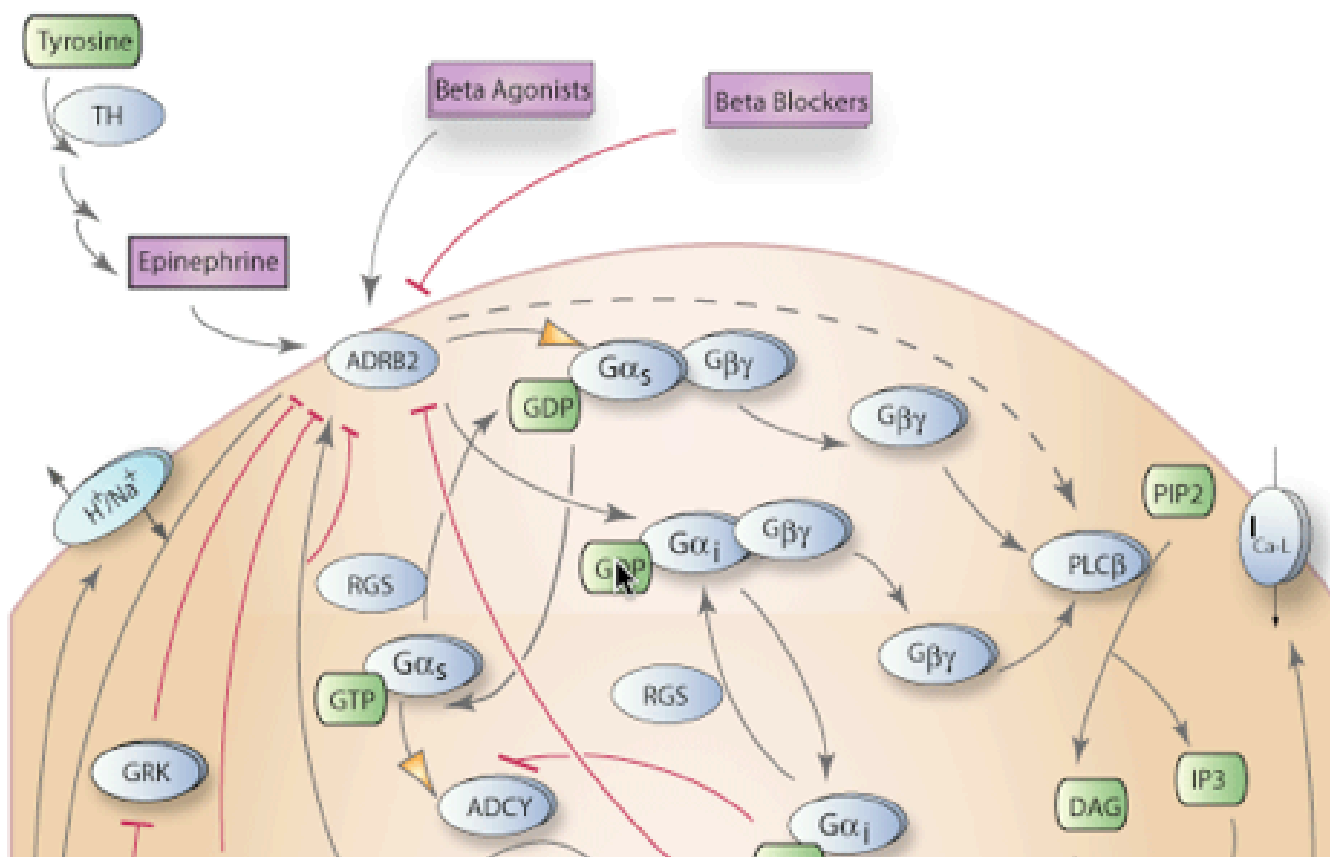
Annotated PGx Gene Information for ADRB2

Submitted by: Gus Litonjua, Jaekyu Shin, Julie A. Johnson and Scott T. Weiss (PHAT and PEAR)
Reviewed by: Reviewed
Submitted date: March 22, 2006

- Jump To:
- Important Variants
- All Annotated Genes

Gene HGNC Name:	_ADRB2_
Gene Common Name:	Beta-2-AR
	The beta-2-adrenergic receptor (Beta-2-AR) is a member of the large superfamily of G-protein-coupled receptors. The gene, ADRB2, was cloned by Kobilka in 1987 [PMID: 3025863] and localized to chromosome 5q31-q32. The gene consists of one exon (2015 nucleotides) and it encodes a 413-amino acid protein. Beta-2-AR is expressed in many cell types throughout the body and plays a pivotal role in the regulation of the cardiac, pulmonary, vascular, endocrine and central nervous system. The coding region of the gene has nine single base substitutions occurring at position 46 (Arg16Gly), 79 (Gln27Glu), 100 (Val34Met), 252, 491 (Thr164Ile), 523, 1053, 1098, and 1239. Five of these polymorphisms are degenerate and are not likely to be functionally significant, although Silverman _et al._ [PMID: 14610472] recently showed that SNP 523 is associated with bronchodilator responsiveness among asthmatics. Of the four non-synonymous SNPs, the two

Related Drugs from Literature

[legend]

	Drug	Relationship				Details
Φλ▤	Beta adrenergic antagonists	CO PD		FA GN		View
Φλ▤	albuterol	CO PD PK	FA GN			View
▤	albuterol sulfate	CO PD		GN		View
▤	atenolol	CO PD		FA GN		View
▤	beta adrenergic agonists	PD		GN		View
▤	beta-adrenergic blocking agents	CO				View
▤	carvedilol	PD		GN		View

Related Diseases from Literature

[legend]

	Disease	Relationship		Details
▤	Acquired Long QT Syndrome (aLQTS)		GN	View
▤	Angina Pectoris	PD	GN	View
Φλ▤	Asthma	CO PD	FA GN	View
▤	Cardiomyopathy, Congestive	CO PD	GN	View
Φλ▤	Cardiovascular Diseases	PD	GN	View
▤	Coronary Disease	CO PD	GN	View

11
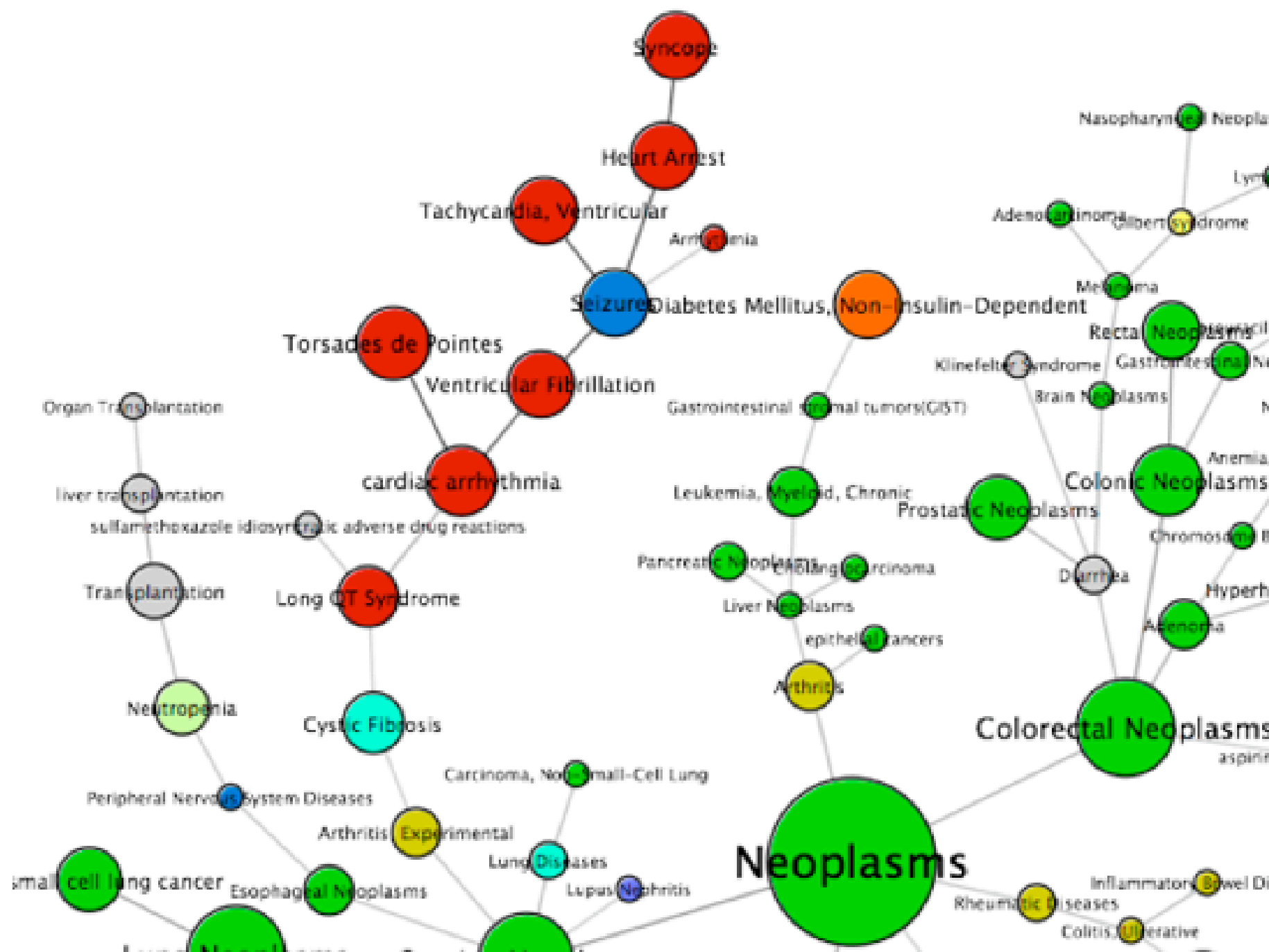
How can i2b2-type infrastructure help pharmacogenomics? 5 opportunities

Opportunity #1

- **Identify drugs with variable outcomes (no variability, no pharmacogenomics)**
  - variability in dose
  - variability in side effects
  - variability in outcomes

- **Population based databases allow us to**

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Opportunity #2

- **Identify cohorts of patients to participate in studies of PGx**

  - establish hereditability

  - find cases/controls

  - ensure sufficient genetic/cultural diversity

- **Population based databases allow us to identify study cohorts.**

Opportunity #3

- **Provide information about the environmentome (environome?)**
  - infection disease history
  - occupational/environmental exposure history
  - cultural environment

- **Population based databases allow us to define the Env-500K which along with genotypes will predict PGx phenotypes.**

Opportunity #4

- **Provide large, diverse cohorts for replication**
  - Multiple sites
  - Large numbers of study subjects
  - Rapid turnaround

- **<u>Networked</u> Population based databases allow us to define appropriate cohorts for replication and transferability.**

Opportunity #5

- **Provide a mechanism for dissemination and implementation of PGx in practice**
  - **Network for disseminating new PGx interventions**
  - **Electronic medical record infrastructure for decision support (MDs/Patients/Admins)**
- **i2b2-type networks allow us to imagine a mechanism for implementing genome-informed medicine**

Promises & Challenges

- Focused treatment by pre-identifying genetic backgrounds likely to respond.

- Reduce adverse events by predicting who is at risk

- Way to save drugs in the pipeline that are very effective only in subpopulations.

- Better understanding of drug interactions

Promises & Challenges

- Science still early.

- Fragmentation of drug markets is not always attractive to drug companies.

- Finding significant variants

- Ethical issues in testing/storing individual genotype

- Unclear how to deliver information to the practitioner

- "Big N" alone is not enough.

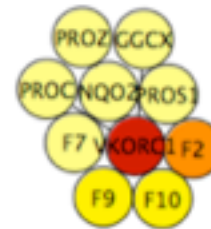# Methods for prioritizing genes in the analysis of GWAS.
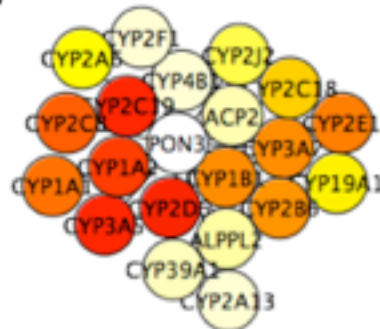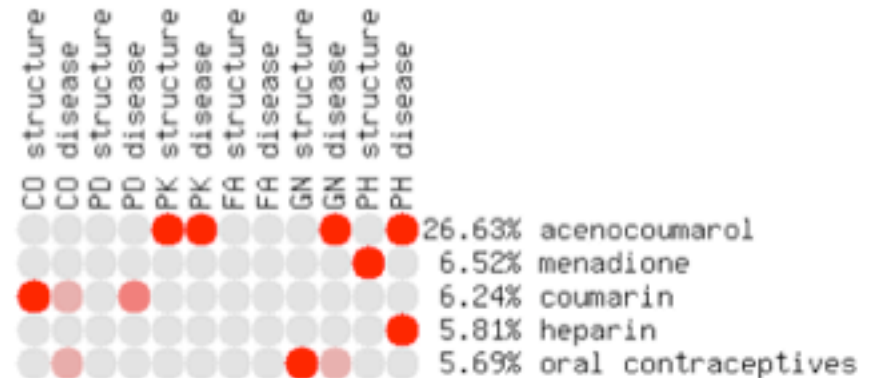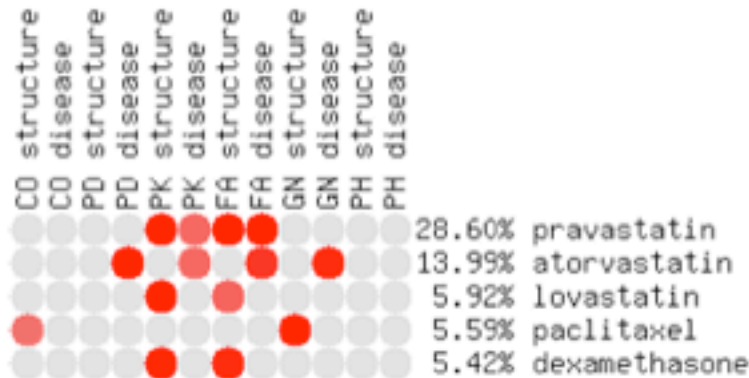
Thanks.

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http://www.pharmgkb.org/

Thanks to NIH (NIGMS, NLM, NHGRI)

POLICY FORUM

GENETICS

Genomic Research and Human Subject Privacy

Zhen Lin,[1] Art B. Owen,[2] Russ B. Altman[1]*

Interest in understanding how genetic variations influence heritable diseases and the response to medical treatments is intense. The academic community relies on the availability of public databases for the distribution of the DNA sequences and their variations. However, like other types of medical information, human genomic data are private, intimate, and sensitive. Genomic data have raised special concerns about discrimination, stigmatization, or loss of insurance or employment for individu-

Trade-offs between SNPs and privacy.

(Figure labels: Insufficient for future genomic research; High; Privacy; Medium; Needed to find genetic relationships; Low; Insufficient for privacy protection; Independent SNPs: 5, 75, 100, 125, 1000, 2000, 3000, 4000)
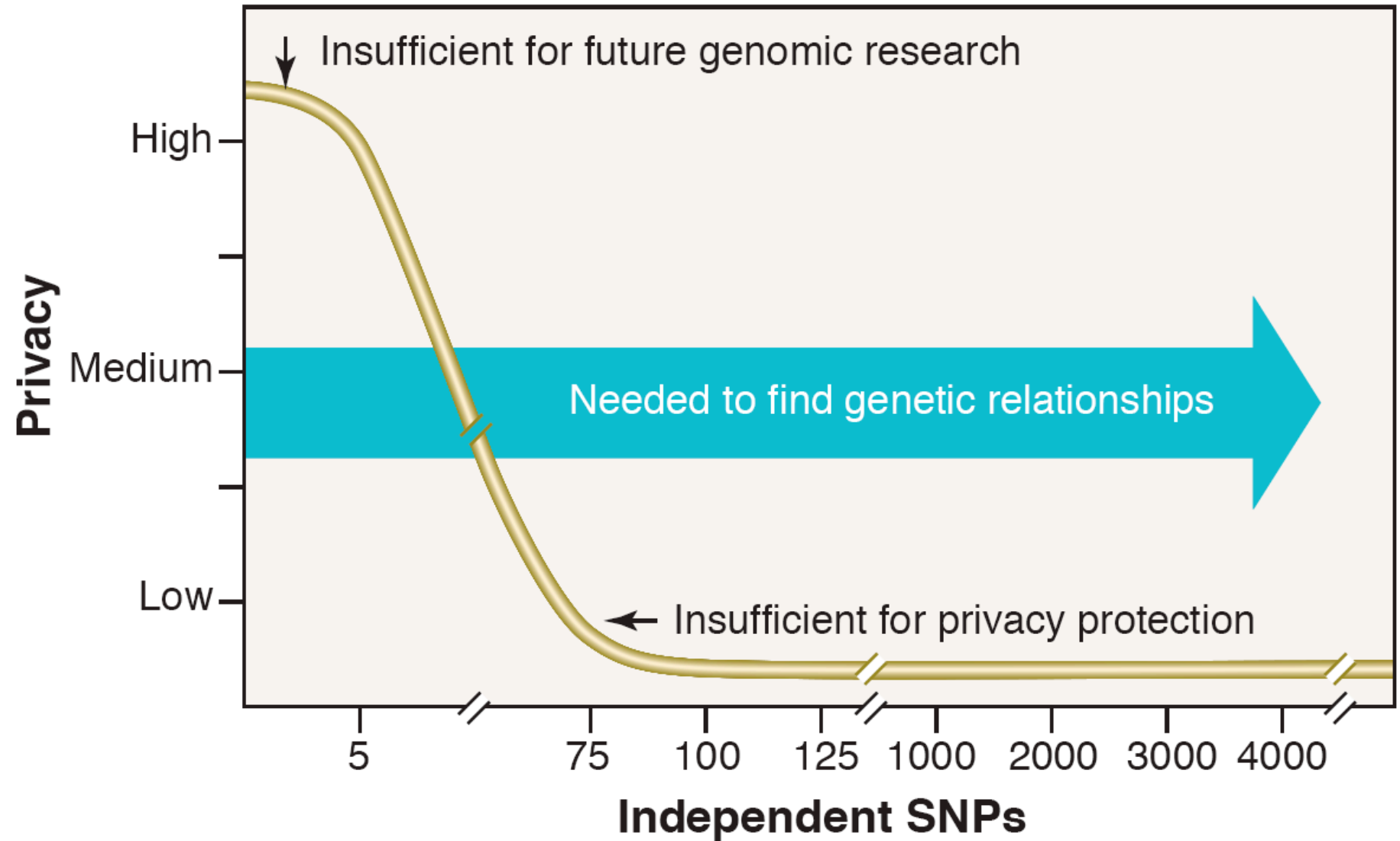
mation. No genetic data will be provided unless a user can demonstrate that he or she is associated with a bona fide academic, industrial, or governmental research unit and agrees to our usage policies (including audit of data access) (10). Although this does not prevent data abuse, it provides a way to monitor usage.

Social concerns about privacy are intricately connected to beliefs about benefits of research and trustworthiness of researchers and governmental agencies. In the United States, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the associated Privacy Rules of 2003 (11) generally forbid sharing identifiable data without patient consent. However, they do not specifically address use or disclosure policies for human genetic data. Recent debates in Iceland, Estonia, Britain, and elsewhere (12–15), reveal a
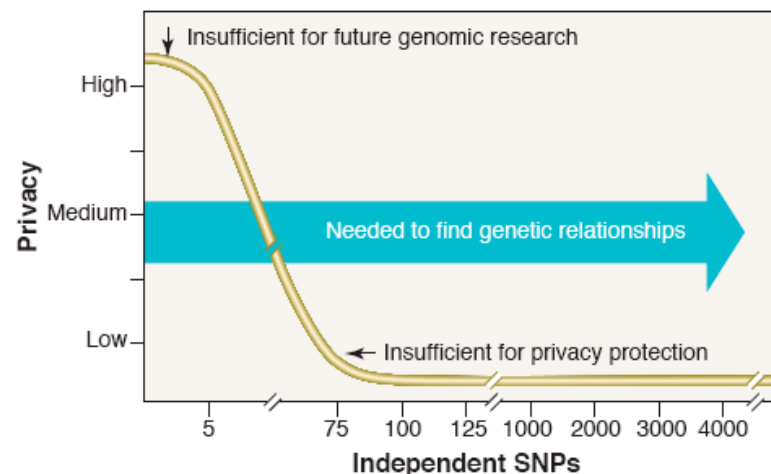
9 July 2004 (Science)

Trade-offs between SNPs and privacy.