Welcome to the PharmGKB Tutorial

PharmGKB (http://www.pharmgkb.org)

A comprehensive resource for pharmacogenomics

Curate knowledge about the impact of genetic variation on drug response with focuses on:

- **Clinical interpretation of variants associated with drug response**
- **Drug dosing guidelines, FDA labels and genetic tests**
- **Drug-centered pathways**
- **Very Important PGx gene (VIP) summaries**
- **Potentially clinically actionable gene-drug associations and genotype-phenotype relationships**

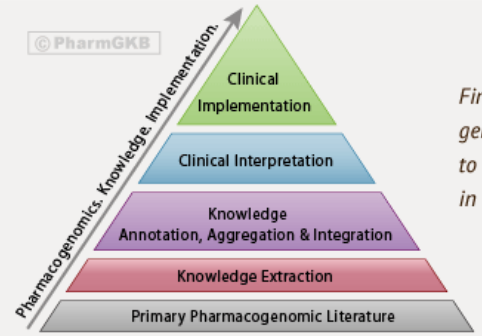
Welcome to the PharmGKB Tutorial

PharmGKB
The Pharmacogenomics Knowledgebase

Pharmacogenomics. Knowledge. Implementation.

PharmGKB is a comprehensive resource for pharmacogenomics that curates knowledge about the impact of genetic variation on drug response.

Search PharmGKB: Submit



What is the PharmGKB?

Find out how we go from extraction of gene-drug relationships in the literature to implementation of pharmacogenomics in the clinic...

Find out more

- PharmGKB Knowledge Pyramid
- CPIC: PGx Drug Dosing Guidelines
- Welcome To Our New Site Design
- Drug-Drug Interaction Adverse Events
- Tenofovir Pathway Update

Clinically-Relevant PGx

- Well-known PGx associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- Genetic tests for PGx
- Star (*) allele translations

find interpretations

hint: enter a gene, rsid, drug, disease

PGx-Based Drug Dosing Guidelines

- HLA-B/abacavir: article and supplement
- CPY2D6/codeine: article and supplement
- more guidelines...

CPIC Gene-Drug Pairs

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

PGx Research

- VIP: Very important pharmacogene summaries
- PharmGKB pathways
- Annotated SNPs by gene
- Drugs with genetic information

find PGx Research

hint: enter a gene, rsid, drug, disease

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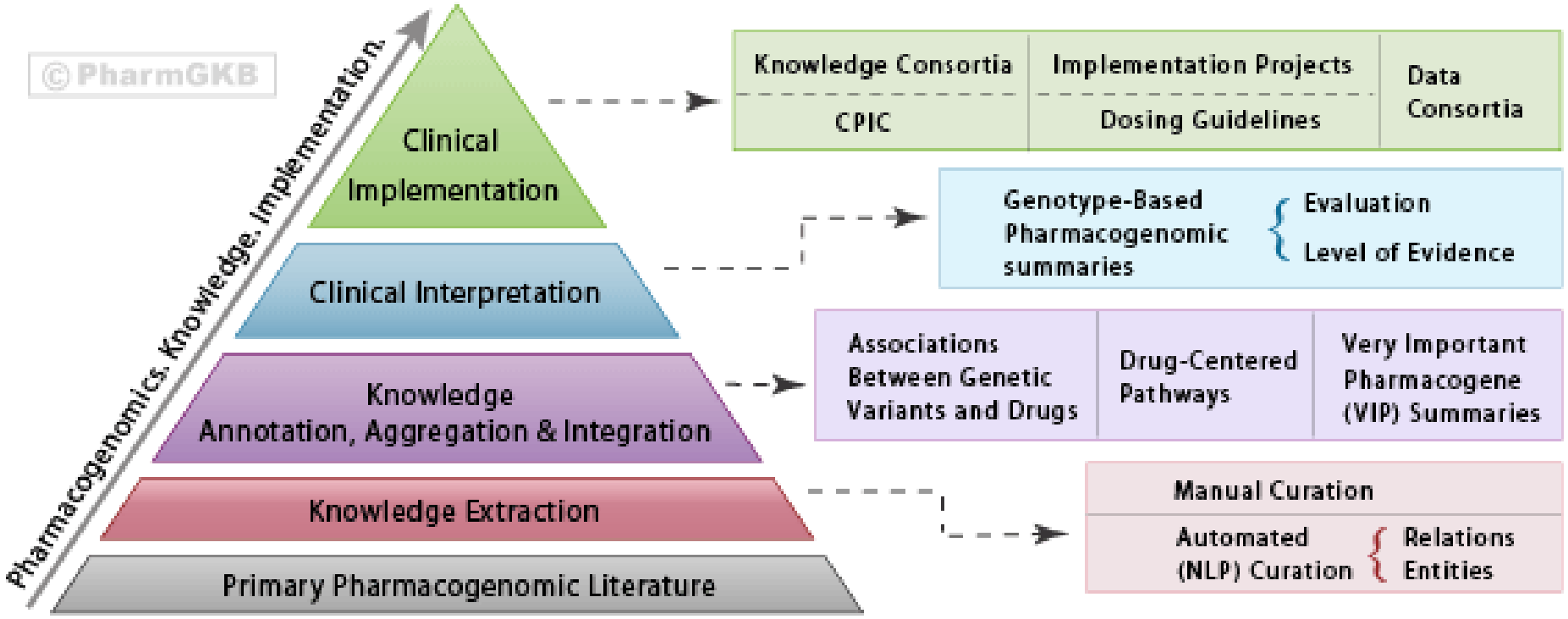
PharmGKB is a partner of the PGRN Pharmacogenomics Research Network

PharmGKB Knowledge Pyramid



PharmGKB
The Pharmacogenomics Knowledgebase

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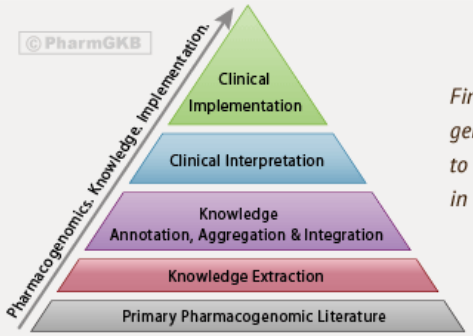

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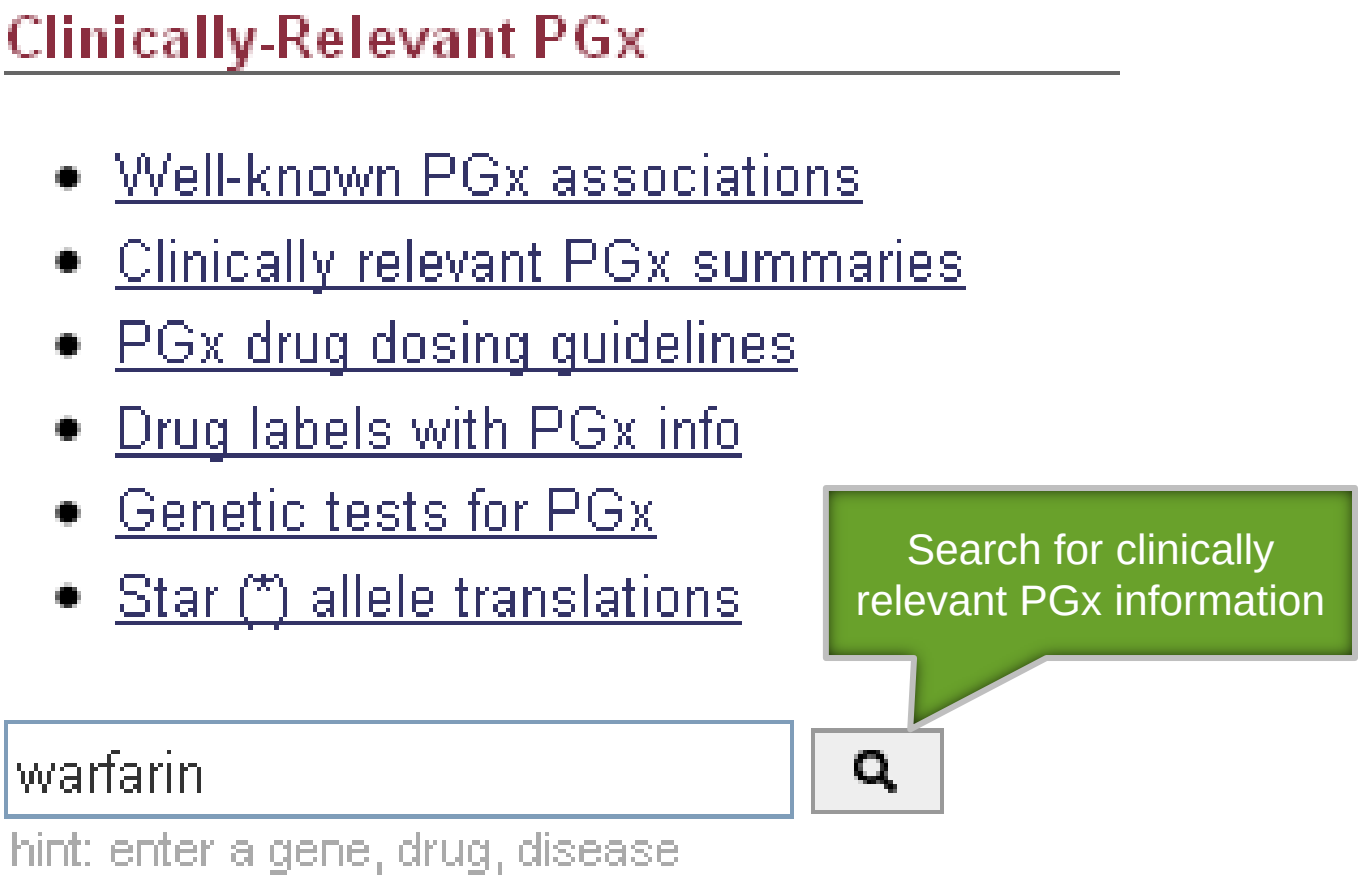
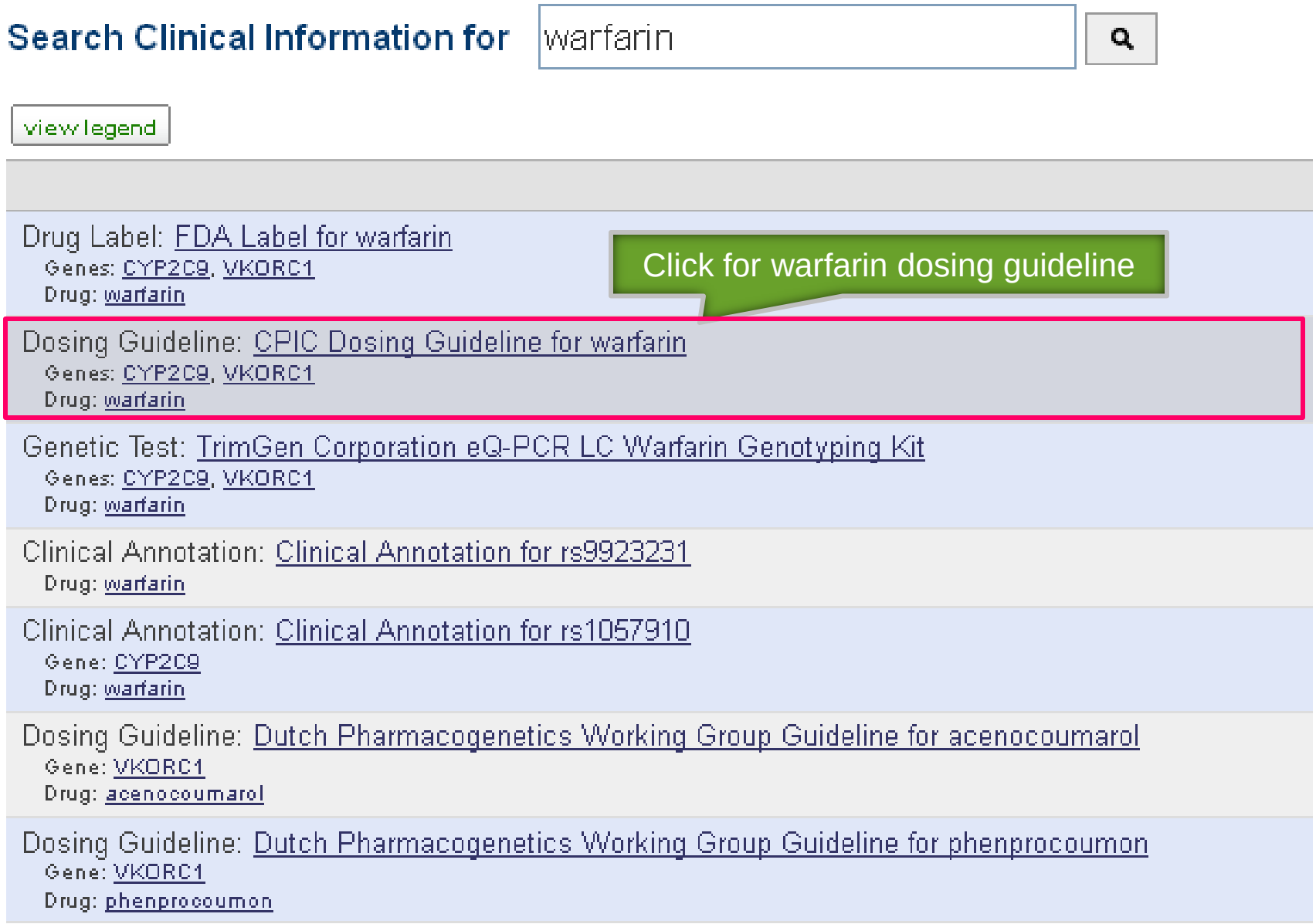
Clinically Relevant PGx



Clinical Information Associated with Warfarin Response



DRUG/SMALL MOLECULE:
warfarin

Clinical PGx | PGx Research | Overview | Pathways | Is Related To | Downloads/LinkOuts

Dosing Guidelines | Drug Labels | Clinical Annotations | Genetic Tests

CPIC Dosing Guideline - warfarin

Guidelines regarding the use of pharmacogenomic tests in dosing for warfarin have been published in Clinical Pharmacology and Therapeutics by the Clinical Pharmacogenetics Implementation Consortium (CPIC).

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing.
Julie A. Johnson, Li Gong, Michelle Whirl-Carrillo, Brian F. Gage, Stuart A. Scott, C., Michael Stein, Jeffrey L. Anderson, Stephen E. Kimmel, Ming Ta Michael Lee, Munir Pirmohamed, Mia Wadelius, Teri E. Klein, and Russ B. Altman.

Download: article and supplement

Pharmacogenetic algorithm-based warfarin dosing

Excerpt from the warfarin dosing guidelines:
Numerous studies have derived warfarin dosing algorithms that use both genetic and non-genetic factors to predict warfarin dose [Article:18305455, 19228618, 18574025]. Two algorithms perform well in estimating stable warfarin dose across different ethnic populations [Article:18305455, 19228618], and were created using more than 5000 subjects. Dosing algorithms using genetics outperform non-genetic clinical algorithms and fixed-dose approaches in dose prediction [Article:18305455, 19228618].

The best way to estimate the anticipated stable dose of warfarin is to use the algorithms available on http://www.warfarindosing.org (offering both high-performing algorithms [Article:18305455, 19228618]). Additionally, the dosing algorithm published by the International Warfarin Pharmacogenetics Consortium (IWPC) is also online at http://www.pharmgkb.org/do/serve?objId=PA162372936&objCls=Dataset#tabview=tab2.
The two algorithms provide very similar dose recommendations.

Download: IWPC Pharmacogenetic Dosing Algorithm

Approach to pharmacogenetic-based warfarin dosing without access to dosing algorithms

Excerpt from the warfarin dosing guidelines:
In 2007 the FDA modified the warfarin label stating that *CYP2C9* and *VKORC1* genotypes may be useful in determining the optimal initial dose of warfarin [Article:17906972]. The label was further updated in 2010 to include a table **(Table 1)** describing recommendations for initial dosing ranges for patients with different combinations of *CYP2C9* and *VKORC1* genotypes.

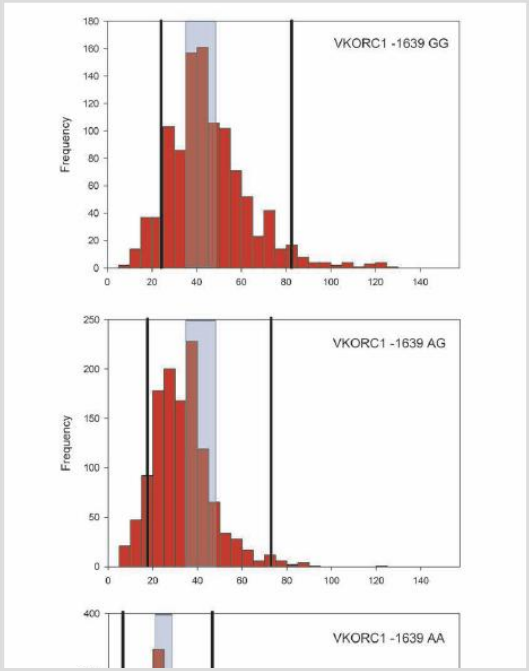


Table 1: Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1* genotype using the warfarin product insert approved by the Food and Drug Administration in the United States:

VKORC1 Genotype (-1639G>A, rs9923231)	CYP2C9*1/*1	CYP2C9*1/*2	CYP2C9*1/*3	CYP2C9*2/*2	CYP2C9*2/*3	CYP2C9*3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Reproduced from updated warfarin (Coumadin®) product label.

Supplemental Table S1. Genotypes that constitute the * alleles for *CYP2C9*

Allele	Constituted by genotypes at:	Amino acid changes	Enzymatic Activity
*1	reference allele at all positions		Normal
*2	C>T at rs1799853	R144C	Decreased
*3	A>C at rs1057910	I359L	Decreased

DRUG/SMALL MOLECULE:
warfarin

from search: warfarin

Clinical PGx

Click for FDA drug label

Click for clinical annotations

Dosing Guidelines | Drug Labels | Clinical Annotations | Genetic Tests

Information regarding PGx on FDA drug labels is derived from the FDA's Table of Pharmacogenomic Biomarkers in Drug Labels. Excerpts from the label and downloadable highlighted label PDFs are manually curated by PharmGKB

FDA Label - warfarin, CYP2C9, VKORC1

The FDA recommends genetic testing prior to initiating treatment with warfarin.

Excerpt from the warfarin drug label:

> The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants. Consider these ranges in choosing the initial dose.

The VKORC1:G-1639A polymorphism is associated with lower dose requirements for warfarin in Caucasian and Asian patients. Increased bleeding risk and lower initial warfarin dose requirements have been associated with the CYP2C9*2 and CYP2C9*3 alleles. Approximately 30% of the variance in warfarin dose could be attributed to genetic variation in VKORC1, and about 40% of dose variance could be explained taking into consideration both VKORC1 and CYP2C9 genetic polymorphisms. Accounting for genetic variation in both VKORC1 and CYP2C9, age, height, body weight, interacting drugs, and indication for warfarin therapy explained about 55% of the variability in warfarin dose.

For the complete drug label text with sections containing pharmacogenetic information highlighted, see the warfarin drug label. Pharmacogenomics-related dosing information is found in Table 5 on page 27.

DRUG/SMALL MOLECULE:
warfarin

Clinical PGx | PGx Research | Overview | Properties | Pathways | Is Related To | Publications | Downloads/LinkOuts

Dosing Guidelines | Drug Labels | Clinical Annotations | Genetic Tests

Clinical Variants that meet the highest level of criteria, manually curated by PharmGKB, are shown below. Please follow the link in the "Position" column for more information about a particular variant. Each link in the "Position" column leads to the corresponding PharmGKB Variant Page. The Variant Page ated information about variant-drug pairs based on individual PubMed publications. The PMIDs Page.

ck the button at the bottom of the table.

Click to see clinical annotation and variant specific info

Positi	Gene ?	Relevance ?	Strength of Evidence ?
rs1057910	CYP2C9	To see relevance please register or sign in.	1
rs9923231	PRSS53 VKORC1	To see relevance please register or sign in.	1

Show lower-evidence Clinical Annotations

Download a summary of all Clinical Annotations available.

Disclaimer: The PharmGKB's clinical annotations reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision-making and to identify questions for further research. New evidence may have emerged since the time an annotation was submitted to the PharmGKB. The annotations are limited in scope and are not applicable to interventions or diseases that are not specifically identified.

The annotations do not account for individual variations among patients, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. PharmGKB assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of the PharmGKB clinical annotations, or for any errors or omissions.

? = Mouse-over for quick help

Clinical annotation is a summary of the clinical impact of a genomic variant on drug response phenotype.

VARIANT:

rs1057910 at chr10:96741053 in CYP2C9 (VIP)

Alleles
A/C

Amino Acid Translation
Ile358Leu

Alternate Names:
c.1075A>C, g.47545517A>C, g.47639A>C, g.96731043A>C, p.Ile359Leu

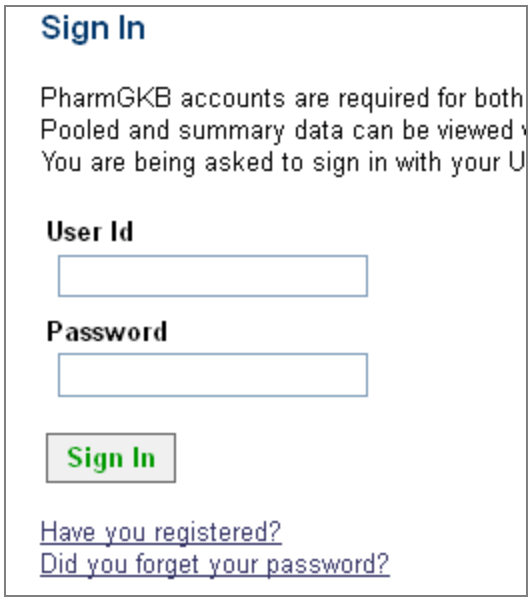
Haplotypes
This variant is used to determine: CYP2C9*3, CYP2C9*18

Clinical PGx | PGx Research | VIP | Downloads

User login required to view full clinical annotation

Clinical Annotations

To see the clinical annotation for this variant please register or sign in.



VARIANT:

rs1057910 at chr10:96741053 in CYP2C9 (VIP)

Alleles
A/C

Amino Acid Translation
Ile358Leu

Alternate Names:
c.1075A>C, g.475[illegible]

Haplotypes
This variant is used[illegible]

Click for article-level variant annotation

Clinical PGx | PGx Research | VIP | Downloads/LinkOuts

Clinical Annotations

PharmGKB clinical annotations provide information about variant-drug pairs based on a summary of the individual variant annotations in the database. Therefore, each clinical annotation could represent information from a single paper or multiple papers. The rating system used to assign "Strength of Evidence" levels is described here. Manually curated by PharmGKB.

All alleles are displayed on the positive chromosomal strand.

Strength of Evidence: Level 1

Drugs: warfarin

AA	Patients with the AA genotype: 1) may require an increased dose of warfarin as compared to patients with the AC or CC genotype 2) may have a decreased risk for adverse events as compared to patients with the AC or CC genotype. Patients with the AA genotype may still be at risk for adverse events when taking warfarin based on their genotype. Other genetic and clinical factors may also influence a patient's risk for adverse events.
AC	Patients with the AC genotype: 1) may require a decreased dose of warfarin as compared to patients with the AA genotype 2) may have an increased risk for adverse events as compared to patients with the AA genotype.
CC	Patients with the CC genotype: 1) may require a decreased dose of warfarin as compared to patients with the AA genotype 2) may have an increased risk for adverse events as compared to patients with the AA genotype.

Race: Unknown

Type: Dosage, Toxicity/ADR

VARIANT:

rs1057910 at chr10:96741053 in CYP2C9 (VIP)

Alleles
A/C

Amino Acid Translation
Ile359Leu

Alternate Names:
A>C, CYP2C9*3, CYP2C9*3:Ile359Leu, CYP2C9: I359L, CYP2C9:359Ile>Leu, CYP2C9:Ile359Leu, c.1075A>C, c.1075A>C, g.47545517A>C, g.47639A>C, g.96731043A>C, mRNA 11A>C, p.Ile359Leu, p.Ile359Leu

Haplotypes
This variant is used to determi

Important PGx gene summary

Clinical PGx | PGx Research | VIP | Downloads/LinkOuts

Variant Annotations

PharmGKB variant annotations provide information about variant-drug pairs based on individual PubMed publications. Therefore, each annotation represents information from a single paper and the goal is to report the information that the author states, not an interpretation of the paper. Manually curated by PharmGKB.

Genotype AA is associated with increased dose of warfarin in people with a stable therapeutic international normalized ratio between two and three as compared to g

[stat_test: AN

Click to go to the original article

Associated Drugs: warfarin

Evidence: 21383771

Study Size (cases/controls)	Allele Frequency	OMB Race Category ?	Population Characteristics	Association P-value
248 /		Asian	Disease: Stable INR 2-3	1.61E-4

Paper Discusses:

PD

VARIANT:

rs1057910 at chr10:96741053 in CYP2C9 (VIP)

VIP: Very Important Pharmacogene Summary

Alleles (on + chromosomal strand)

A > T
A > C
A > G

Amino Acid Translation

Ile359Leu

Alternate Names:

CYP2C9*3, CYP2C9*3:Ile359Leu, CYP2C9: I359L, CYP2C9:359Ile>Leu, CYP2C9:Ile359Leu, c.1075A>C, g.47545517A>C, g.47639A>C, g.96731043A>C, mRNA 11A>C, p.Ile359Leu

Haplotypes

This variant is used to determine: CYP2C9*3, CYP2C9*18

Clinical PGx | PGx Research | VIP | Is Related To | Publications | Downloads/LinkOuts

VIP Variant in CYP2C9

The variant at this position is the defining allele for the *CYP2C9*3* haplotype. Other variant positions delineate between haplotypes in the *3 series (see http://www.imm.ki.se/CYPalleles for defining website), but a C allele at this position defines a *CYP2C9*3* haplotype. For further information about the *CYP2C9*3* haplotype see the Haplotype page.

The catalytic activity of the *3 haplotype is significantly reduced for most CYP2C9 substrates because of both an increase in Km and a reduction in Vmax [Articles:11927841, 15637526, 14597963].
Leu/Leu homozygotes have lower metabolic activity for CYP2C9 substrates in general, including tolbutamide and phenytoin [Article:10761997]. However, much of the supporting data are from *in-vitro* studies and homozygous individuals are rare [Article:19082874]. In other studies, it has been found that heterozygotes have about half the clearance as wild-type, for the following drugs: S-warfarin, tolbutamide, fluvastatin, glimepiride, tenoxicam, candesartan, celecoxib, phenytoin [Article:15637526].
The clearance of S-ibuprofen is reduced in *CYP2C9*3/*3* homozygotes compared with wild-type homogozygotes [Article:15289789]. In *in-vivo* studies, the *CYP2C9*3* haplotype in heterozygote subjects has been associated with a lower clearance and longer half-life of flurbiprofen [Article:12698304].

Population	N subjects	Allele Frequency of "C"	PMID
Chinese (Shanghai)	394	0.036	[Article:12803577]
Korean	574	0.011	[Article:11298075]
Japanese	147	0.007	[Article:16111713]
Japanese	140	0.054	[Article:9631918]

DRUG/SMALL MOLECULE:
warfarin

Click for pathway (PK, PD)

Clinical PGx | PGx Research | Overview | Properties | Pathways | Is Related To | Downloads/LinkOuts

PharmGKB Curated Pathways

Pathways created internally by PharmGKB based primarily on literature evidence.

1. Warfarin Pathway, Pharmacodynamics
   Simplified diagram of the target of warfarin action and downstream genes and effects.

2. Warfarin Pathway, Pharmacokinetics
   Representation of the candidate genes involved in transport, metabolism and clearance of warfarin

External Pathways

Links to non-PharmGKB pathways.

PharmGKB contains no links to external pathways for this drug. To report a pathway, click here.

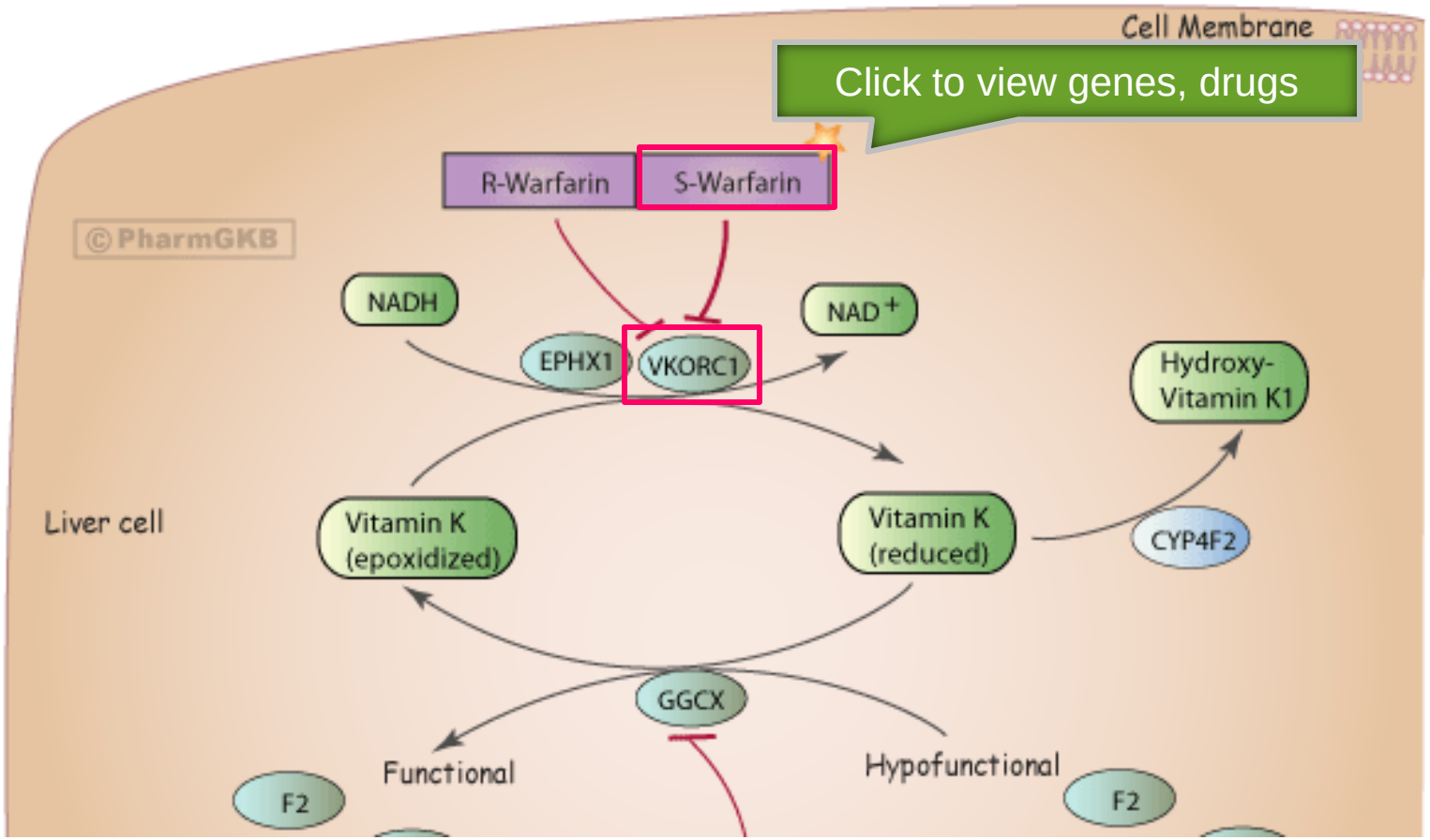
PATHWAY:

Warfarin Pathway, Pharmacodynamics [UNDER REVIEW]

Overview | Components | Related Pathways | Downloads/LinkOuts

Pharmacodynamics

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



The PharmGKB Knowledge Pyramid

Posted: 3/6/112

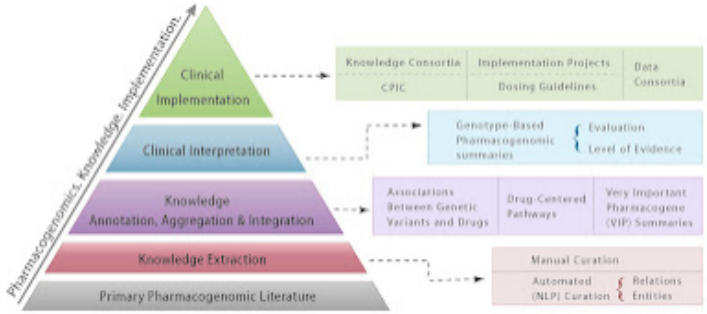


Figure 1: The PharmGKB Knowledge Pyramid. A visual representation of the information available at www.pharmgkb.org and the research by the PharmGKB team.

The PharmGKB Knowledge Pyramid (**Figure 1**) provides users with a visualization of the different types of information found in our knowledge base and, how this information is acquired and integrated together – from the accumulation of gene-drug knowledge at the bottom of the pyramid, to the implementation of pharmacogenomics in the clinic at the top. Each step of the pyramid is described here on our website: [Link].

The Clinical Pharmacogenetics Implementation Consortium (CPIC)

Posted: 3/6/112

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

The **Clinical Pharmacogenetics Implementation Consortium (CPIC)** was established in order to provide

PGx in the News

- ALK Mutation Testing for NSCLC on the Rise among Oncologists, BioTrends Survey Finds
- HTG, Sanofi Collaborating to Identify B-Cell Response Markers for Cancer Drug
- With Large Study, Interleukin Hopes to Drive Adoption

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PharmGKB Preview
Pharmacogenomics. Knowledge. Implementation.

Downloads and Web Services

All downloaded data is available for individual research purposes only, and may NOT be redistributed.

Downloads / PharmGKB Accession Ids

- Genes: genes.zip (3 MB, last updated on 4/6/12)
- Drugs: drugs.zip (323 KB, last updated on 4/6/12)
- Diseases: diseases.zip (261 KB, last updated on 4/6/12)
- Relationships: relationships.zip (358 KB, last updated on 4/6/12)
- RSID mapping: rsid.zip (92 MB, last updated on 4/6/12)
- Pathways (in BioPAX format): pathways-biopax.zip (804 KB, last updated on 4/6/12)
- Pathways (in tsv format): pathways-tsv.zip (119 KB, last updated on 4/6/12)

Variant and clinical annotations: Please read and agree to the PharmGKB Data Usage Agreement to receive variant and clinical annotations, these files may not be redistributed.
See list of groups who have downloaded these annotations.

Web Services

A selected subset of data from PharmGKB is accessible via a SOAP interface:

1. Search Service
   - WSDL
   - API
2. Variant Cross-Reference Service
   - WSDL
   - API
3. PharmGKB Data Service
   - WSDL
   - API

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