Informatics challenges for pharmacogenomics

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PharmGKB, http://www.pharmgkb.org/
Stanford University
Four stories about pharmacogenomics

1. Building a knowledge repository for research community
2. An algorithm for predicting gene–drug interactions
3. A consortium for data sharing to solve big problems in pharmacogenomics
Pharmacogenomics

Patients with same diagnose

Response to treatment

No response to treatment

Experience adverse events
http://www.pharmgkb.org/
Example: warfarin (coumadin)

- Used to thin blood, prevent clots, strokes, heart attacks
- Very difficult to dose—can’t predict based on size of patient
- Overdose & underdose both dangerous
- Two genes explain much of variability—CYP2C9 (PK) and VKORC1 (PD)
- We can use genetics to predict best dose, and perhaps minimize adverse events.
Genes

- Important PGx genes
- Pharmacokinetic genes
- Pharmacodynamic genes
- Genotyped genes

[Image of ABCB1 gene with exon, synonymous, and UTR annotations]

[Search bar for warfarin]

hint: enter a gene, rsid, drug, disease
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROC</td>
<td>protein C (inactivator of coagulation factors Va and VIIIa)</td>
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<tr>
<td>PROS1</td>
<td>protein S (alpha)</td>
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<tr>
<td>F7 [ variants ]</td>
<td>coagulation factor VII (serum prothrombin conversion accelerator)</td>
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<td>VKORC1 [ VIP annotation ] [ variants ] [ genetics ]</td>
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<td>bone gamma-carboxyglutamate (gla) protein</td>
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<tr>
<td>GGCX</td>
<td>gamma-glutamyl carboxylase</td>
</tr>
<tr>
<td>F9</td>
<td>coagulation factor IX</td>
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**Gene:**
VKORC1
vitamin K epoxide reductase complex, subunit 1

---

**PharmGKB Non-Array Variant Data**

All features below come from the default feature set. Alleles are reported on the strand the gene is on, the minus strand. Note that not all variants in dbSNP or known variants may be listed here.

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<th>Feature</th>
<th>Amino Acid Translation</th>
<th>Annotated Variant Curation Level</th>
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Export options: CSV | Excel | XML
Variants

- VKORC1: G3673A
  - Causative allele for the low dose phenotype
  - Related drug: Warfarin
  - rs9923231

- Annotated SNPs by gene
- Annotated SNPs by drug
- Annotated SNPs by disease
- Download all annotated SNPs

hint: enter a gene, rsid, drug, disease
<table>
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<tr>
<th>Variant</th>
<th>Gene</th>
<th>Drug</th>
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DRUG:
warfarin

In-Depth Annotations (★★★)

1. **rs1799853 at chr10:96692037** in CYP2C9
   This variant has been shown to influence warfarin dose as well as affecting the clearance of several other drugs.

   **Variant Name:**
   CYP2C9*2; CYP2C9:144Arg>Cys

   **Related Drugs:**
   fluvastatin, glipizide, phenytoin, tolbutamide, warfarin

   **Evidence:**
   http://www.pharmgkb.org/search/annotatedGene/cyp2c9/variant.jsp#ImportantVariantInformationforCYP2C9-111

2. **rs1057910 at chr10:96731043** in CYP2C9
   This variant has been shown to correlate significantly with warfarin dose as well as affecting the clearance of several other drugs.

   **Variant Name:**
   CYP2C9*3; CYP2C9:359Ile>Leu

   **Related Drugs:**
   fluvastatin, glipizide, phenytoin, tolbutamide, warfarin

   **Evidence:**
   http://www.pharmgkb.org/search/annotatedGene/cyp2c9/variant.jsp#ImportantVariantInformationforCYP2C9-222
4. rs9934438 at chr16:31012379 in VKORC1
   Tagging SNP for low dose phenotype

   Variant Name:
   VKORC1:C6484T; VKORC1:1173C>T

   Related Drugs:
   warfarin

   Evidence:
   http://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp#ImportantVariantInformationforVKORC1-6484

5. rs9923231 at chr16:31015190 in VKORC1
   Believed to be the causative allele for the low dose phenotype in warfarin therapy based on both in vitro and in vivo evidence

   Variant Name:
   VKORC1:G3673A; VKORC1:-1639G>A

   Related Drugs:
   warfarin

   Evidence:
   http://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp#ImportantVariantInformationforVKORC1-3673
Drugs & Small Molecules

- Related gene: TPMT
- Disease: Leukemia
- Mercaptopurine

- Drugs by therapeutic categories
- Drugs with genetic information
- Drugs with data

search bar: warfarin

hint: enter a gene, rsid, drug, disease
Drug:

warfarin

Overview

**Generic Names:** Warfarin sodium

**IUPAC Name:** 2-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-4-one

**Trade Names:** Athrombin; Athrombin-K; Athrombine-K; Brumolin; Co-Rax; Coumadin; Coumafen; Coumafene; Coumaphen; Coumaphene; Coumarins; Coumarin; D-Con; Dethmor; Dethnel; Dicusat E; Frass-Ratron; Jantoven; Kumader; Kumadu; Kumatox; Kypfarin; Latka 42; Mar-Grin; Marevan; Maveran; Panwarfin; Place-Pax; Prothromadin; RAX; Rosex; Sofarin; Solfarin; Sorexa Plus; Temus W; Tintorane; Tox-Hid; Vampirinip II; Vampirinip III; Waran; Warf 42; Warfarat; Warfarin Plus; Warfarin Q; Warfarine; Warficide; Warfilone; Zoocoumarin

**PharmGKB Accession Id:** PA451906

Description

An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors. Warfarin is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, and atrial fibrillation with embolization. It is also used as an adjunct in the prophylaxis of systemic embolism after myocardial infarction. Warfarin is also used as a rodenticide. [PubChem]

Indication

For the treatment of retinal vascular occlusion, pulmonary embolism, cardiomyopathy, atrial fibrillation and flutter, cerebral embolism, transient cerebral ischaemia, arterial embolism and thrombosis.

Therapeutic Category

- B01AA: Vitamin K antagonists
Simplified diagram of the target of warfarin action and downstream genes and effects.

Legend

- R-Warfarin
- S-Warfarin
- NADH
- EPHX1
- VKORC1
- NAD+
- Vitamin K (oxidized)
- Vitamin K (reduced)
- Vitamin K
- GGCX
- CALU
- Functional
- Hypofunctional
- F2
- F9
- F10
- PROZ
- F7
- GA56
- BGLAP
- PROC
- PROST1
- MCP
- clotting
- bone metabolism & connective tissue calcification
- apoptosis

Related genes
- CYP2F2

Downloads
- Supporting Evidence (xls)
Pharmacokinetics:

Representation of the candidate genes involved in transport, metabolism and clearance of warfarin.
Our Mission: To collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response. We curate primary genotype and phenotype data, annotate gene variants and gene-drug-disease relationships via literature review, and summarize important PGx genes and drug pathways.

Find Data By Type

Genes
- Important PGx genes
- Pharmacokinetic genes
- Pharmacodynamic genes
- Genotyped genes

Variants
- Annotated SNPs by gene
- Annotated SNPs by drug
- Annotated SNPs by disease
- Download all annotated SNPs

Pathways
- Pathways by therapeutic categories
- Pharmacokinetic pathways
- Pharmacodynamic pathways
- All pathways

Drugs & Small Molecules
- Drugs by therapeutic categories
- Drugs with genetic information
- Drugs with data

Diseases
- Diseases with genetic information
- Diseases with curated information
- All diseases

Opportunities to Contribute:
Seeking Input on PGx Drug Relabeling Opportunities

Curators’ Favorite Papers
- Clinical pharmacology and pharmacogenetics in a genomics era: the CMET platform
- Pharmacogenetics in reproductive and perinatal medicine
- Pharmacogenetics of antidepressive treatment

Updated 1/11/10.
See the archives for more.

PGx in the News
- Pathway Genomics Launches Online Educational Tool
- Navigenics Agrees Not to Market Genetic Testing Services Directly to NY Residents
- Will 2009 Be Remembered as the Year Personalized Medicine Went Mainstream?
- Perlegen Defunct: PGx Firm Shuts Doors After R&D Disappointments, Mounting Losses

See more news.
Subscribe to RSS feed.
Pharmspresso Search Tool

The search tool allows for any combination of category and keyword searches.

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<thead>
<tr>
<th>Query</th>
<th>Keywords</th>
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Exact match

Search
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<th>Year</th>
<th>Number of matching sentences</th>
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</table>
Cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1) genotypes as determinants of acenocoumarol sensitivity (PMID: 15790782)

Sentence 14: Up to 14 of the interindividual variability of the AC pharmacodynamic response can be explained based on this genotypic-haplotype approach among white subjects. Recent works have also suggested that genetic variations within vitamin K-dependent protein genes could also be useful for predicting anticoagulant response. The vitamin K epoxide reductase multiprotein complex 1 (VKORC1) gene has been hypothesized to play a role in the variability of the AC response based upon a seminal study showing that an intronic 1173C T polymorphism was associated with warfarin dose requirement.

Sentence 15: Patients carrying the T allele required a lower dose of warfarin compared with those carrying the C allele (the mean daily dose decreased 43 for homozygous TT carriers and 22 for heterozygous). The aim of this study was to evaluate the contribution of genetic variability of the VKORC1 gene, in addition to the 1173C T polymorphism, on the pharmacodynamic outcome after AC intake.

Sentence 120: A recent publication by DAndrea et al suggested, for the first time, the role of VKORC1 genetic polymorphisms on warfarin dose requirements.

Sentence 147: DAndrea et al found that the 1173C T intronic mutation, associated with low-dose requirement of warfarin, did not affect the processing of VKORC1 mRNA. Altogether, these results suggested that a clear functional SNP in the VKORC1 gene was not yet identified, although both SNPs were linked in the pharmacologic response to anticoagulant.


Go to previous or next page.
Using PharmGKB and text mining to predict genes that modulate drug response
PGx Flow

- Variants (GN)
- Genes (PK)
- Drugs
  - Delivery
    - Absorption
    - Distribution
    - Metabolism
    - Excretion
  - Site of action
    - Target
    - Mechanism of action
    - Drug response
  - Pharmacological effect
- CO (Clinical Outcome)
- PD (Pharmacodynamics & Drug Responses)
- PK (Pharmacokinetics)
- FA (Molecular & Cellular Functional Assays)
- GN (Genotype)
Current PharmGKB content
SPARSE

844 Genes

PharmGKB

\[
\frac{2529}{(844 \times 485)} = 6.18 \times 10^{-3}
\]
Similar drugs may interact with similar genes

844 Genes

>485 Drugs
Related genes may interact with related drugs

- Protein interaction networks
- >844 Genes
- >485 Drugs
- Disease treatment similarity
- Structural similarity
Goal

Given a drug and putative indication, rank all genes in the genome for the likelihood that they are involved in the PK or PD of a drug, i.e. that they are pharmacogenes.

GOAL: Combine this information with high-throughput data to aid in interpretation.
INPUT:

Drug = D
Structure
Indication
Gene = G

INTERACTIONS:

PPI =
PGx =
DTI =

DATA STRUCTURE:

F1:
PGx + structure

F2:
PGx + indication

F3:
DTI + structure

F4:
DTI + indication
Score for Gene
Genomewide and external validation

AUC
- Cross-validation: 0.82
- Genome-wide: 0.86
- External validation: 0.81
Simvastatin – PON3

Indications:
Cardiovascular diseases,
Arteriosclerosis,
Hypercholesterolemia, Hyperlipidemia ...

Simvastatin modulates **PON1** expression
protecting LDL cholesterol (PMID14500290)

**PON3** a good biomarker for simvastatin
treatment effectiveness (PMID 12644596)
Validation on warfarin

PGx pipeline ranks:
- VKORC1 no. 10 of 12,460 genes
- CYP2C9 no. 13 of 12,460 genes
Warfarin – VKORC1

Indications:
Myocardial infarction, venous thrombosis, thrombolytic disease, venous thromboembolism, pulmonary embolism ...

Gene contribution (100%)

Acenocoumarol (48.8%)
Phenprocoumon (22.6%)
Oral contraceptives (15.9%)
Menadione (8.2%)
Others (4.6%)

Drug contribution (100%)

VKORC1 71.3%


**Validation on warfarin**

Cooper et al made a genome-wide association study listing:

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<td>TRPM3</td>
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<td>6329 0.508312585</td>
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</table>

**Genes on this list rank higher than average (P=1.20e-3)**
Warfarin – FAM113B

Indications:
Myocardial infarction, venous thrombosis, thrombolytic disease, venous thromboembolism, pulmonary embolism ...

Drug contribution (100%)
- acenocoumarol (50.8%)
- pravastatin (14.5%)
- oral contraceptives (11.1%)
- doxorubicin hydrochloride (8.3%)
- others (15.3%)

Gene contribution (100%)
- APOE 44.4%
- F2 18.0%
- SCN5A 10.8%
- ALB 10.8%
- APOA4 14.5%
- FAM113B 0.0%
- PRSS1 0.2%
- CROT 1.3%
Curated vs. Mined vs. Predicted

Text-Mining identified relationships (5,312)

PharmGKB identified relationships (1,782)

Text-mining-based classifier's high scoring relationships

Putative Relationships: High scoring, found by text-mining, not in PharmGKB

Extrapolated Knowledge: High scoring, missed by text-mining, in PharmGKB;
Doxorubicin prediction
Trimipramine prediction
Diltiazem prediction
PGx pipeline 1.0 Server

The PGx pipeline 1.0 server can be used to prioritize pharmacogene candidates. By comparing an input drug (or a set of input drugs) being involved in the pharmacogenetic response to the inputted drug(s). As the method utilizes protein-protein interactions to infer chi

NOTE: The method integrates several large datasets in each run, so expect 2-3 minutes delay when running the pipeline.

The JME applet (Java Molecular Editor) used below has been provided by courtesy of dr Peter Ertl.

SUBMISSION

Paste or import molecules in SMILES-format:

```
CC(=O)CC(c1ccc(ccc1)c2c3cccc3c2=O)O
```

Construct a molecule:

Submit a file in SMILES format directly from your local disk:

Choose File

Submit a file in SDF format directly from your local disk:

Choose File

Select Indications (at least one, use CTRL - LEFT_CLICK to select multiple indications)

- Choroidal neovascularization [PA446974]
- Chromosome breakage [PA446834]
- Chronic fatigue syndrome [PA446215]
- Chronic hepatitis C [PA446883]
- Chronic kidney failure [PA446894]
- Chronic myeloid leukemia [PA446171]
- Chronic obstructive pulmonary disease [PA447178]
- Coagulation protein disorders [PA446900]
- Cocaine-related disorders [PA446878]
- Codeine dependence [PA447250]
PGx pipeline 1.0 running on genome

Converting SMI to SDF ........................................... done
Generating structural fingerprints ............................... done
Running whole genome rank:
Reading drug fingerprints ................................. 1 read
Reading drug indications ................................ 1 read
Reading hugo gene nomenclature .................... 18069 read
Reading drug-disease relations ......................... 401 read
Reading drug-fingerprint relations ................... 1257 read
Reading gene-drug interactions ...................... 1555 read
Reading node_id => ensembl id translations ...... 22998 read
Reading Inweb interactome ............... 12454 pulldowns created
compound1 data generated (75 sec.)

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<th>Score</th>
<th>-log(P)</th>
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<td>GAS6</td>
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<td>ORM1</td>
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<td>KIAA0562</td>
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<tr>
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<td>PALM</td>
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<td>3.25</td>
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<td>ENSG00000163430</td>
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<td>TCTE1</td>
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<td>ENSG00000101000</td>
<td>PROCR</td>
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<tr>
<td>ENSG00000167397</td>
<td>VKORC1</td>
<td>0.31</td>
<td>2.78</td>
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</table>
PharmGKB as a convener of data sharing consortia
Warfarin Dosing & FDA Issues

• Several warfarin pgx dosing algorithms published
  – Typically derived in single ethnic group
  – Usually in geographically confined area

• FDA modified package insert to “suggest” using genetic information (August 2007)
  – No information about how to use genetic data

• Need for a global dosing algorithm

• Planned clinical trials need validated dosing algorithm for the genotype vs. clinical–only vs. fixed + adjust
International Warfarin Pharmacogenetics Consortium (IWPC)

- PharmGKB noticed many groups working on warfarin independently.
- 21 research groups from 11 countries, 4 continents
- Formed consortium in July 2006 meeting
- Genetic and clinical data submitted on 5,701 warfarin-treated patients (~300 patients/center)
- Data centralized and curated by PharmGKB
- Joint data analysis & writing
- GOAL: Create and compare: clinical algorithm, pharmacogenetic algorithm, fixed initial dose.
Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data  

The International Warfarin Pharmacogenetics Consortium*  

**ABSTRACT**  

**BACKGROUND**  
Genetic variability among patients plays an important role in determining the dose of warfarin that should be used when oral anticoagulation is initiated, but practical methods of using genetic information have not been evaluated in a diverse and large population. We developed and used an algorithm for estimating the appropriate warfarin dose that is based on both clinical and genetic data from a broad population base.

**METHODS**  
Clinical and genetic data from 4043 patients were used to create a dose algorithm that was based on clinical variables only and an algorithm in which genetic information was added to the clinical variables. In a validation cohort of 1009 subjects, we evaluated the potential clinical value of each algorithm by calculating the percentage of patients whose predicted dose of warfarin was within 20% of the actual stable therapeutic dose; we also evaluated other clinically relevant indicators.

**RESULTS**  
In the validation cohort, the pharmacogenetic algorithm accurately identified larger
Average warfarin doses for stable INR (median – 2.5)

![Box plot showing the distribution of therapeutic warfarin doses by race.](image)

**Median:**
- Asian: **3.0 mg/d**
- Black or African American: **5.4 mg/d**
- White: **4.5 mg/d**

*Distribution of Therapeutic Warfarin Dose by Race*
*Boxes show median, 25th and 75th percentile; whiskers show 10th and 90th percentile, and points show 5th and 95th percentile.*
**Clinical Algorithm**

(Available at: warfarindosing.org)

<table>
<thead>
<tr>
<th>Warfarin clinical dosing algorithm</th>
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<tbody>
<tr>
<td>4.0376</td>
</tr>
<tr>
<td>- 0.2546 x Age in decades</td>
</tr>
<tr>
<td>+ 0.0118 x Height in cm</td>
</tr>
<tr>
<td>+ 0.0134 x Weight in kg</td>
</tr>
<tr>
<td>- 0.6752 x Asian race</td>
</tr>
<tr>
<td>+ 0.4060 x Black or African American</td>
</tr>
<tr>
<td>+ 0.0443 x Missing or Mixed race</td>
</tr>
<tr>
<td>+ 1.2799 x Enzyme inducer status</td>
</tr>
<tr>
<td>- 0.5695 x Amiodarone status</td>
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<tr>
<td>= Square root of weekly warfarin dose**</td>
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### Warfarin Pharmacogenetic Dosing Algorithm

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<th>Term</th>
<th>Coefficient</th>
<th>Description</th>
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<td>Age in decades</td>
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<tr>
<td>Height in cm</td>
<td>0.2614 x</td>
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</tr>
<tr>
<td>Weight in kg</td>
<td>0.0087 x</td>
<td></td>
</tr>
<tr>
<td>VKORC1&lt;sup&gt;A/G&lt;/sup&gt;</td>
<td>0.0128 x</td>
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</tr>
<tr>
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<tr>
<td>CYP2C9&lt;sup&gt;*1/3&lt;/sup&gt;</td>
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<tr>
<td><strong>= Square root of weekly warfarin dose</strong></td>
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Observed vs. Predicted Dose with PGx
B

Weekly Warfarin Dose (mg)

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<th>Pharmacogenetic Algorithm</th>
<th>Clinical Algorithm</th>
<th>No variants</th>
<th>VKORC1 A/A and CYP2C9 *3/*3</th>
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<td>Asian</td>
<td>25</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>African</td>
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<td>10</td>
</tr>
<tr>
<td>White</td>
<td>35</td>
<td>30</td>
<td>5</td>
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Are these differences clinically significant?
Dose within 20% of actual

**Figure 2.** Percentage of Patients with Dose Estimates within 20% of the Actual Dose, as Derived with the Use of a Pharmacogenetic Algorithm, a Clinical Algorithm, and a Fixed-Dose Approach.
The “Patient 0” Genome
Single-molecule sequencing of an individual human genome

Dmitry Pushkarev, Norma F Neff, and Stephen R Quake

Recent advances in high-throughput DNA sequencing technologies have enabled order-of-magnitude improvements in both cost and throughput. Here we report the use of single-molecule methods to sequence an individual human genome. We aligned billions of 24- to 70-bp reads (32 bp average) to ~90% of the National Center for Biotechnology Information (NCBI) reference genome, with 28× average coverage. Our results were obtained on one sequencing instrument by a single operator with four data collection runs. Single-molecule sequencing enabled analysis of human genomic information without the need for cloning, amplification or ligation. We determined ~2.8 million single nucleotide polymorphisms (SNPs) with a false-positive rate of less than 1% as validated by Sanger sequencing and 99.8% concordance with SNP genotyping arrays. We identified 752 regions of copy number variation by analyzing coverage depth alone and validated 27 of these using digital PCR. This milestone should allow widespread application of genome sequencing to many aspects of genetics and human health, including personal genomics.

on a surface can be extended asynchronously, thereby allowing substantial flexibility in the kinetics of sequencing chemistry. Previous reports of single-molecule sequencing have been proofs of principle, and their sequencing throughput has not been competitive with alternative approaches. Generally, read lengths have been relatively short and error rates have been dominated by deletions; it has not been clear whether the resulting sequence quality is suitable for human genome sequencing applications.

The Heliscope Single Molecule Sequencer (Helicos Biosciences) is the first commercial release of a single-molecule sequencing instrument. It allows one to follow ~1 billion individual molecules as they are sequenced over the course of a week — a throughput that is practical for human genome sequencing. There have been several technical improvements to the platform since the reported sequencing of a viral genome, including more than a 1,000-fold improvement in parallelism, a new generation of sequencing reagents that allows digital measurement of homopolymer sequences, and a new software algorithm, IndexDP, for performing alignments to the entire human genome.

We used two of the instrument’s 50 flow-cell channels to resequence the Staphylococcus aureus genome as a calibration of sequencer perform-
Patient zero

40 year old male in good health presents to his doctor with his whole genome
No symptoms
Exercises regularly
Takes no medication
Family history of aortic aneurysm
Family history of sudden death
Clinical examination

Normal appearing male
Comfortable at rest
HS 1,2+0
No murmurs, rubs or gallops
Chest clear, abdomen nad
Musculoskeletal, neuropsych examinations grossly normal
Afebrile
HR 60pm, BP 128/80
PharmGKB Annotation Method

- Evaluate 2500 SNP annotations for direct drug relevance to patient 0
- Evaluate CNVs in known important genes (VIP, PK, PD)
- Evaluate novel SNPs in known important genes (VIP, PK, PD)
• Patient is heterozygous for a null mutation of CYP2C19 (metabolizing enzyme)

• CYP2C19 critical for metabolism of:
  • proton pump inhibitors (lansoprazole, omeprazole, pantoprazole, rabeprazole)
  • antiepileptics (diazepam, Norphenytoin, phenobarbitone)
  • Amitryptyline, citalopram, chloramphenicol, clopidogrel, indomethacin, nelfinavir, propranolol, R-warfarin, imipramine...
<table>
<thead>
<tr>
<th>Drug</th>
<th>Summary</th>
<th>Level of Evidence</th>
<th>PMID</th>
<th>Gene</th>
<th>rsID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel &amp; CYP2C19</td>
<td>CYP2C19 poor metabolizer, many drugs may need adjustment.</td>
<td>High</td>
<td>19106084</td>
<td>CYP2C19</td>
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<td>Warfarin</td>
<td>Requires lower dose</td>
<td>High</td>
<td>15888487</td>
<td>VKORC1</td>
<td>rs9923231</td>
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<tr>
<td>Warfarin</td>
<td>Requires lower dose</td>
<td>High</td>
<td>19270263</td>
<td>CYP4F2</td>
<td>rs2108622</td>
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<td>Metformin</td>
<td>Less likely to respond</td>
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<td>Troglitazone</td>
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<td>Cisplatin</td>
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<td>SLC22A2</td>
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<td>Citalopram</td>
<td>May increase risk of suicidal ideation during therapy</td>
<td>Low</td>
<td>17898344</td>
<td>GRIA3</td>
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<td>Escitalopram; Nortriptyline</td>
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<td>Low</td>
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<td>NR3C1</td>
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<td>Morphine</td>
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<td>17156920</td>
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<td>Paclitaxel</td>
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<td>SLCO1B1</td>
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<td>Talinolol</td>
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<td>Sildenafil</td>
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<td>12576843</td>
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## Summary of Pharmacogenetic Good News

<table>
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<th>Drug</th>
<th>Summary</th>
<th>Level of Evidence</th>
<th>PMID</th>
<th>Gene</th>
<th>rsID</th>
</tr>
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<tbody>
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<td>HMG CoA Reductase Inhibitors (statins)</td>
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<td>High</td>
<td>18650507</td>
<td>SLCO1B1</td>
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<tr>
<td>Statins</td>
<td>No increased risk of myopathy</td>
<td>High</td>
<td>12811365</td>
<td>SLCO1B1</td>
<td>rs4149056</td>
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<tr>
<td>Desipramine; Fluoxetine</td>
<td>Depression may improve more than average</td>
<td>Medium</td>
<td>19414708</td>
<td>BDNF</td>
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<tr>
<td>Fluvastatin</td>
<td>Good response</td>
<td>Medium</td>
<td>18781850</td>
<td>SLCO1B1</td>
<td>rs11045819</td>
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<tr>
<td>Metoprolol and other CYP2D6 substrates</td>
<td>Normal CYP2D6 metabolizer.</td>
<td>Medium</td>
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<td>CYP2D6</td>
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</tr>
<tr>
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<tr>
<td>Pravastatin, Simvastatin</td>
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<td>HMGCR</td>
<td>rs17244841</td>
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<td>Caffeine</td>
<td>No increased risk of heart problems with caffeine</td>
<td>Low</td>
<td>16522833</td>
<td>CYP1A2</td>
<td>rs762551</td>
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<tr>
<td>Calcium channel blockers</td>
<td>No increased risk of Torsades de Pointe</td>
<td>Low</td>
<td>15522280</td>
<td>KCNH2</td>
<td>rs36210421</td>
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<td>Carbamazepine</td>
<td>SNP is part of protective haplotype for hypersensitivity to carbamazepine</td>
<td>Low</td>
<td>16538175</td>
<td>HSPA1A</td>
<td>rs1043620</td>
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<tr>
<td>Neviraprine</td>
<td>Reduced risk of hepatotoxicity</td>
<td>Low</td>
<td>16912957</td>
<td>ABCB1</td>
<td>rs1045642</td>
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<td>Efavirenz; Nevirapine</td>
<td>Reduced risk of hepatotoxicity</td>
<td>Low</td>
<td>16912956</td>
<td>ABCB1</td>
<td>rs1045642</td>
</tr>
<tr>
<td>Epoetin Alfa</td>
<td>Lower dose of iron and epo required</td>
<td>Low</td>
<td>18025780</td>
<td>HFE</td>
<td>rs1799945</td>
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<tr>
<td>Fexofenadine</td>
<td>Average blood levels expected</td>
<td>Low</td>
<td>11503014</td>
<td>ABCB1</td>
<td>rs1045642</td>
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<tr>
<td>Irbesartan</td>
<td>Irbesartan may work better than beta-blocker</td>
<td>Low</td>
<td>15453913</td>
<td>APOB</td>
<td>rs1367117</td>
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<tr>
<td>Lithium</td>
<td>Increased likelihood of response</td>
<td>Low</td>
<td>18408563</td>
<td>CACNG2</td>
<td>rs5750285</td>
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<tr>
<td>Paroxetine</td>
<td>May have improved response</td>
<td>Low</td>
<td>17913323</td>
<td>ABCB1</td>
<td>rs2032582</td>
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<tr>
<td>Pramipexole</td>
<td>More likely to respond</td>
<td>Low</td>
<td>19396436</td>
<td>DRD3</td>
<td>rs6280</td>
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</table>
Equivocal evidence for some drugs

- Beta-blockers: may be better than other classes, but may not work
- Methotrexate: may be more or less likely to respond, more likely to be toxic
- Iloperidone: may or may not cause arrhythmias
- Olanzapine: more or less likely to gain weight
- Risperidone: may or may not respond well
Copy Number Variations

No interpretable CNVs for drug response

No CNVs in CYP2D6, CYP2C9, CYP3A4, CYP3A5

So any variation in these is due to SNPs.
<table>
<thead>
<tr>
<th>SNP_loc</th>
<th>Ref</th>
<th>pt0</th>
<th>Coding</th>
<th>PK/PD?</th>
<th>Gene</th>
<th>related drugs</th>
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<tr>
<td>1:33251518</td>
<td>G</td>
<td>CG</td>
<td>H191D</td>
<td>PK</td>
<td>AK2</td>
<td>adefovir dipivoxil; tenofovir;</td>
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<td>G</td>
<td>AG</td>
<td>V793M</td>
<td>PD</td>
<td>CARD15</td>
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<td>12:54774480</td>
<td>C</td>
<td>CT</td>
<td>H578Y</td>
<td>PD</td>
<td>ERBB3</td>
<td>trastuzumab; erlotinib; gefitinib; lapatinib; PHA-665752; chloroquine; cisplatin; gemcitabine; cetuximab;</td>
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<tr>
<td>3:124923809</td>
<td>T</td>
<td>AA</td>
<td>I485F</td>
<td>PD</td>
<td>MYLK</td>
<td>mercaptopurine; methotrexate;</td>
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<td>13:98176691</td>
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<td>CT</td>
<td>Y21C</td>
<td>PK</td>
<td>SLC15A1</td>
<td>atorvastatin; fluvastatin; hmg coa reductase inhibitors; lovastatin; pravastatin; rosvastatin; simvastatin;</td>
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<td>9:86090799</td>
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<td>AG</td>
<td>S443F</td>
<td>PK</td>
<td>SLC28A3</td>
<td>cladribine; fludarabine; uridine; mercaptopurine; thioguanine; antineoplastic agents; gemcitabine; azathioprime; folic acid;</td>
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<td>20:32342227</td>
<td>G</td>
<td>AG</td>
<td>P246L</td>
<td>PD</td>
<td>AHCY</td>
<td>antimetabolites; mercaptopurine; methotrexate; adenosine; antineoplastic agents; azathioprime; folic acid; thioguanine;</td>
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<td>16:49302615</td>
<td>C</td>
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<td>S431L</td>
<td>PD</td>
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<td>6:32593811</td>
<td>G</td>
<td>TT</td>
<td>T262K</td>
<td>PD</td>
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<td>clozapine;</td>
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<td>6:31484467</td>
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<td>CT</td>
<td>I14T</td>
<td>PD</td>
<td>MICA</td>
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<td>CT</td>
<td>R534Q</td>
<td>PK</td>
<td>SLC22A8</td>
<td>cimetidine; estrone; antiinflammatory and antirheumatic products, non-steroids; ibuprofen; indomethacin; ketoprofen; methotrexate; phenylbutazone; piroxicam; probenecid; atorvastatin; fluvastatin; hmg coa reductase inhibitors; lovastatin; pravastatin; rosvastatin; simvastatin; adefovir dipivoxil; tenofovir; antineoplastic agents; cyanocobalamin; folic acid; leucovorin; pyridoxine;</td>
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<td>16:31012227</td>
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<td>CT</td>
<td>G64R</td>
<td>VKORC1</td>
<td>warfarin</td>
<td></td>
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</table>
Summary

• PharmGKB provides access to current knowledge of genetic variation that impacts drug response
• It provides annotated variants, pathways, literature refs, tools for data mining, and prediction.
• We have used it to do a state-of-art annotation of a full human genome for drug response
• Imperfect, imprecise but potentially useful clinical advice
Thanks!
Thanks.

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International Warfarin Pharmacogenetics Consortium

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