# Genomics & Personalized Medicine: Pharmacogenomics

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# Outline of comments today

- Introduction to the PharmGKB resource, www.pharmgkb.org)

- Annotation of a complete humam genome sequence for anticipated drug response

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Pharmacogenomics Knowledge Base

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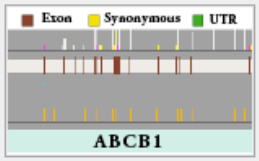
**Our Mission:** To collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response. We curate primary genotype and phenotype data, annotate gene variants and gene-drug-disease relationships via literature review, and summarize important PGx genes and drug pathways.

## Find Data By Type

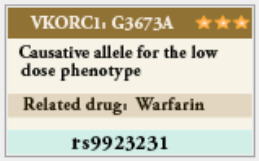
You can find what you're looking for by browsing or searching the four major data types we store. If you need a pointer, check out our **tutorial**. You can also do a general search in the search box at the top of the page.

### Genes




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

### Variants

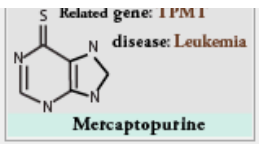



- Annotated SNPs by gene
- Annotated SNPs by drug
- Annotated SNPs by disease
- Download all annotated SNPs


categories
- Pharmacokinetic pathways
- Pharmacodynamic pathways
- All pathways

find pathways | examples

hint: enter a gene, drug, disease

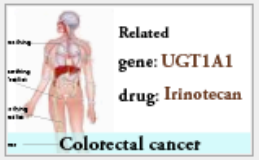



categories
- Drugs with genetic information
- Drugs with data

find drugs | examples

hint: enter a gene, rsid, drug, disease

### Diseases




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

find diseases | examples

hint: enter a gene, rsid, drug, disease

**Opportunities to Contribute:**

Seeking Input on PGx Drug Relabeling Opportunities

**PGx Toolbox**

**Useful Links**

### Curators' Favorite Papers

- Clinical pharmacology and pharmacogenetics in a genomics era: the DMET platform
- Pharmacogenetics in reproductive and perinatal medicine GN
- Pharmacogenetics of antidepressive treatment PD GN

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

### News

- Genomics 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 Shutters Doors After R&D Disappointments, Mounting Losses

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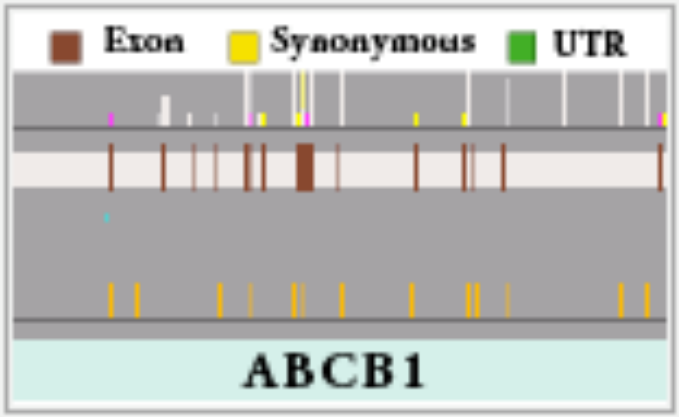



- Important PGx genes
- Pharmacokinetic genes
- Pharmacodynamic genes
- Genotyped genes

warfarin

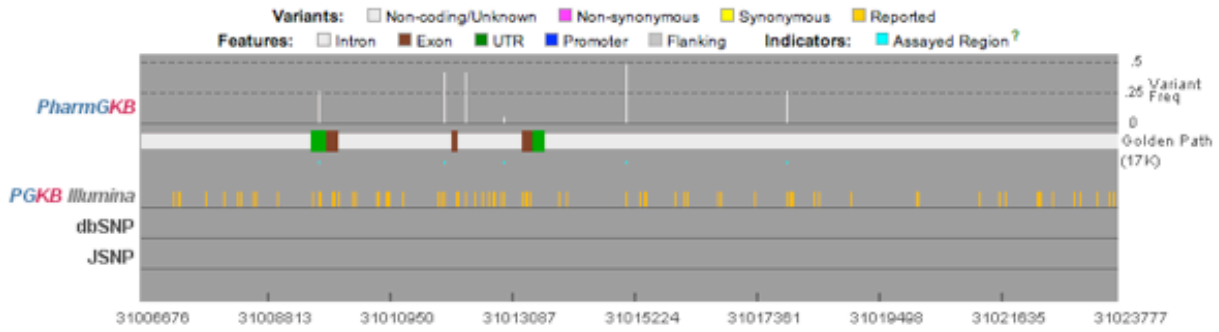
examples

hint: enter a gene, rsid, drug, disease

| | |
|---|---|
| | Gene: PROC<br>Name: protein C (inactivator of coagulation factors Va and VIIIa)<br>Alternate symbols: PC, PROC1 |
| | Gene: PROS1<br>Name: protein S (alpha)<br>Alternate symbols: PROS, PS21, PS22, PS23, PS24, PS25, PSA |
| | Gene: F7 [ variants ]<br>Name: coagulation factor VII (serum prothrombin conversion accelerator)<br>Alternate symbols: |
| VIP | Gene: VKORC1 [ VIP annotation ] [ variants ] [ genetics ]<br>Name: vitamin K epoxide reductase complex, subunit 1<br>Alternate symbols: EDTP308, FLJ00289, IMAGE3455200, MGC2694, MST134, MST576, UNQ308, VKCFD2, VKOR |
| | Gene: BGLAP<br>Name: bone gamma-carboxyglutamate (gla) protein<br>Alternate symbols: BGP, OC, PMF1 |
| | Gene: GGCX<br>Name: gamma-glutamyl carboxylase<br>Alternate symbols: FLJ26629, VKCFD1 |
| | Gene: F9<br>Name: coagulation factor IX<br>Alternate symbols: FIX, Factor IX, HEMB, MGC129641, MGC129642, PTC |

GENE:
**VKORC1**
vitamin K epoxide reductase complex, subunit 1






Expand Variants View | Comparative Genomics

## PharmGKB Non-Array Variant Data

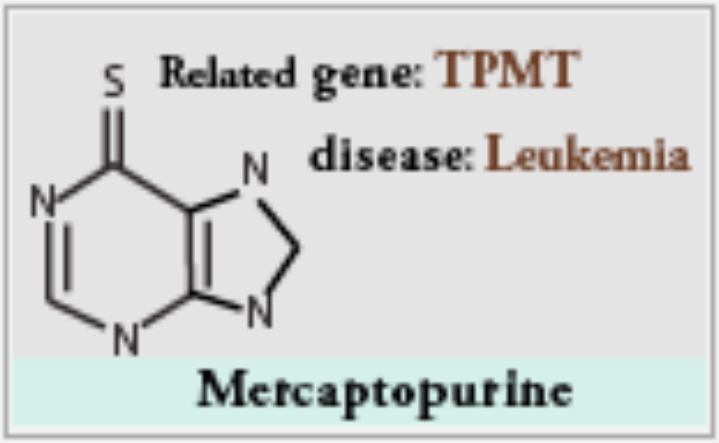
All features below come from the default feature set. Alleles are reported on the strand the gene is on, the minus strand. Note that not all variants in dbSNP or known variants may be listed here.

view legend

| GP Position (hg18) | dbSNP Id (build 130) | Variant | Feature | Amino Acid Translation | Annotated Variant Curation Level |
|---|---|---|---|---|---|
| chr16:31009822 | rs7294 | G/A | 3' UTR | | ★★★ [ view ] |
| chr16:31010090 | rs7200749 | | | | ★★ [ view ] |
| chr16:31011297 | rs2359612 | | | | ★★ [ view ] |
| chr16:31012010 | rs8050894 | G/C | Intron | | ★★ [ view ] |
| chr16:31012379 | rs9934438 | A/G | Intron | | ★★★ [ view ] |
| chr16:31012854 | rs17708472 | | | | ★★ [ view ] |
| chr16:31013055 | rs2884737 | T/G | Intron | | |
| chr16:31013380 | rs28940304 | | | | ★★ [ view ] |
| chr16:31013418 | rs28940303 | | | | ★★ [ view ] |
| chr16:31013467 | rs28940302 | | | | ★★ [ view ] |
| chr16:31015190 | rs9923231 | T/C | NA | | ★★★ [ view ] |
| chr16:31018002 | rs17880887 | C/A | Intron | | |

Export options: CSV | Excel | XML

## Drugs & Small Molecules




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

warfarin

examples

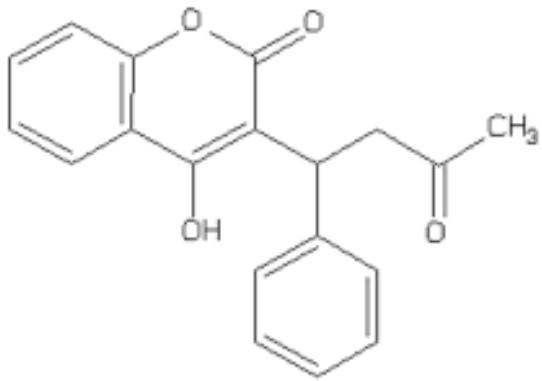
hint: enter a gene, rsid, drug, disease

DRUG:
# warfarin

Overview | Properties | Genetics | Related Genes | Pathways | Related Drugs | Related Diseases | Datasets | Downloads/LinkOuts

## 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; Coumefene; D-Con; Dethmor; Dethnel; Dicusat E; Frass-Ratron; Jantoven; Kumader; Kumadu; Kumatox; Kypfarin; Latka 42; Mar-Frin; 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

## Pathways


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

warfarin

examples

hint: enter a gene, drug, disease

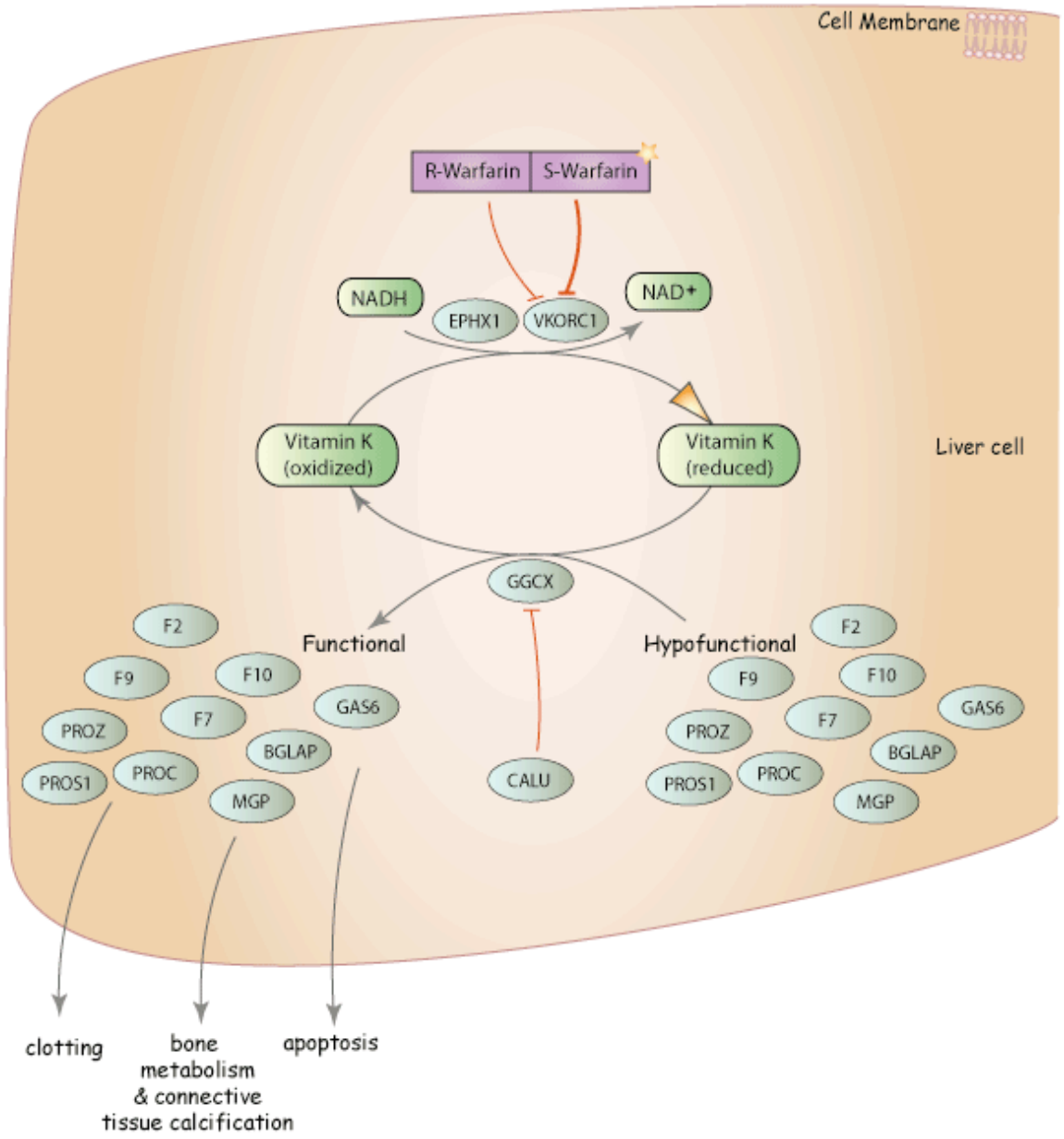
# Warfarin Pathway

UNDER REVIEW

## Pharmacodynamics:

Simplified diagram of the target of warfarin action and downstream genes and effects.

Legend




All Pathways

PD

Go

RELATED genes

- CYPYF2

DOWNLOADS

- Supporting Evidence (xls)

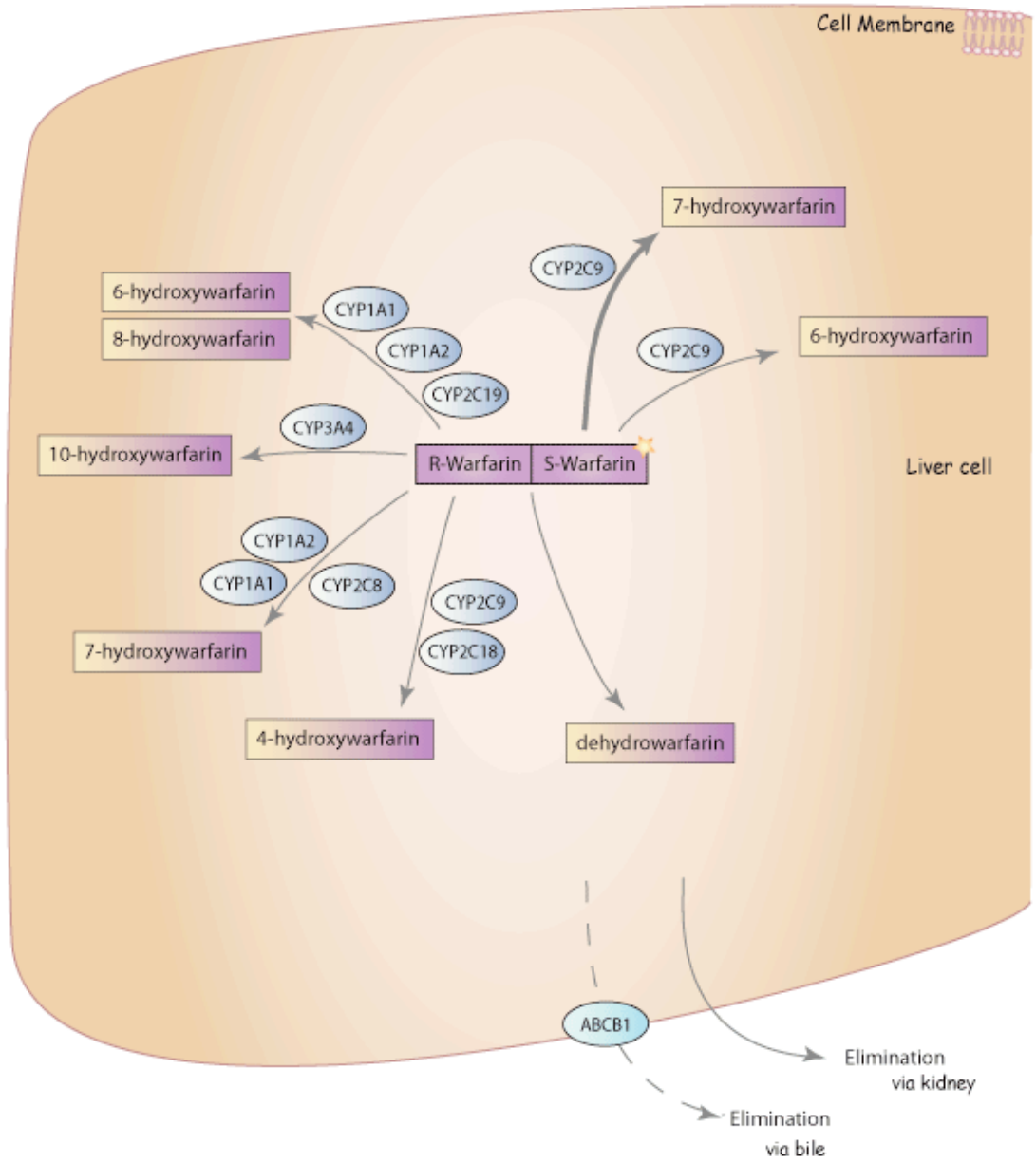
# Warfarin Pathway

UNDER REVIEW

## Pharmacokinetics :

Representation of the candidate genes involved in transport, metabolism and clearance of warfarin.

Legend





All Pathways

PK

Go

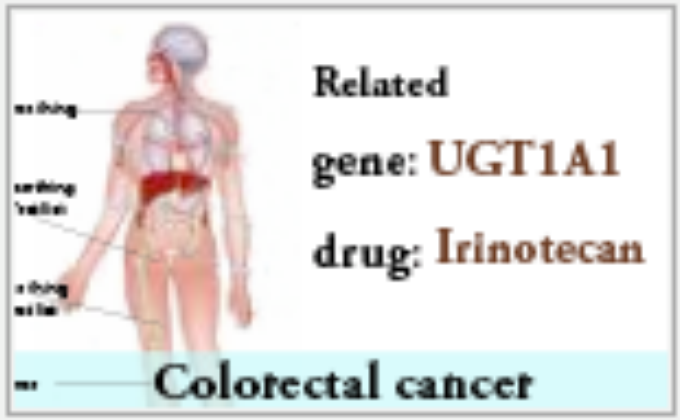

RELATED genes

- CYPYF2

DOWNLOADS

- Supporting Evidence (xls)

## Diseases




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

warfar

examples

- Warfarat
- Warfarin Plus
- Warfarin Q
- Warfarin sodium
- Warfarine
- warfarin

Web Services

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**Search Diseases for** warfarin

view legend

Disease: Arterial Occlusive Diseases
Alternate names: Arterial Obstructive Disease, Arterial Obstructive Diseases, Arterial Occlusive Disease, Disease, Arte
Obstructive, Diseases, Arterial Occlusive...

Disease: Chondrodysplasia Punctata
Alternate names: Chondrodysplasia calcificans, Chondrodysplasia punctata, Chondrodysplasia punctata (stippled ep
Chondrodystrophia Calcificans Congenita, Conradi Hunermann Syndrome...

Disease: Coagulation Protein Disorders
Alternate names: Blood Coagulation Factor Deficiencies, Coagulation Protein Disorder, Coagulation Proteins Disorde
Protein, Disorder, Coagulation Proteins, Disorders, Coagulation Protein...

Disease: thrombolytic disease

Disease: Pulmonary Embolism [ genetics ]
Alternate names: Embolism, Pulmonary, Embolisms, Pulmonary, Infarction, Pulmonary, Infarctions, Pulmonary, Pulmo
Pulmonary Thromboembolism, Pulmonary Thromboembolisms...

Disease: Intracranial Hemorrhages [ genetics ]
Alternate names: Brain Hemorrhage, Brain Hemorrhages, Hemorrhage, Brain, Hemorrhage, Intracranial, Hemorrhage
Intracranial, Hemorrhages, Posterior Fossa, Intracranial Hemorrhage...

Disease: Blood Coagulation Disorders
Alternate names: Bleeding disorder, Blood Coagulation Disorder, Clotting disorder, Coagulation Disorder, Blood, Coa
Coagulation, Disorders, Blood Coagulation...

Disease: Peripheral Vascular Diseases [ genetics ]

## 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

warfarin

examples

hint: enter a gene, rsid, drug, disease

| | |
|---|---|
| | Variant: rs7200749 @ chr16:31010090<br>Gene: VKORC1<br>Drug: warfarin |
| | Variant: rs17708472 @ chr16:31012854<br>Gene: VKORC1<br>Drug: warfarin |
|  | Variant: rs7294 @ chr16:31009822<br>Gene: VKORC1<br>Drug: warfarin |
| | Variant: rs4086116 @ chr10:96697192<br>Gene: CYP2C9<br>Drug: warfarin |
| | Variant: rs4917639 @ chr10:96715525<br>Gene: CYP2C9<br>Drug: warfarin |

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

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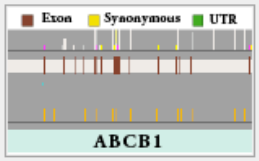


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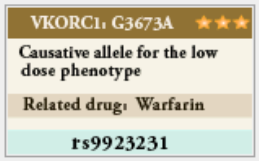


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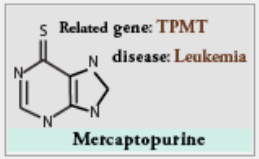
### Drugs & Small Molecules

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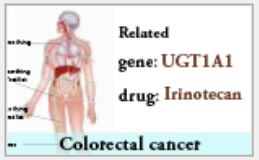


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# Drugs for “Patient 0” Genome

nature biotechnology

LETTERS

Published online August 10, 2009

# Single-molecule sequencing of an individual human genome

Dmitry Pushkarev[1,2], Norma F Neff[1,2] & Stephen R Quake[1]

**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.**

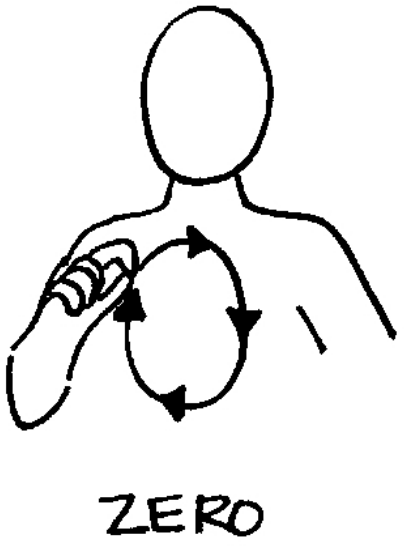
on a surface can be extended asynchronously, thereby allowing substantial flexibility in the kinetics of sequencing chemistry. Previous reports of single-molecule sequencing have been proofs of principle[11–13], and their sequencing throughput has not been competitive with alternative approaches. Generally, 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.

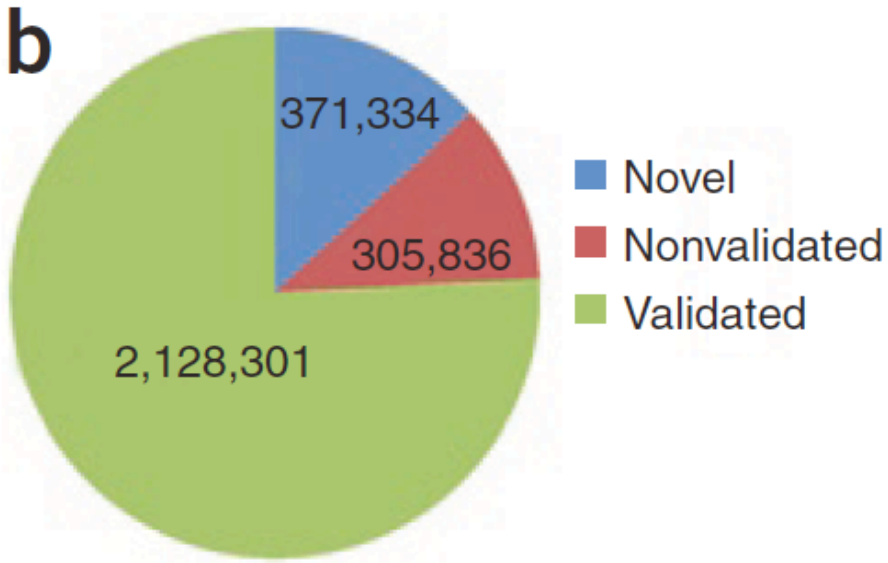
The Heliscope Single Molecule Sequencer (Helicos Biosciences) is the first commercial release of a single-molecule sequencing instrument. It allows one to follow ~1 billion individual molecules as they are sequenced over the course of a week—a throughput that is practical for human genome sequencing. There have been several technical improvements to the platform since the reported sequencing of a viral genome[12], 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.

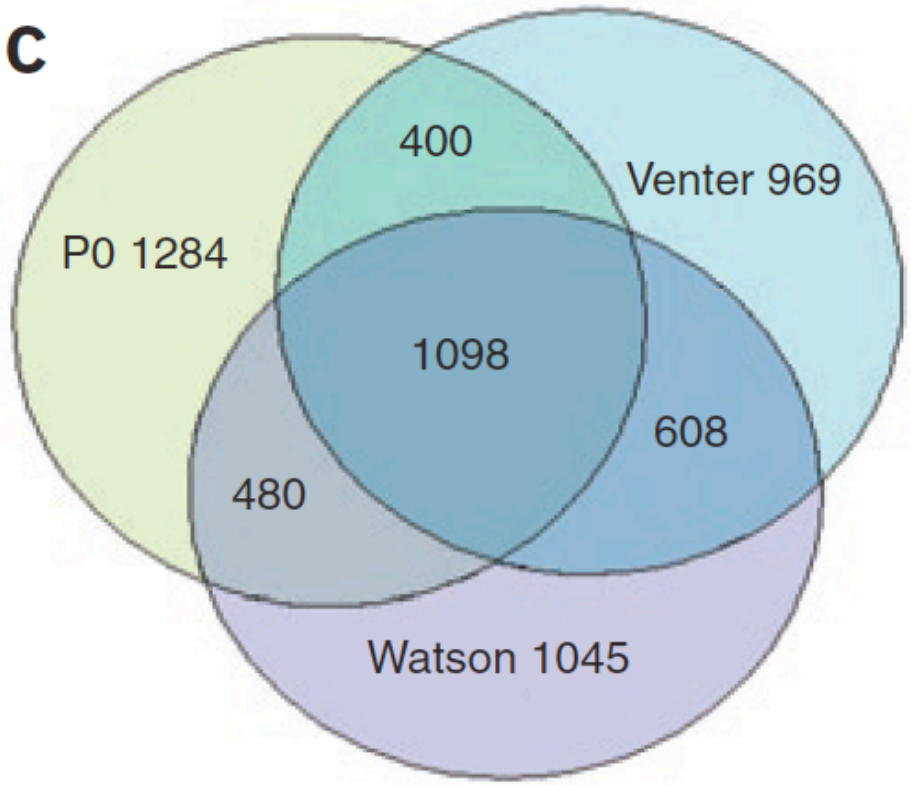
We used two of the instrument's 50 flow-cell channels to resequence the *Staphylococcus aureus* genome as a calibration of sequencer perfor-

# 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



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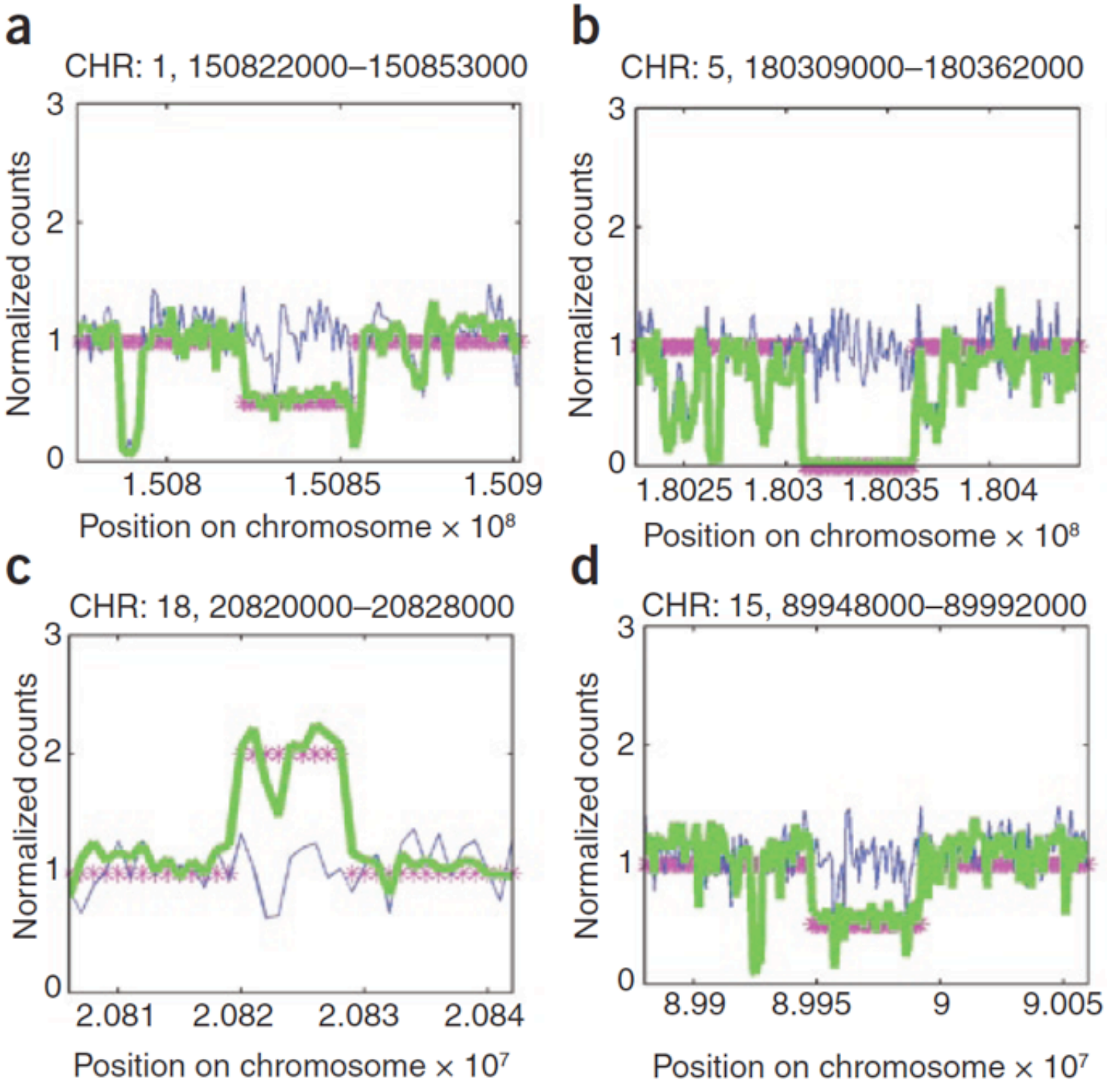
a
CHR: 1, 150822000–150853000
Normalized counts
0
1
2
3
1.508
1.5085
1.509
Position on chromosome × 10^8
b
CHR: 5, 180309000–180362000
Normalized counts
0
1
2
3
1.8025
1.803
1.8035
1.804
Position on chromosome × 10^8
c
CHR: 18, 20820000–20828000
Normalized counts
0
1
2
3
2.081
2.082
2.083
2.084
Position on chromosome × 10^7
d
CHR: 15, 89948000–89992000
Normalized counts
0
1
2
3
8.99
8.995
9
9.005
Position on chromosome × 10^7

# 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)

# Variant annotation highlight

- 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...

# Summary of Pharmacogenetic Bad News

| Drug | Summary | Level of Evidence | PMID | Gene | rsID |
|---|---|---|---|---|---|
| Clopidogrel & CYP2C19 substrates | CYP2C19 poor metabolizer, many drugs may need adjustment. | High | 19106084 | CYP2C19 | rs4244285 |
| Warfarin | Requires lower dose | High | 15888487 | VKORC1 | rs9923231 |
| Warfarin | Requires lower dose | High | 19270263 | CYP4F2 | rs2108622 |
| Metformin | Less likely to respond | Medium | 18544707 | CDKN2A/B | rs10811661 |
| Troglitazone | Less likely to respond | Medium | 18544707 | CDKN2A/B | rs10811661 |
| Cisplatin | Increased risk of nephrotoxicity | Low | 19625999 | SLC22A2 | rs316019 |
| Citalopram | May increase risk of suicidal ideation during therapy | Low | 17898344 | GRIA3 | rs4825476 |
| Escitalopram; Nortriptyline | Depression may not respond as well | Low | 19365399 | NR3C1 | rs10482633 |
| Morphine | May require higher dose for pain relief | Low | 17156920 | COMT | rs4680 |
| Paclitaxel | Cancer may respond less well | Low | 18836089 | ABCB1 | rs1045642 |
| Pravastatin | May require higher dose | Low | 15116054 | SLCO1B1 | rs2306283 |
| Talinolol | May require higher dose | Low | 18334920 | ABCC2 | rs2273697 |
| Sildenafil | May not respond as well | Low | 12576843 | GNB3 | rs5443 |

# Summary of Pharmacogenetic Good News

| Drug | Summary | Level of Evidence | PMID | Gene | rsID |
|---|---|---|---|---|---|
| HMG CoA Reductase Inhibitors (statins) | No increased risk of myopathy | High | 18650507 | SLCO1B1 | rs4149056 |
| Statins | No increased risk of myopathy | High | 12811365 | SLCO1B1 | rs4149056 |
| Desipramine; Fluoxetine | Depression may improve more than average | Medium | 19414708 | BDNF | rs61888800 |
| Fluvastatin | Good response | Medium | 18781850 | SLCO1B1 | rs11045819 |
| Metoprolol and other CYP2D6 substrates | Normal CYP2D6 metabolizer. | Medium | 19037197 | CYP2D6 | rs3892097/ rs1800716 |
| Pravastatin | May have good response | Medium | 15199031 | HMGCR | rs17238540 |
| Pravastatin, Simvastatin | No reduced efficacy | Medium | 15199031 | HMGCR | rs17244841 |
| Caffeine | No increased risk of heart problems with caffeine | Low | 16522833 | CYP1A2 | rs762551 |
| Calcium channel blockers | No increased risk of Torsades de Pointe | Low | 15522280 | KCNH2 | rs36210421 |
| Carbamazepine | SNP is part of protective haplotype for hypersensitivity to carbamazepine | Low | 16538175 | HSPA1A | rs1043620 |
| Neviraprine | Reduced risk of hepatoxicity | Low | 16912957 | ABCB1 | rs1045642 |
| Efavirenz; Nevirapine | Reduced risk of hepatoxicity | Low | 16912956 | ABCB1 | rs1045642 |
| Epoetin Alfa | Lower dose of iron and epo required | Low | 18025780 | HFE | rs1799945 |
| Fexofenadine | Average blood levels expected | Low | 11503014 | ABCB1 | rs1045642 |
| Irbesartan | Irbesartan may work better than beta-blocker | Low | 15453913 | APOB | rs1367117 |
| Lithium | Increased likelihood of response | Low | 18408563 | CACNG2 | rs5750285 |
| Paroxetine | May have improved response | Low | 17913323 | ABCB1 | rs2032582 |
| Pramipexole | More likely to respond | Low | 19396436 | DRD3 | rs6280 |
| Pravastatin | No reduced efficacy | Low | 15226675 | SLCO1B1 | rs4149015 |

# 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

# Novel nonsynonymous damaging SNPs

| SNP_loc | Ref | pt0 | Coding | PK/ PD? | Gene | related drugs |
|---|---|---|---|---|---|---|
| 1:33251518 | G | CG | H191D | **PK** | AK2 | **adefovir dipivoxil; tenofovir;** |
| 16:49303700 | G | AG | V793M | PD | CARD15 | **infliximab;** |
| 12:54774480 | C | CT | H578Y | PD | ERBB3 | **trastuzumab; erlotinib; gefitinib; lapatinib; PHA-665752; chloroquine; cisplatin; gemcitabine; cetuximab;** |
| 3:124923809 | T | AA | I485F | PD | MYLK | **mercaptopurine; methotrexate;** |
| 13:98176691 | T | CT | Y21C | **PK** | SLC15A1 | **atorvastatin; fluvastatin; hmg coa reductase inhibitors; lovastatin; pravastatin; rosuvastatin; simvastatin;** |
| 9:86090799 | G | AG | S443F | **PK** | SLC28A3 | **cladribine; fludarabine; uridine; mercaptopurine; thioguanine; antineoplastic agents; gemcitabine; azathioprine; folic acid;** |
| 20:32342227 | G | AG | P246L | PD | AHCY | **antimetabolites; mercaptopurine; methotrexate; adenosine; antineoplastic agents; azathioprine; folic acid; thioguanine;** |
| 16:49302615 | C | CT | S431L | PD | CARD15 | **infliximab;** |
| 6:32593811 | G | TT | T262K | PD | HLA-DRB5 | **clozapine;** |
| 6:31484467 | T | CT | I14T | PD | MICA | **mercaptopurine; methotrexate;** |
| 11:62517376 | C | CT | R534Q | **PK** | SLC22A8 | **cimetidine; estrone; antiinflammatory and antirheumatic products, non-steroidals; hmg coa reductase inhibitors;; adefovir dipivoxil; tenofovir; antineoplastic agents; cyanocobalamin; folic acid; leucovorin; pyridoxine;** |
| 16:31012227 | C | CT | G64R | | VKORC1 | **warfarin** |

## Important Limitations of our analysis

- For CNVs and novel SNPs only looked at PharmGKB "VIP" genes
  - We have drug pathways suggesting many other genes, though perhaps not VIPs
- Level of evidence varied widely even for variants that were previously studied
- Errors in sequence are always a concern
- Didn't use all information available in non-coding regions
- Most of these drugs not relevant to Pt 0… today

# Summary 1

- 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

# Summary 2

- Some problems of disease risk assessment are avoided with PGx.
- MD is involved in prescribing decision
- MDs are comfortable with considering many factors in prescribing
- Noisy, imprecise data is OK
- Bad decisions can be reversed
- Even for rare variants “caution, no idea” can be useful

Thanks!

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http://www.pharmgkb.org/

NIH GM61374

The Pharmacogenomics Knowledge Base = PharmGKB

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