PharmGKB

Pharmacogenomics Knowledge Base

Pharmacogenomics Knowledge for Personalized Medicine

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PharmGKB
Pharmacogenomics Knowledge Base

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

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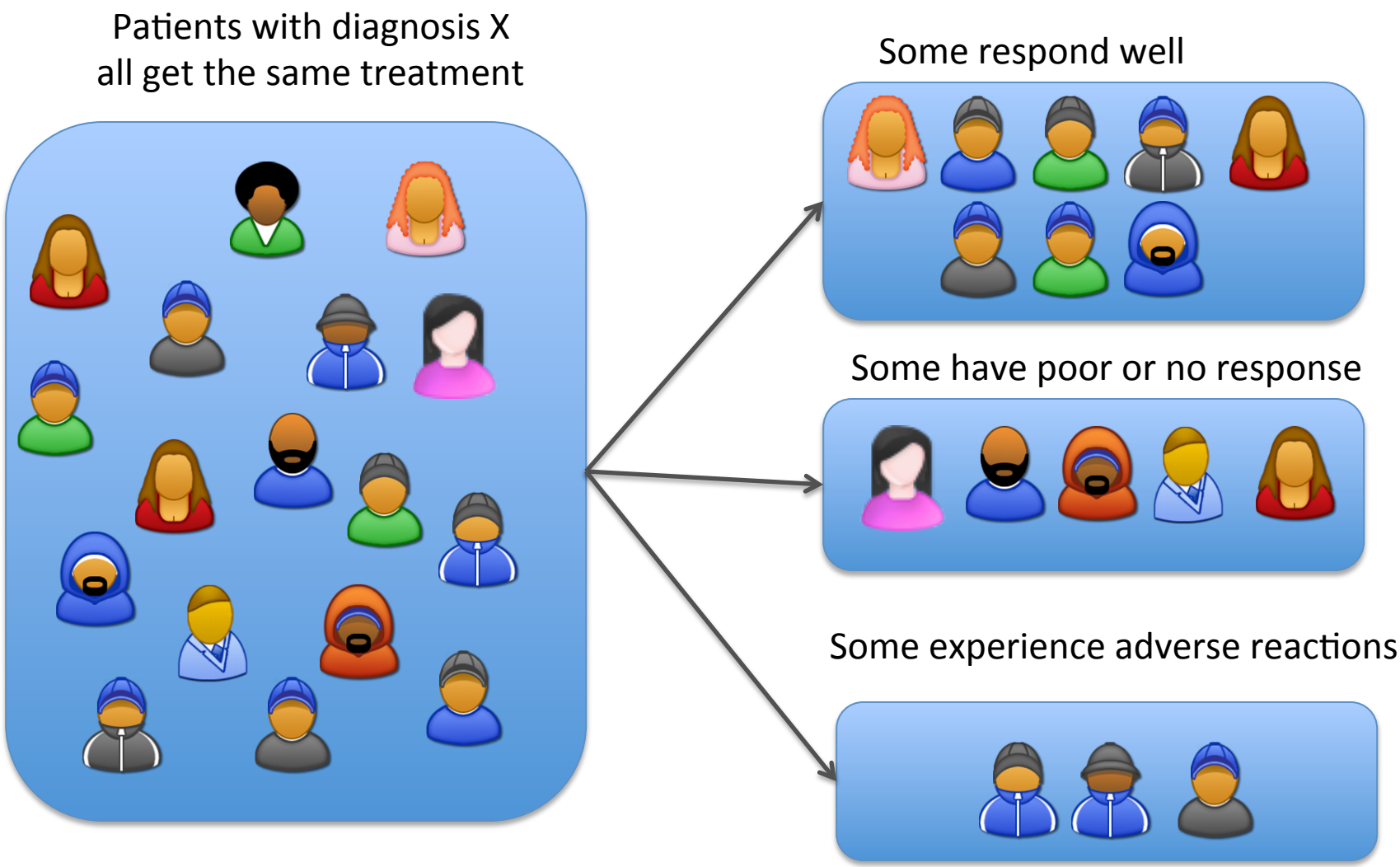
Overview

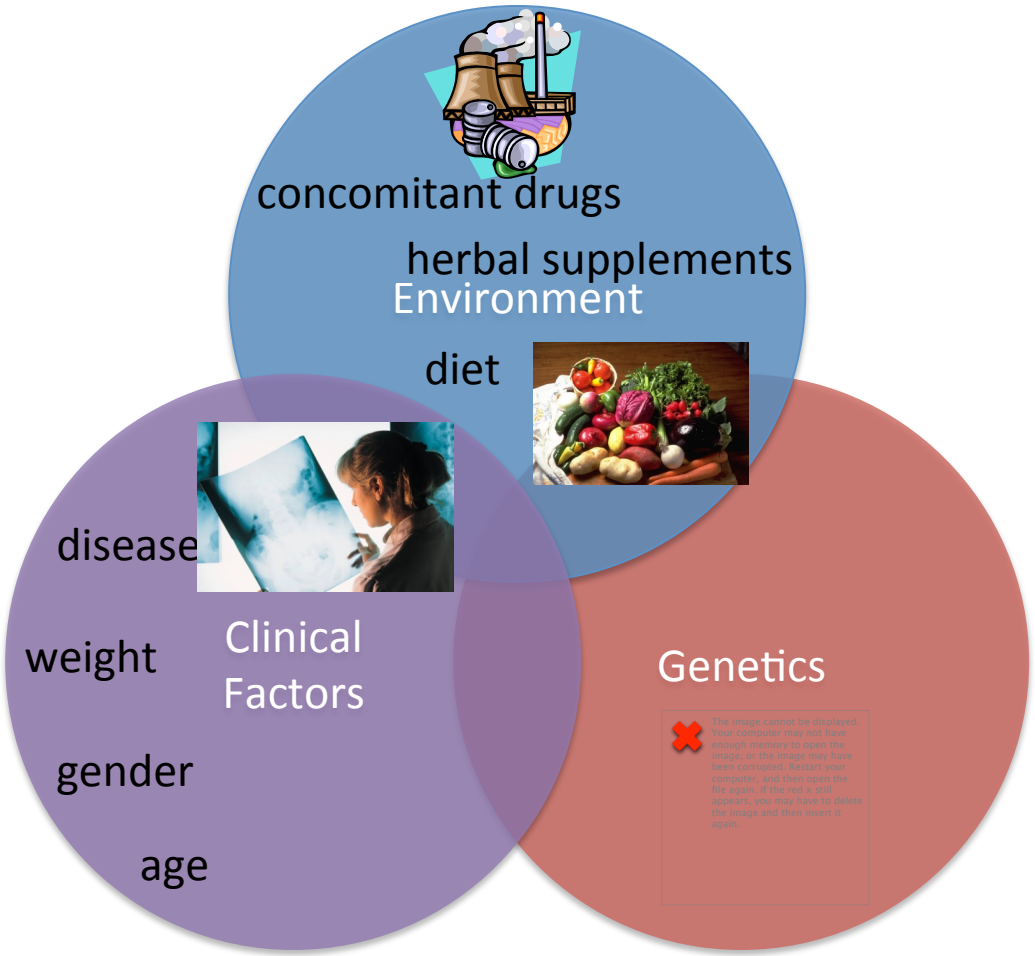
PGx Knowledge → Implementation → Impact

1. PharmGKB and resources for PGx
2. Clinical PGx Implementation
3. Does PGx truly have a role in personalized medicine?

Variation in Drug Response



Factors Affecting Drug Response



Clinical Applications of PGx

- Focus treatment by identifying patients with genetic backgrounds likely to respond
- Reduce adverse events by predicting who is at risk
- Potential to save drugs in the pipeline that are effective in subpopulations
- Better understanding of drug interactions

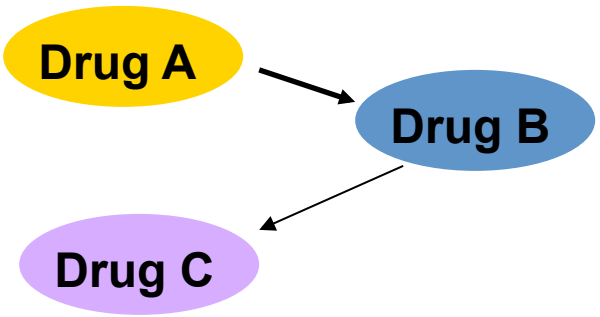
Definitions

- Pharmacogenetics: study of individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response (SIMPLE relationship)
- Pharmacogenomics: study of genomic influence on drug response, often using high-throughput data (sequencing, SNP chip, expression, proteomics) (COMPLEX interactions)

Clinical Promises of PGx

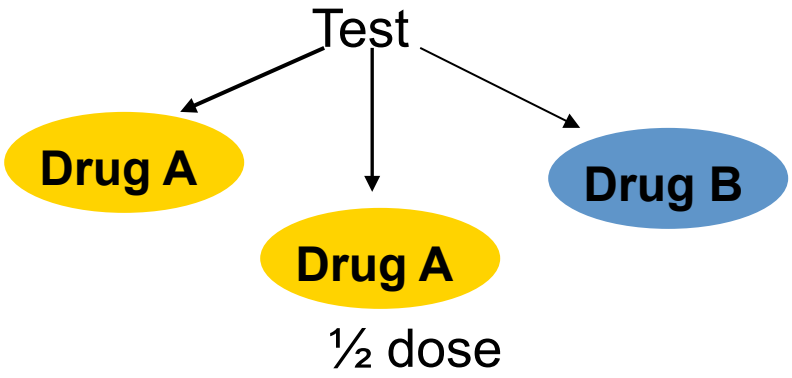
- Personalized Medicine: Selecting the right dose of the right drug to the right patient at the right time

Today:
- empirical selection of drug



- Efficacy may vary widely
- Adverse effects are common & unpredictable

Future:
- Genetically guided drug and dose selection



- Avoid adverse drug reactions
- Maximize drug efficacy
- Select responsive patients

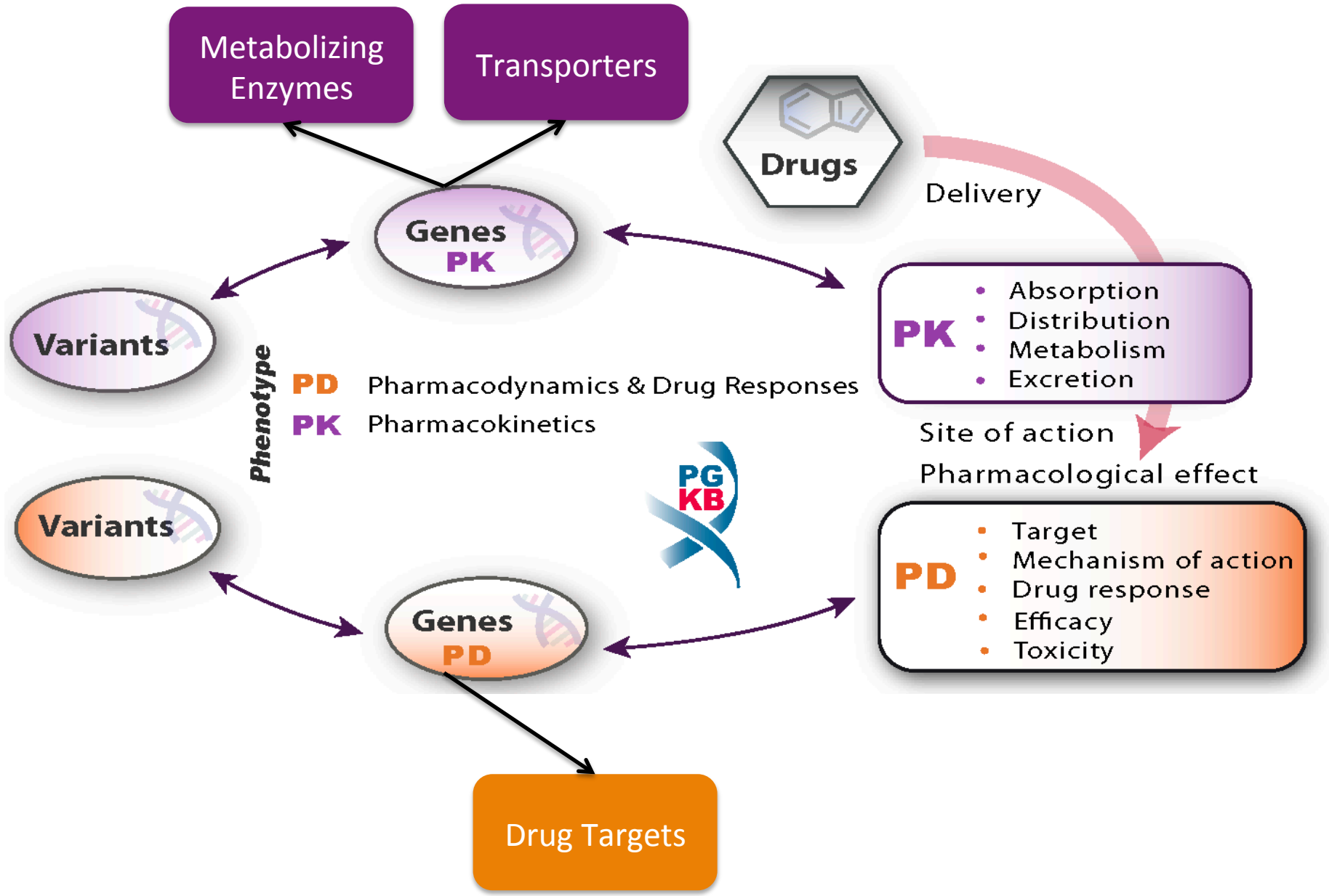
PharmGKB Content & Activities

- **Mission**
  - Collect, encode and disseminate knowledge about the impact of human genetic variation on drug response

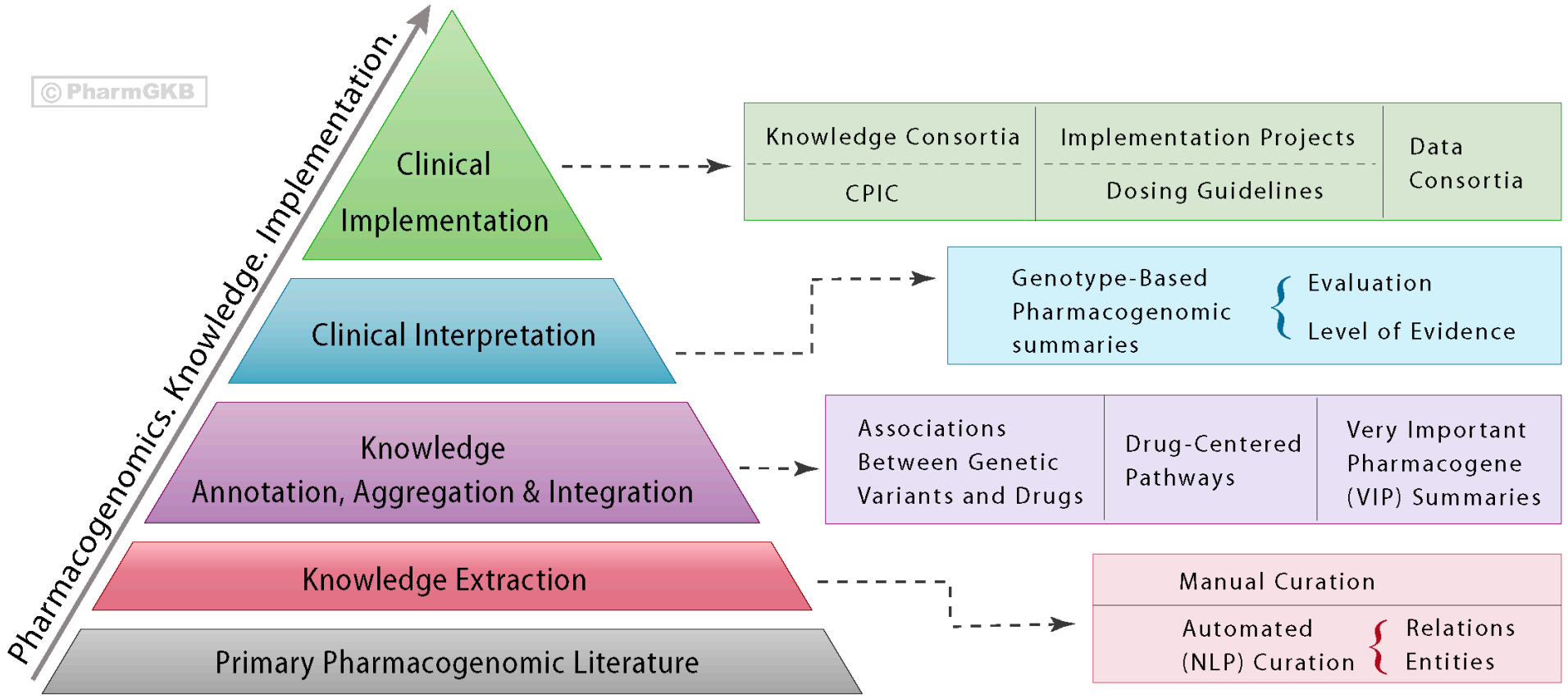
- **Research**
  - Manual curation of PGx literature
  - Drug-centered pathways
  - Important PGx gene summaries

- **Implementation**
  - Clinical summaries of PGx variants
  - Drug label annotations
  - CPIC guidelines
  - PGx data consortia (IWPC, ITPC, etc.)
  - Genome annotations

Pharmacogenetics Information Flow



PharmGKB Knowledge Pyramid



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PharmGKB
The Pharmacogenomics Knowledgebase

Pharmacogenomics. Knowledge. Implementation.

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

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Clinically-Relevant PGx

- Well-known PGx associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- Genetic tests for PGx
- PGx gene haplotypes

find interpretations
hint: enter a gene, drug, rsid, disease

PGx-Based Drug Dosing Guidelines

- IFNL3 (IL28B)/pegIntron and ribavirin: article and supplement
- DPYD/capecitabine, 5FU and tegafur: article and supplement
- See all CPIC guidelines
- CPIC gene-drug pairs of interest
- TPP gene tables

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

PGx Research

- VIP: Very Important PGx gene summaries
- View PharmGKB pathways
  - Alphabetically
  - By therapeutic category
- Annotated SNPs by gene
- Drugs with genetic information

find PGx Research
hint: enter a gene, rsid, drug, disease

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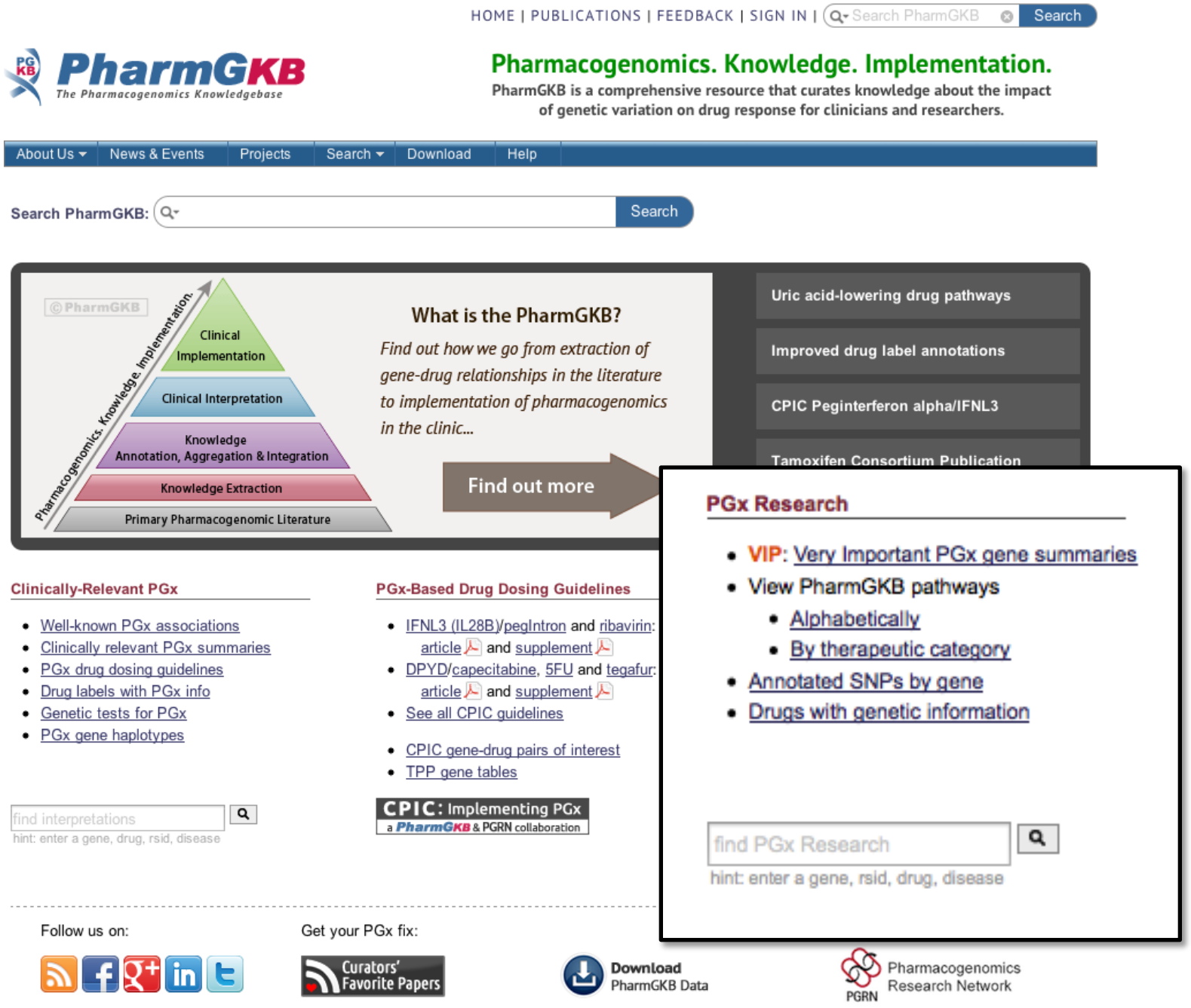

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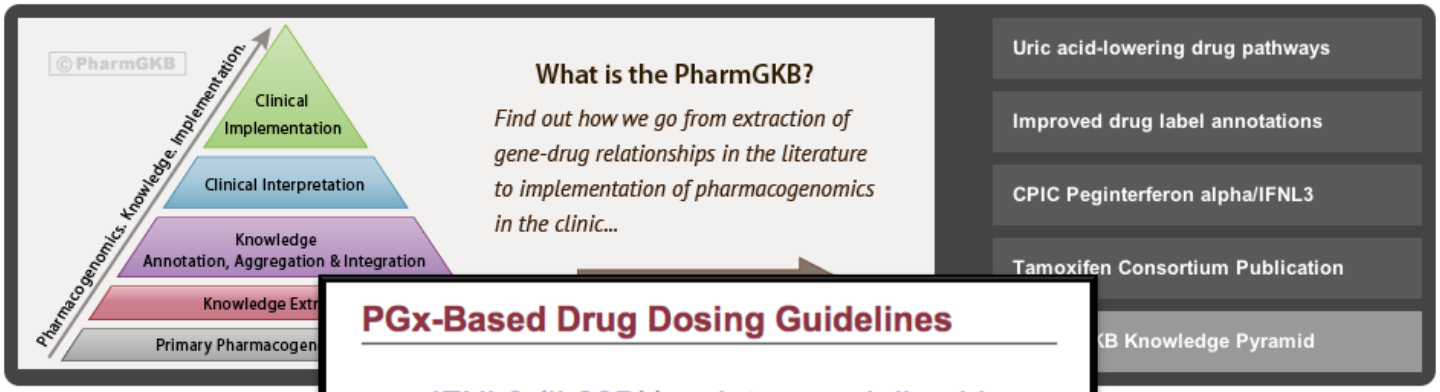

PGx-Based Drug Dosing Guidelines

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Clinically-Relevant PGx

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- Important PGx gene summaries
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- abetically
- erapeutic category
- d SNPs by gene
- n genetic information

arch
e, rsid, drug, disease

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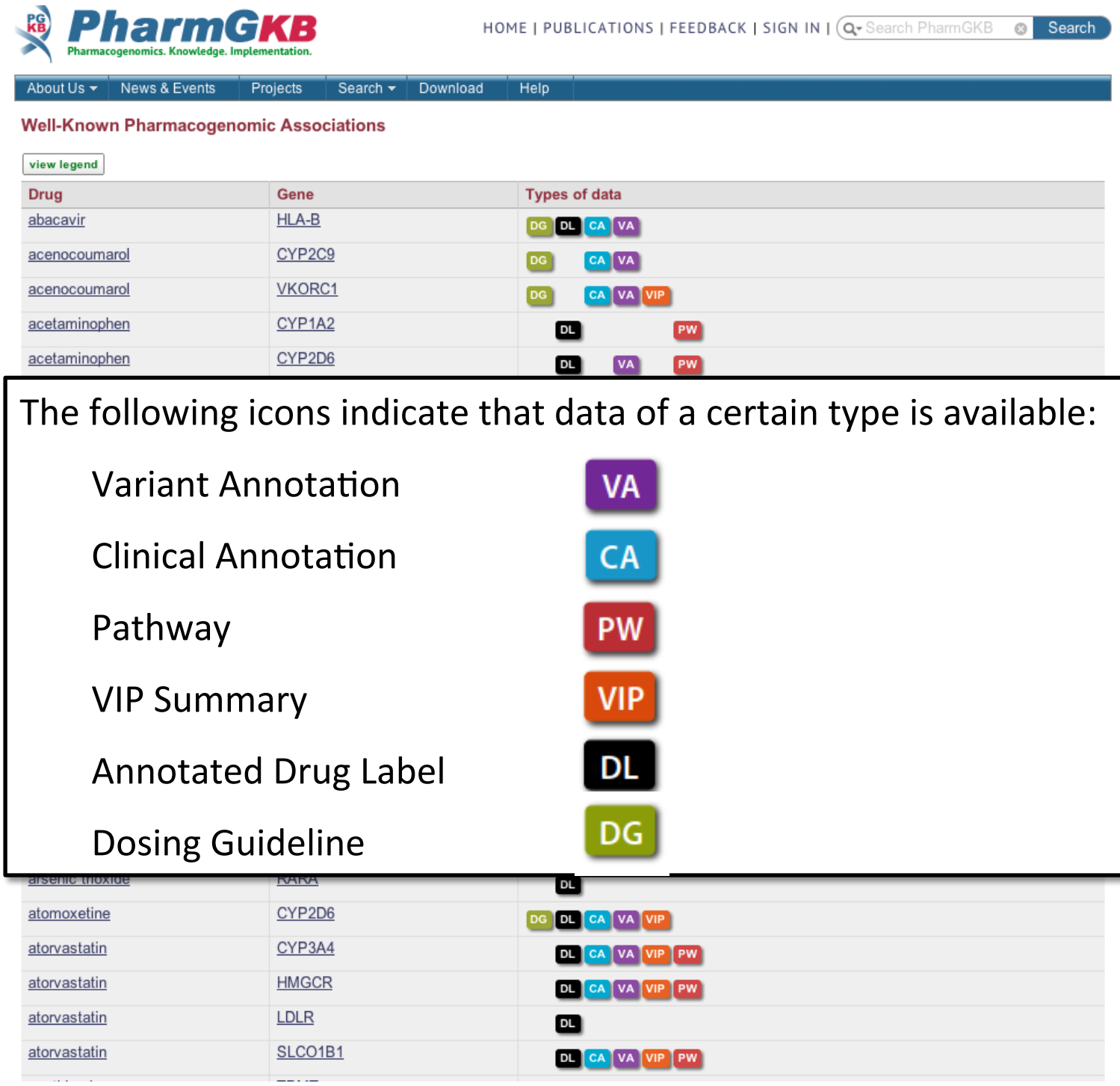
Well-Known Pharmacogenomic Associations

view legend

Drug	Gene	Types of data
abacavir	HLA-B	DG DL CA VA
acenocoumarol	CYP2C9	DG CA VA
acenocoumarol	VKORC1	DG CA VA VIP
acetaminophen	CYP1A2	DL PW
acetaminophen	CYP2D6	DL VA PW
acetaminophen	CYP2E1	DL VA VIP PW
acetaminophen	CYP3A4	DL PW
afatinib	EGFR	DL VIP
allopurinol	HLA-B	DG CA VA
amitriptyline	CYP2C19	DG CA VA VIP
amitriptyline	CYP2D6	DG DL CA VA VIP
anastrozole	ESR1	DL
anastrozole	ESR2	DL
anastrozole	PGR	DL
aripiprazole	CYP2D6	DG DL CA VA
aripiprazole	CYP3A4	DL VIP
aripiprazole	HTR1A	DL
aripiprazole	HTR2A	DL
arsenic trioxide	PML	DL
arsenic trioxide	RARA	DL
atomoxetine	CYP2D6	DG DL CA VA VIP
atorvastatin	CYP3A4	DL CA VA VIP PW
atorvastatin	HMGCR	DL CA VA VIP PW
atorvastatin	LDLR	DL
atorvastatin	SLCO1B1	DL CA VA VIP PW



DRUG/SMALL MOLECULE:
warfarin

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

Dosing Guidelines (1) | Drug Labels (1) | Clinical Annotations (37) | Genetic Tests (18)

CPIC Dosing Guideline for warfarin and CYP2C9, VKORC1

last updated 12/18/2013

Summary

The best way to estimate the anticipated stable dose of warfarin is to use the algorithms available on http://www.warfarindosing.org

Annotation

CPIC guideline authors are aware of several recently published studies on warfarin pharmacogenetics [Articles:24251361, 24251363, 24251360]. These papers have prompted several opinion pieces [Articles:24328463, 24251364]. The authors are evaluating the information, which will be incorporated into the next update of the CPIC guideline on warfarin.

Look up your warfarin dosing guideline using the IWPC Pharmacogenetic Dosing Algorithm.

This dosing recommendation applies to adults only. Please see below for full details of these guidelines, with supporting evidence and disclaimers.

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 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. Clinical Pharmacology & Therapeutics (2011) Oct;90(4):625-629.

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 [Articles:18305455, 19228618, 18574025]. Two algorithms perform well in estimating stable warfarin dose across different ethnic populations; [Articles:18305455, 19228618] these were created using more than 5,000 subjects. Dosing algorithms using genetics outperform nongenetic clinical algorithms and fixed-dose approaches in dose prediction [Articles: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 [Articles:18305455, 19228618]). The dosing algorithm published by the International Warfarin Pharmacogenetics Consortium 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

DRUG/SMALL MOLECULE:
warfarin

Clinical PGx | PGx Research | Click for FDA | Click for clinical annotations | kOuts

Dosing Guidelines (1) | **Drug Labels (1)** | **Clinical Annotations (37)** | **Genetic Tests (18)**

PharmGKB gathers information regarding PGx on FDA drug labels from the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels", and from FDA-approved FDA and EMA-approved (European Medicines Agency) EMA labels brought to our attention. Excerpts from the label and downloadable highlighted label PDFs are manually curated by PharmGKB.

Please note that some drugs may have been removed from or added to the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels" without our knowledge. We periodically check the table for additions to this table and update PharmGKB accordingly.

There is currently no such list for European drug labels - we are working with the EMA to establish a list of European Public Assessment Reports (EPAR)s that contain PGx information. We are constructing this list by initially searching for drugs for which we have PGx-containing FDA drug labels - of these 44 EMA EPARs were identified and are being curated for pgx information.

We welcome any information regarding drug labels containing PGx information approved by the FDA, EMA or other Medicine Agencies around the world - please contact feedback.

view legend

FDA Label for warfarin and CYP2C9, VKORC1 *last updated 10/25/2013*

This label is on the **FDA Biomarker List**

Actionable PGx

Summary

Warfarin *(Coumadin)* is an anticoagulant used as a prophylaxis and to treat venous thrombosis, pulmonary embolism, thromboembolic complications from atrial fibrillationa and cardiac valve replacement, and to reduce the recurrence of myocardial infarction. The FDA recommends genetic testing for CYP2C9 and VKORC1 variants prior to initiating treatment with warfarin.

Annotation

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.

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.

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.

*Disclaimer: The contents of this page have not been endorsed by the FDA and are the sole responsibility of PharmGKB.

Full label available at DailyMed

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

DRUG/SMALL MOLECULE:
warfarin

Clinical PGx | PGx Research | Overview | Properties | Pathways | Is Related To | Publications

Strength based on:
- Implementation
- Statistics
- Replications
- Population size

Dosing Guidelines (1) | Drug Labels (1) | Clinical Annotations (37) | Genetic Tests (18)

Clinical Variants that meet the highest level of criteria, manually curated by PharmGKB, are shown below.

To see more Clinical Variants with lower levels of criteria, click the button at the bottom of the page.

Clinical Annotation for rs1799853 in CYP2C9 and warfarin

Level of Evidence what's this?
Level 1A

Type
Dosage

Genes
CYP2C9

OMB Race
Mixed Population

Race Notes
white, black, asian

User ID
jhebert

CC	Patients with the CC genotype who are treated with warfarin may require a higher dose as compared to patients with the CT or TT genotype. Other genetic and clinical factors may also influence a patient's dose of warfarin.
CT	Patients with the CT genotype who are treated with warfarin may require a lower dose as compared to patients with the CC genotype. Other genetic and clinical factors may also influence a patient's dose of warfarin.
TT	Patients with the TT genotype who are treated with warfarin may require a lower dose as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patient's dose of warfarin.

▾ Show Evidence ▾

1. CYP2C9 *2 + *3 is associated with decreased dose of warfarin as compared to CYP2C9 *1.
Patients carrying at least one copy of the CYP2C9 *2 or *3 alleles needed significantly lower doses of warfarin and also showed significantly greater variability in dose as compared to patients with the wildtype *1/*1 genotype.
PMID:22990331 Annotation Page

Study Size	Frequency	Race	Population Characteristics	P-value	Ratio	Type
206 /	0.129 *2 / 0.032 *3	Brazilian	Drug: warfarin	< .03		prospective

VARIANT:
rs4149056 at 12:21331549 in SLCO1B1 (VIP)

update from dbSNP

Alleles (on + chromosomal strand)
T > C

Amino Acid Translation
Val174Ala

Alternate Names:
14091673T>C, 21331549T>C, 521T>C, 52422T>C, SLCO1B1*5, Val174Ala

Haplotypes
Variant allele present in: SLCO1B1*5, SLCO1B1*15, SLCO1B1*17

Variant annotation lists impact of a genomic variant on drug response phenotype based on individual publication

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

Variant Annotations

PharmGKB variant annotations provide information about variant-drug pairs or variant-disease pairs based on individual PubMed publications. 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. The PMID for supporting PubMed publications is found in the "Evidence" field.

Information presented, including study size, allele frequencies and statistics is taken directly from the publication. However, if the author does not correct p-values in cases of multiple hypotheses, curators may apply a Bonferroni correction. Curators attempt to report study size based on the actual number of participants used for the calculation of the association statistics, so the number may vary slightly from what is reported in the abstract of the paper. OMB Race Category information is derived from the paper and mapped to standardized categories. Category definitions may be found by clicking on the "OMB Race Category" link.

Add filter: pick column

PMID	Drug	Sentence	Significance	pValue	# of Cases	Race
21878834	mycophenolate mofetil	Allele T is not associated with increased incidence of diarrhea when treated with mycophenolate mofetil in people with Kidney Transplantation as compared to allele C.	no	0.654	338	
21878834	mycophenolate mofetil	Allele T is not associated with increased risk of developing leukopenia when treated with mycophenolate mofetil in people with Kidney Transplantation as compared to allele C.	no	0.395	338	

DRUG/SMALL MOLECULE:
warfarin

Click for pathway (PK, PD)

Clinical PGx | PGx Research | Overview | Properties | Pathways | Is Related To | Publications | 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.

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Browse Pathways by Therapeutic Categories

Table of Contents

Browse alphabetically.

126 PK and PD pathways

Anti-infective agents (7)

- Abacavir Pathway, Pharmacokinetics/Pharmacodynamics
- Amodiaquine Pathway, Pharmacokinetics
- Artemisinin and Derivatives Pathway, Pharmacokinetics
- Lamivudine Pathway, Pharmacokinetics/Pharmacodynamics
- Nevirapine Pathway, Pharmacokinetics
- Tenofovir/Adefovir Pathway, Pharmacokinetics
- Zidovudine Pathway, Pharmacokinetics/Pharmacodynamics PubMed

Anticancer agents (33)

- Antimetabolite Pathway - Folate Cycle, Pharmacodynamics
- Aromatase Inhibitor Pathway (Breast Cell), Pharmacodynamics
- Aromatase Inhibitor Pathway (Multiple Tissues), Pharmacodynamics PubMed
- Busulfan Pathway, Pharmacodynamics
- Cyclophosphamide Pathway, Pharmacodynamics
- Cyclophosphamide Pathway, Pharmacokinetics
- Doxorubicin Pathway (Cancer Cell), Pharmacodynamics PubMed
- Doxorubicin Pathway (Cardiomyocyte Cell), Pharmacodynamics PubMed
- Doxorubicin Pathway, Pharmacokinetics PubMed
- EGFR Inhibitor Pathway, Pharmacodynamics
- Erlotinib Pathway, Pharmacokinetics
- Etoposide Pathway, Pharmacokinetics/Pharmacodynamics PubMed
- Fluoropyrimidine Pathway, Pharmacodynamics PubMed
- Fluoropyrimidine Pathway, Pharmacokinetics PubMed
- Gefitinib Pathway, Pharmacokinetics

GENE:
CYP2C19
cytochrome P450, family 2, subfamily C, polypeptide 19

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

Introduction
The cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19) gene is located within a cluster of cytochrome P450 genes (Centromere-CYP2C18-CYP2C19-CYP2C9-CYP2C8-Telomere) on chromosome 10q23.33. The CYP2C19 enzyme contributes to the metabolism of a large number of clinically relevant drugs and drug classes such as antidepressants [Article:15199661], benzodiazepines [Article:8148870], mephenytoin [Article:8195181], proton pump inhibitors (PPIs) [Article:15258107], and the antiplatelet prodrug clopidogrel [Article:16772608]. Like other CYP450 genes, inherited genetic variation in *CYP2C19* and its variable hepatic expression contributes to interindividual phenotypic variability in CYP2C19-substrate metabolism. The *CYP2C19* "poor metabolism" phenotype was initially discovered by studies on impaired mephenytoin metabolism and the major molecular defect responsible for the trait is the *CYP2C19**2 (c.681G>A; rs4244285) loss-of-function allele [Article:8195181]. *CYP2C19* genotype has since been shown to affect the metabolism of several drugs and clinical *CYP2C19* genetic testing is currently available [Article:21716271, 21412232].

Expression
CYP2C19 is predominantly expressed in the liver and, to a lesser extent, in the small intestine [Article:10487415]. Constitutive expression of CYP2C19 is largely mediated by hepatic nuclear factors 4 alpha (HNF4alpha, HNF4A) and 3 gamma (HNF3gamma, FOXA3) [Article:17827783, 17576804, 15130783], and transcriptional activation is mediated by the drug responsive nuclear receptors CAR (NR1I3), PXR (NR1I2), and GRalpha (NR3C1) [Article:12869636, 11181490], suggesting regulation by endogenous hormones and by drugs such as rifampicin [Article:2223426, 20086032]. In addition to rifampicin, human CYP2C19 can be induced by ritonavir, nelfinavir, hyperforin, St. John's wort, dexamethasone, and artemisinin [Article:19702536]. *In vitro* expression studies have recently shown that the GATA-4 (GATA4) transcription factor also upregulates CYP2C19 transcriptional activity by binding to two predicted GATA-specific promoter elements [Article:20206639]. Reduced CYP2C19 activity among women using steroid oral contraceptives results from transcriptional down-regulation of CYP2C19 expression through binding of ligand-activated estrogen receptor alpha to a specific ERE consensus half-site in the CYP2C19 promoter [Article:20675569].

Certain selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, fluvoxamine) [Article:18691982, 8880055] and PPIs (e.g. omeprazole, and lansoprazole) [Article:11309556, 9433390, 9224780] have an inhibitory effect on CYP2C19, which may cause drug-drug interactions with co-administered CYP2C19-metabolized drugs. For example, early studies suggested that omeprazole (a common PPI) diminished the pharmacodynamic antiplatelet effects of clopidogrel and increased corresponding cardiovascular risks [Article:19258584, 18206732]. However, it is currently not clear if identified changes in *ex vivo* platelet aggregation due to concomitant omeprazole and clopidogrel administration translates into clinically meaningful outcome differences (for review see [Article:21126648]).

Clinical CYP2C19 Pharmacogenetic Testing
Although a number of genotyping technologies can be used to interrogate variant CYP2C19 alleles in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories, two genotyping platforms have been approved by the U.S. Food and Drug Administration (FDA) at the time of this writing: the AmpliChip,Â® CYP450 Test (Roche Molecular Systems, Inc., Pleasanton, CA) that interrogates *CYP2C19**2 and *3 (plus *CYP2D6* variant alleles) and the Infiniti,Â® CYP2C19 Assay (AutoGenomics, Inc., Vista, CA) that interrogates *CYP2C19**2, *3, and *17. For test interpretation and clopidogrel dosing suggestions, see the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *CYP2C19* genotype and clopidogrel therapy [Article:21716271]. Additionally, a recent clinical pharmacogenetics practice review provides dosing guidelines for clopidogrel and other CYP2C19-metabolized drugs [Article:21412232] and *CYP2C19/CYP2D6* genotype-based antidepressant dosing recommendations have been previously reported [Article:11531654].

Citation PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 19. *Pharmacogenetics and genomics*. 2011. Scott Stuart A, Sangkuhl Katrin, Shuldiner Alan R, Hulot Jean-Sébastien, Thorn Caroline F, Altman Russ B, Klein Teri E. PubMed

Browse VIP Genes

The following icons indicate that data of a certain type is available:

- DG Dosing Guideline information is available
- DL Drug Label information is available
- CA High-level Clinical Annotation is available
- VA Variant Annotation is available
- VIP VIP information is available
- PW Pathway is available

[close]

Result: 50

VA VIP	ABCB1 PGx Summary ATP-binding cassette, sub-family B (MDR/TAP), member 1
VA VIP	ACE PGx Summary angiotensin I converting enzyme (peptidyl-dipeptidase A) 1
VA VIP	ADH1A PGx Summary alcohol dehydrogenase 1A (class I), alpha polypeptide
VA VIP	ADH1B PGx Summary alcohol dehydrogenase 1B (class I), beta polypeptide
VA VIP	ADH1C PGx Summary alcohol dehydrogenase 1C (class I), gamma polypeptide
VA VIP	ADRB1 PGx Summary adrenoceptor beta 1
DL VA VIP	ADRB2 PGx Summary adrenoceptor beta 2, surface
VA VIP	AHR PGx Summary aryl hydrocarbon receptor
VA VIP	ALDH1A1 PGx Summary aldehyde dehydrogenase 1 family, member A1
VA VIP	ALOX5 PGx Summary arachidonate 5-lipoxygenase
VIP	BRCA1 PGx Summary breast cancer 1, early onset
VA VIP	COMT PGx Summary catechol-O-methyltransferase
DL VA VIP	CYP1A2 PGx Summary cytochrome P450, family 1, subfamily A, polypeptide 2
VA VIP	CYP2A6 PGx Summary cytochrome P450, family 2, subfamily A, polypeptide 6
VA VIP	CYP2B6 PGx Summary cytochrome P450, family 2, subfamily B, polypeptide 6
DG DL CA VA VIP	CYP2C19 PGx Summary cytochrome P450, family 2, subfamily C, polypeptide 19
VA VIP	CYP2C8 PGx Summary cytochrome P450, family 2, subfamily C, polypeptide 8
DG DL CA VA VIP	CYP2C9 PGx Summary cytochrome P450, family 2, subfamily C, polypeptide 9

50 VIPs

GENE:
CYP2C19

cytochrome P450, family 2, subfamily C, polypeptide 19

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

Haplotype Overview

The Translational Pharmacogenetics Project (TPP) is a PGRN-led initiative with the goal to operationalize the work of CPIC by translating widely accepted actionable pharmacogenetics discoveries into real-world clinical practice. Download the TPP file for CYP2C19 here: CYP2C19 lookup table *(updated 11th July 2013)*.

Haplotypes are derived from the Human Cytochrome P450 (CYP) Allele Nomenclature Database. The Human Cytochrome P450 (CYP) Allele Nomenclature Database states that nucleotide changes listed below are based on NCBI Reference Sequence NT_030059.13. Note that the nucleotide positions from the Human Cytochrome P450 (CYP) Allele Nomenclature Database do not directly match the given NCBI reference sequence. For questions about nucleotide positions, please contact the Human Cytochrome P450 (CYP) Allele Nomenclature Database directly, as they are the authoritative source on cytochrome P450 nomenclature.

PharmGKB has added some alleles below (e.g. the rows for *1 and *2), inserted for star alleles with subgroups (e.g. A, B etc). These rows reflect only the defining SNP for the star allele to accommodate how the star allele is referred to in the literature.

Source: PharmGKB

- CYP2C19*1 (reference haplotype)
- CYP2C19*1A
- CYP2C19*1B
- CYP2C19*1C
- CYP2C19*2
- CYP2C19*2A
- CYP2C19*2B
- CYP2C19*2C
- CYP2C19*2D
- CYP2C19*3
- CYP2C19*3A
- CYP2C19*3B
- CYP2C19*4
- CYP2C19*4A
- CYP2C19*4B
- CYP2C19*5
- CYP2C19*5A
- CYP2C19*5B
- CYP2C19*6
- CYP2C19*7
- CYP2C19*8
- CYP2C19*9

Download Translation Table

Downloadable index tables map SNPs/variants to * allele nomenclature

Additional Resources in PGx

- **Genes and variants:**
  - **NCBI dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/)**
  - **Entrez GENE (http://www.ncbi.nlm.nih.gov/sites/entrez)**
  - **UCSC genome browser (http://genome.ucsc.edu/cgi-bin/hgGateway)**
  - **CYP allele nomenclature committee (http://www.cypalleles.ki.se/)**
  - **HuGE Navigator (http://hugenavigator.org/)**

- **Drugs:**
  - **DrugBank (http://www.drugbank.ca/)**
  - **NCBI PubChem (http://pubchem.ncbi.nlm.nih.gov/)**
  - **KEGG (http://www.genome.jp/kegg/ligand.html)**
  - **Drug interaction table (http://www.medicine.iupui.edu/flockhart/table.htm)**

- **Pharmacogenomics Biomarkers for approved drugs at FDA**
  - **http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm**

Summary: PharmGKB and resources for PGx

- PGx - variation in genetics impacts drug response
- Drug efficacy and safety can be improved via genome-informed drug use
- Non-genetic factors (environment, life style) are also important
- PharmGKB curates knowledge about the impact of human genetic variation on drug response and its clinical implementation
- Long term goal: *genome-informed drug use that increases efficacy and decreases side effects*

Overview:

PGx Knowledge → Implementation → Impact

1. PharmGKB and resources for PGx

2. Clinical PGx Implementation (Moving from PharmGKB to the Clinic)

3. Does PGx truly have a role in personalized medicine?

Moving from PharmGKB to the Clinic

- Clinical applications of the pharmacogenomics data and knowledge in the PharmGKB include:
  - Data-centric Consortia (PharmGKB-PGRN initiated)
  - Knowledge-centric Consortia
    - Practical guidelines for pharmacogenomics in the clinic

- Clinical Annotation of Human Genomes

Data-centric Consortia

PharmGKB is a broker of pharmacogenomic data for data sharing consortia

- International Warfarin Pharmacogenetics Consortium (IWPC) and the International Warfarin Pharmacogenetics Consortium - Genome Wide Association Studies (IWPC-GWAS)
  - devoted to pooling genotype and phenotype data relevant to the anticoagulant warfarin
- International Tamoxifen Pharmacogenomics Consortium (ITPC)
  - gather genetic and clinical data on the efficacy and toxicity of tamoxifen from around the world to test for specific associations between genetic variants and clinical effects

- International SSRI Pharmacogenomics Consortium (ISPC)
  - Discover new genetic variants that are important for predicting response of depression to SSRIs using genome wide association studies (GWAS)
- International Clopidogrel Pharmacogenomics Consortium (ICPC)
  - Discover additional common and rare gene variants associated with clopidogrel response through GWAS and other genome-wide approaches
- International Consortium for Antihypertensives Pharmacogenomics Studies (ICAPs)
  - Advance the pharmacogenomics of antihypertensive drugs by facilitating collaboration between research groups, and by amassing large samples sizes for GWAS meta-analyses

Success of the IWPC & ITPC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 19, 2009 VOL. 360 NO. 8

Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium*

Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study

Minoli A Perera*, Larisa H Cavallari*, Nita A Limdi*, Eric R Gamazon, Anuar Konkashbaev, Roxana Daneshjou, Anna Pluzhnikov, Dana C Crawford, Jelai Wang, Nianjun Liu, Nicholas Tatonetti, Stephane Bourgeois, Harumi Takahashi, Yukiko Bradford, Benjamin M Burkley, Robert J Desnick, Jonathan L Halperin, Sherief I Khalifa, Taimour Y Langaee, Steven A Lubitz, Edith A Nutescu, Matthew Oetjens, Mohamed H Shahin, Shitalben R Patel, Hersh Sagreiya, Matthew Tector, Karen E Weck, Mark J Rieder, Stuart A Scott, Alan H B Wu, James K Burmester, Mia Wadelius, Panos Deloukas, Michael J Wagner, Taisei Mushiroda, Michiaki Kubo, Dan M Roden, Nancy J Cox, Russ B Altman, Teri E Klein, Yusuke Nakamura, Julie A Johnson

Lancet 2013; 382: 790–96
Published Online June 5, 2013

Summary

Background *VKORC1* and *CYP2C9* are important contributors to warfarin dose variability, but explain less variability for individuals of African descent than for those of European or Asian descent. We aimed to identify additional variants contributing to warfarin dose requirements in African Americans.

THROMBOSIS AND HEMOSTASIS

Warfarin pharmacogenetics: a single *VKORC1* polymorphism is predictive of dose across 3 racial groups

Nita A. Limdi[1], Mia Wadelius[2], Larisa Cavallari[3], Niclas Eriksson[4], Dana C. Crawford[5], Ming-Ta M. Lee[6], Chien-Hsiun Chen[6], Alison Motsinger-Reif[7], Hersh Sagreiya[8], Nianjun Liu[1], Alan H. B. Wu[9], Brian F. Gage[10], Andrea Jorgensen[11], Munir Pirmohamed[11], Jae-Gook Shin[12], Guilherme Suarez-Kurtz[13], Stephen E. Kimmel[14], Julie A. Johnson[15,*], Teri E. Klein[8,*], Michael J. Wagner[16,*], on behalf of the International Warfarin Pharmacogenetics Consortium

Clinical Pharmacology & Therapeutics advance online publication 18 December 2013; doi: 10.1038/clpt.2013.186

CYP2D6 Genotype and Adjuvant Tamoxifen: Meta-Analysis of Heterogeneous Study Populations

OPEN

M A Province[1], M P Goetz[2], H Brauch[3], D A Flockhart[4], J M Hebert[5], R Whaley[5], V J Suman[6], W Schroth[3], S Winter[3], H Zembutsu[7], T Mushiroda[8], W G Newman[9], M-T M Lee[10], C B Ambrosone[11], M W Beckmann[12], J-Y Choi[13], A-S Dieudonné[14], P A Fasching[12,15], R Ferraldeschi[9], L Gong[5], E Haschke-Becher[16], A Howell[17], L B Jordan[18], U Hamann[19], K Kiyotani[8], P Krippl[20], D Lambrechts[21], A Latif[9], U Langsenlehner[20], W Lorizio[22], P Neven[23], A T Nguyen[4], B-W Park[24], C A Purdie[18], P Quinlan[25], W Renner[20], M Schmidt[3,26], M Schwab[27], J-G Shin[28,29], J C Stingl[30], P Wegman[31], S Wingren[31], A H B Wu[32], E Ziv[22], G Zirpoli[11], A M Thompson[25], V C Jordan[33], Y Nakamura[7], R B Altman[5,34], M M Ames[35], R M Weinshilboum[35], M Eichelbaum[3], J N Ingle[36] and T E Klein[5] ; on behalf of the International Tamoxifen Pharmacogenomics Consortium

Knowledge-centric Consortia: Moving To The Clinic

Create, curate, review, and update written summaries and recommendations for implementing specific pharmacogenomic tests

- Clinical Pharmacogenetics Implementation Consortium (CPIC)
  - Use well-defined evidence criteria and evaluation
  - Published on the PharmGKB website

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network

MV Relling[1] and TE Klein[2]

The slow rate at which pharmacogenetic tests are being adopted in clinical practice is partly due to the lack of specific guidelines on how to adjust medications on the basis of the genetic test results. One of the goals of the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health's Pharmacogenomics Research Network (http://www.pgrn.org) and the Pharmacogenomics Knowledge Base (PharmGKB, http://www.pharmgkb.org) is to provide peer-reviewed, updated, evidence-based, freely accessible guidelines for gene/drug pairs. These guidelines will facilitate the translation of pharmacogenomic knowledge from bench to bedside.

RATIONALE FOR FORMING THE CPIC

Although there has been substantial hype over the potential of genetic testing to improve medication use, the relatively low uptake of pharmacogenetics into clinical practice provides valu-

fact that little of such testing is done preemptively and therefore the results are not available when the prescribing decision is made. Some of these barriers will persist for many years to come.

One barrier to clinical implementation of pharmacogenetics that is addressable[5] is the lack of clear, curated, peer-reviewed guidelines that translate laboratory test results into actionable prescribing decisions for specific drugs. It is the goal of the CPIC (http://www.pharmgkb.org/views/project.jsp?pId=74) to provide such guidelines, the first of which is published in this same issue.[6] The guidelines will center on genes (e.g., thiopurine methyltransferase (TPMT) and its implications for thiopurines) and drugs (e.g., warfarin and all the major genes that influence its action).

The CPIC, which was established in 2009, consists of Pharmacogenomics Research Network members, PharmGKB staff, and experts in pharmacogenetics, pharmacogenomics, and laboratory medicine. The consortium was created to address the need for very specific guidance to clinicians and laboratories

Clinical Pharmacogenomics Implementation Consortium (CPIC)

- Established by the Pharmacogenomics Research Network and PharmGKB
- GOAL: Address some of the barriers to implementation of PGx tests in clinical practice
- **HOW** available genetic test results should be used to optimize drug therapy, not **WHETHER** tests should be ordered
- Guidelines peer-reviewed and published in *Clinical Pharmacology and Therapeutics*
    - simultaneous posting on PharmGKB

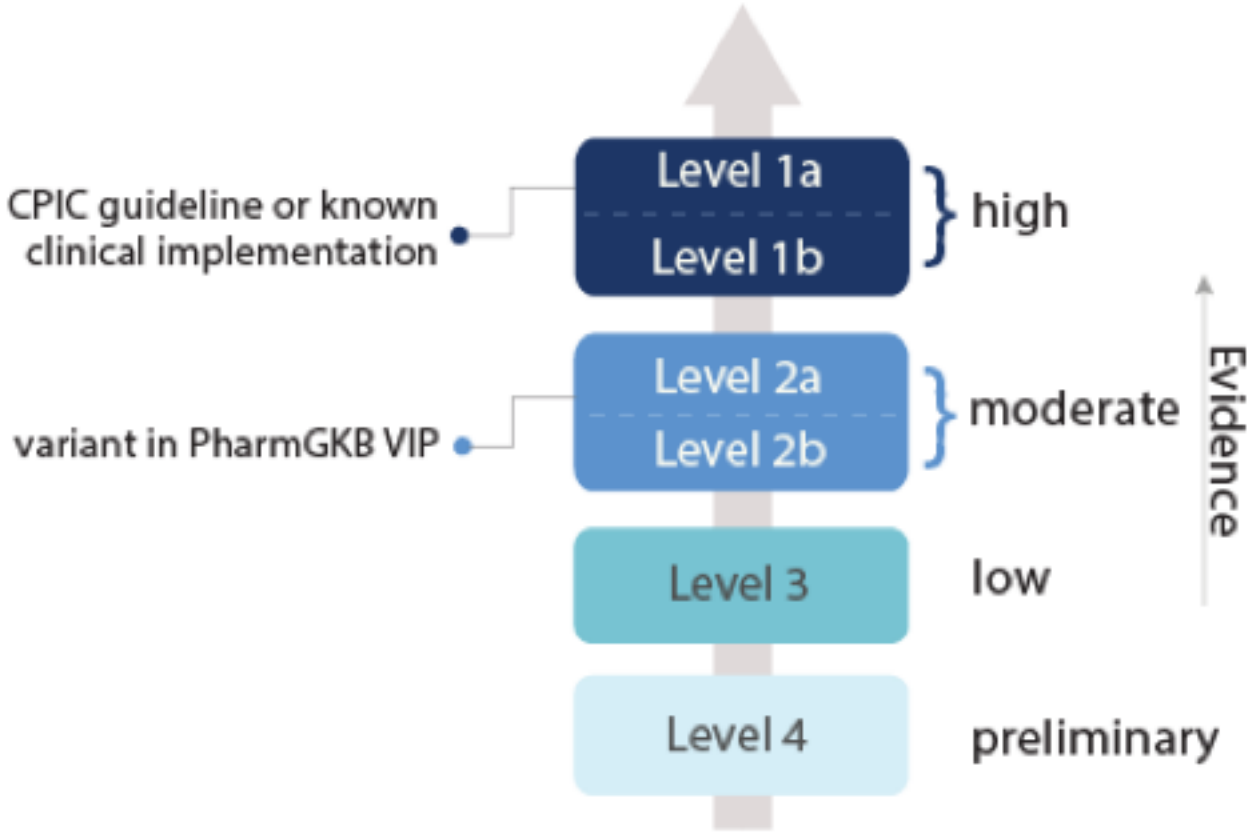
Heart of the CPIC Guideline

- There must be a diplotype that is so "high risk" for the gene that if you knew the patient had that diplotype, you would take it into account in
  - choosing which drug *or*
  - choosing a dose
- If there are no recommendations that you are willing to make based on at least one high-risk diplotype, then it is probably not worth writing the CPIC guideline
- A knowledgeable clinician needs to buy into at least ONE recommendation

Clinical Pharmacogenomics Implementation Consortium (CPIC)

- Thiopurines/TPMT
- Warfarin/CYP2C9 & VKORC1
- Codeine/CYP2D6
- Clopidogrel/CYP2C19
- Carbamazepine/HLA-B*1502
- Abacavir/HLA-B*5701
- Allopurinol/HLA-B*1501
- Simvastatin/SLCO1B1
- Tricyclic Acids/CYP2D6/CYP2C19
- Capecitabine & Fluorouracil/DPYD
- PegIntron/ILFN3 (IL28B)
- others in the pipeline

Clinical Annotations Level of Evidence



Grading Supporting Evidence

- **High:** Evidence includes consistent results from well-designed, well-conducted studies.
- **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
- **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. (Washington, DC, NACB, 2010).

Grading Supporting Evidence

- **High:** Evidence includes consistent results from well-designed, well-conducted studies.
- **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the
  stu
  ind

Note: randomized, controlled trials comparing outcomes with genotype-guided dosing vs not will be RARE

- **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. (Washington, DC, NACB, 2010).

FDA Drug Labeling for Azathioprine

TPMT Testing

It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are *TPMT*2, TPMT*3A and TPMT*3C*. Patients with two non-functional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. TPMT testing may also be considered in patients with abnormal CBC results that do not respond to dose reduction. Early drug discontinuation in these patients is advisable. **TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING AZATHIOPRINE TABLETS** (see **CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS**and **DOSAGE AND ADMINISTRATION**sections).

DOSAGE AND ADMINISTRATION

TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING AZATHIOPRINE TABLETS. TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity from azathioprine tablets if conventional doses are given. Physicians may consider alternative therapies for patients who have low or absent TPMT activity (homozygous for non-functional alleles). Azathioprine tablets should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction.

CPIC Guidelines for Azathioprine

Examples of TPMT Diplotypes	Phenotype	Dosing recommendations for azathioprine	Classification of recommen-dation
*1/*1	Homozygous wild-type or normal, high activity	Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.	Strong
*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4	Heterozygote or intermediate activity	If disease treatment normally starts at the "dose", consider starting at 30–70% of target dose (e.g., 1–1.5 mg/kg/d), and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment.	Strong
*3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4	Homozygous variant, mutant, low, or deficient activity	Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression.	Strong

Clinical Annotation of Human Genomes

Prediction of genetic risk of variants associated with recognized drug responses and for novel variants

Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Summary

Background The cost of genomic information has fallen steeply, but the clinical translation of genetic risk estimates remains unclear. We aimed to undertake an integrated analysis of a complete human genome in a clinical context.

Lancet 2010; 375: 1525–35

See Comment page 1497

Challenges in the clinical application of whole-genome sequencing

Kelly E Ormond, Matthew T Wheeler, Louanne Hudgins, Teri E Klein, Atul J Butte, Russ B Altman, Euan A Ashley, Henry T Greely

As the cost of sequencing the human genome falls, medical use of whole-genome sequencing will rapidly advance.[1] In this Viewpoint, we consider the opportunities or more serious diseases. For example, a patient could learn that he or she has a genetic predisposition for sudden cardiac death. Such risks could be suspected

Lancet 2010; 375: 1749–51
Published Online
April 30, 2010

PharmGKB Annotation Method

- Evaluated 2500 SNP annotations for direct drug relevance to “patient 0”
- Evaluated CNVs in known important genes (VIP, PK, PD)
- Evaluated novel SNPs in known important genes (VIP, PK, PD)

	Gene name	SNP location	Patient genotype	Drug(s) affected	Summary of effects	Level of evidence
SLCO1B1	Solute carrier organic anion transporter family, member 1B1	rs4149056	T/T	HMG-CoA reductase inhibitors (statins)	No increased risk of myopathy	High[32-34]
CYP2C19	Cytochrome P450, family 2, subfamily C, polypeptide 19	rs4244285	A/G	Clopidogrel and CYP2C19 substrates	CYP2C19 poor metaboliser; many drugs might need adjustment	High[35]
VKORC1	Vitamin K epoxide reductase complex, subunit 1	rs9923231	C/T	Warfarin	Reduced dose needed	High[36]
CYP4F2	Cytochrome P450, family 4, subfamily F, polypeptide 2	rs2108622	C/C	Warfarin	Reduced dose needed	High[37]
ADRB1	β1 adrenergic receptor	rs1801252	A/A	Atenolol, metoprolol	Might be preferable to calcium-channel blockers	High[38,39]
SLCO1B1	Solute carrier organic anion transporter family, member 1B1	rs11045819	A/C	Fluvastatin	Good response	Medium[40]
HMGCR	HMG-CoA reductase	rs17238540	T/T	Pravastatin	Patient might have good response	Medium
HMGCR	HMG-CoA reductase	rs17244841	A/A	Pravastatin, simvastatin	No reduced efficacy	Medium
ADRB2	β2 adrenergic receptor, surface	rs1042713	A/G	β blockers	Other treatment options might be preferable	Medium[41]
ADRB2	β2 adrenergic receptor, surface	rs1042714	C/C	β blockers	Other treatment options might be preferable	Medium[41,42]
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6	rs3892097 rs1800716	C/C	Metoprolol and other CYP2D6 substrates	Normal CYP2D6 metaboliser	Medium[43]
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/2B	rs10811661	T/T	Metformin	Reduced likelihood of response	Medium[44]
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/2B	rs10811661	T/T	Troglitazone	Reduced likelihood of response	Medium[44]

SNP=single nucleotide polymorphism. HMG-CoA=3-hydroxy-3-methylglutaryl-coenzyme A.

Table 3: **Pharmacogenomic variants with summary of effects and level of evidence**

	Gene name	SNP location	Patient genotype	Drug(s) affected	Effect type	Coding change
NOD2	Nucleotide-binding oligomerisation domain containing 2	16:49303700	A/G	Infliximab	Pharmacodynamic	V793M
NOD2	Nucleotide-binding oligomerisation domain containing 2	16:49302615	C/T	Infliximab	Pharmacodynamic	S431L
SLC15A1	Solute carrier family 15 (oligopeptide transporter), member 1	13:98176691	C/T	Atorvastatin, fluvastatin, HMG-CoA reductase inhibitors, lovastatin, pravastatin, rosuvastatin, simvastatin	Pharmacokinetic	Y21C
HLA-DRB5	MHC class II, DR beta 5	6:32593811	T/T	Clozapine	Pharmacodynamic	T262K
MICA	MHC class I polypeptide-related sequence A	6:31484467	C/T	Mercaptopurine, methotrexate	Pharmacodynamic	I14T
SLC22A8	Solute carrier family 22 (organic anion transporter), member 8	11:62517376	C/T	Cimetidine, estrone, anti-inflammatory and antirheumatic products, non-steroids, ibuprofen, indometacin, ketoprofen, methotrexate, phenylbutazone, piroxicam, probenecid, atorvastatin, fluvastatin, HMG-CoA reductase inhibitors, lovastatin, pravastatin, rosuvastatin, simvastatin, adefovir dipivoxil, tenofovir, antineoplastic agents, cyanocobalamin, folic acid, folinic acid, pyridoxine	Pharmacokinetic	R534Q

SNP=single nucleotide polymorphism. HMG-CoA=3-hydroxy-3-methylglutaryl-coenzyme A. *Predicted to be damaging by PhD-SNP algorithm.[45]

Table 4: **Pharmacogenomic rare and novel non-synonymous damaging variants***

A Family Quartet

OPEN ACCESS Freely available online

PLoS GENETICS

Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence

Frederick E. Dewey[1], Rong Chen[2], Sergio P. Cordero[3], Kelly E. Ormond[4,5], Colleen Caleshu[1], Konrad J. Karczewski[3,4], Michelle Whirl-Carrillo[4], Matthew T. Wheeler[1], Joel T. Dudley[2,3], Jake K. Byrnes[4], Omar E. Cornejo[4], Joshua W. Knowles[1], Mark Woon[4], Katrin Sangkuhl[4], Li Gong[4], Caroline F. Thorn[4], Joan M. Hebert[4], Emidio Capriotti[4], Sean P. David[4], Aleksandra Pavlovic[1], Anne West[6], Joseph V. Thakuria[7], Madeleine P. Ball[8], Alexander W. Zaranek[8], Heidi L. Rehm[9], George M. Church[8], John S. West[10], Carlos D. Bustamante[4], Michael Snyder[4], Russ B. Altman[4,11], Teri E. Klein[4], Atul J. Butte[2], Euan A. Ashley[1]*

1 Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine, Stanford University, Stanford, California, United States of America, **2** Division of Systems Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, United States of America, **3** Biomedical Informatics Graduate Training Program, Stanford University School of Medicine, Stanford, California, United States of America, **4** Department of Genetics, Stanford University School of Medicine, Stanford, California, United States of America, **5** Center for Biomedical Ethics, Stanford University, Stanford, California, United States of America, **6** Wellesley College, Wellesley, Massachusetts, United States of America, **7** Division of Genetics, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **8** Department of Genetics, Harvard Medical School, Boston, Massachusetts, United States of America, **9** Department of Pathology, Harvard Medical School, Boston, Massachusetts, United States of America, **10** Personalis, Palo Alto, California, United States of America, **11** Department of Bioengineering, Stanford University, Stanford, California, United States of America

Abstract

Whole-genome sequencing harbors unprecedented potential for characterization of individual and family genetic variation. Here, we develop a novel synthetic human reference sequence that is ethnically concordant and use it for the analysis of genomes from a nuclear family with history of familial thrombophilia. We demonstrate that the use of the major allele reference sequence results in improved genotype accuracy for disease-associated variant loci. We infer recombination sites to the lowest median resolution demonstrated to date (<1,000 base pairs). We use family inheritance state analysis to control sequencing error and inform family-wide haplotype phasing, allowing quantification of genome-wide compound heterozygosity. We develop a sequence-based methodology for Human Leukocyte Antigen typing that contributes to disease risk prediction. Finally, we advance methods for analysis of disease and pharmacogenomic risk across the coding and non-coding genome that incorporate phased variant data. We show these methods are capable of identifying multigenic risk for inherited thrombophilia and informing the appropriate pharmacological therapy. These ethnicity-specific, family-based approaches to interpretation of genetic variation are emblematic of the next generation of genetic risk assessment using whole-genome sequencing.

Citation: Dewey FE, Chen R, Cordero SP, Ormond KE, Caleshu C, et al. (2011) Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence. PLoS Genet 7(9): e1002280. doi:10.1371/journal.pgen.1002280

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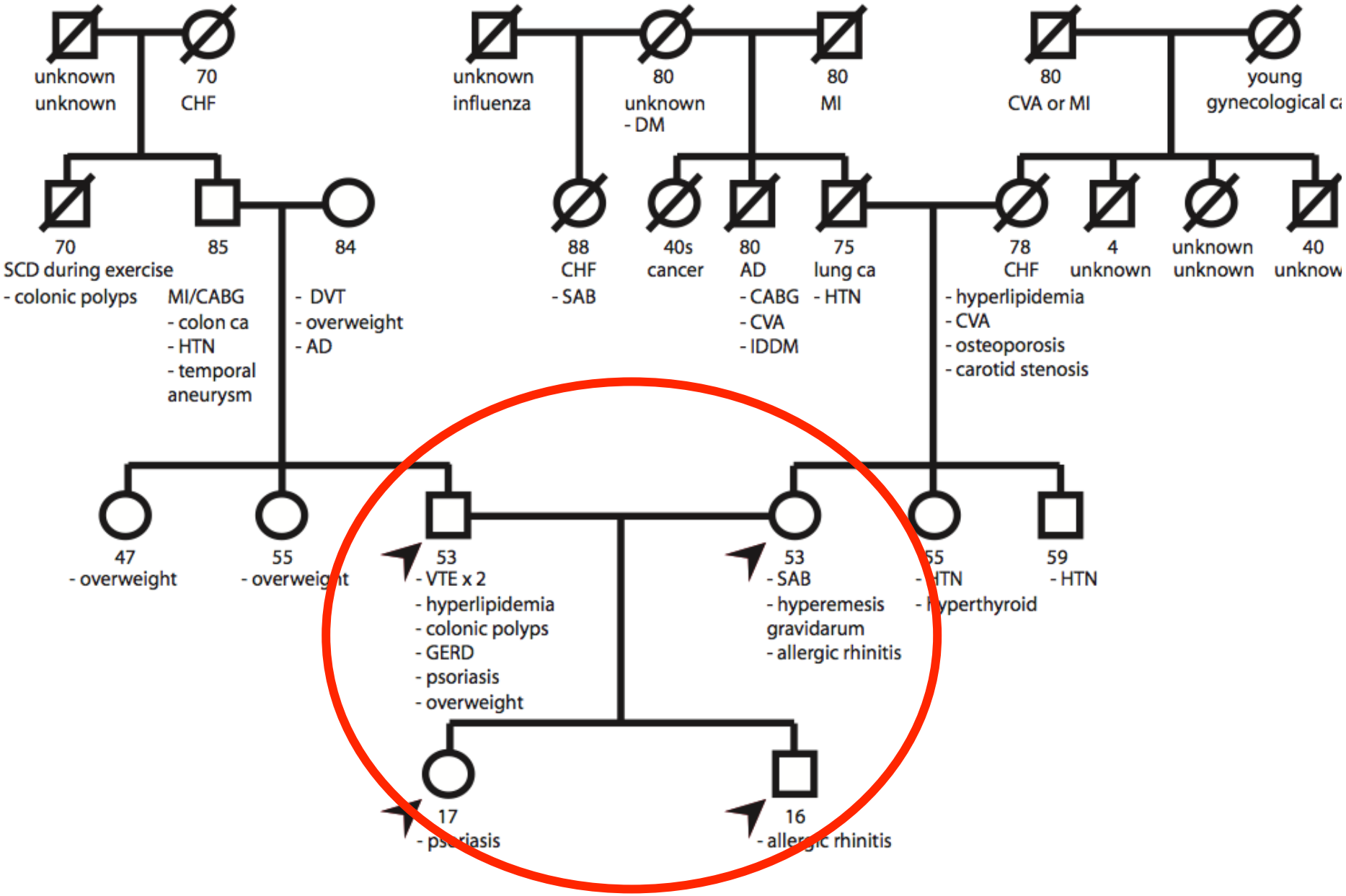


Table S7. Example pharmacogenomics annotation

Proton Pump Inhibitors (such as Prilosec)	
Father	**Probable typical response to proton pump inhibitors.**
Details:	CYP2C19*2/CYP2C19*17, one poor metabolizer allele and one ultra-rapid metabolizer allele: Response to proton pump inhibitors with this combination in alleles is not well-studied. The poor metabolizer allele associates with increased response to treatment for some indications, while the ultra-rapid metabolizer allele associates with decreased response.
Mother	**May not respond well to commonly prescribed dosages due to ultrarapid clearance of these drugs.**
Details:	CYP2C19*17 homozygous, ultra-rapid metabolizer: Is associated with increased proton pump inhibitor clearance and decreased efficacy.
Sister	**May not respond well to commonly prescribed dosages due to ultrarapid clearance of these drugs.**
Details:	CYP2C19*17 homozygous, ultra-rapid metabolizer: Is associated with increased proton pump inhibitor clearance and decreased efficacy.
Brother	**Probable typical response to proton pump inhibitors.**
Details:	CYP2C19*2/CYP2C19*17, one poor metabolizer allele and one ultra-rapid metabolizer allele: Response to proton pump inhibitors with this combination in alleles is not well-studied. The poor metabolizer allele associates with increased response to treatment for some indications, while the ultra-rapid metabolizer allele associates with decreased response.

Table S9. Variants associated with adverse drug response

Key: Father, Mother, Brother, Sister =		■○■○	Family members' genotypes as compared to other possible genotypes; not a population-based statistic			
Gene Symbol	SNP Location	Drug(s)	Drug(s) More Likely to Cause Side Effect	Drug(s) Less Likely to Cause Side Effect	No PGx Action/ Phenotype Unknown	Confidence Level
TPMT	rs1800460	purine analogues	·	■○■○	·	High
HTR3B	rs1800497	antipsychotics	■○■○	·	·	Medium
HTR2C	rs1414334	antipsychotics, clozapine, risperidone	■○	○■	·	Medium
ARVCF, COMT	rs9332377	cisplatin	·	■○■○	·	Medium
FAM119A, CREB1	rs7569963	citalopram	■	■	○○	Medium
ABCC2	rs17222723	doxorubicin	■■	○○	·	Medium
ABCB1	rs1045642	efavirenz, nelfinavir	■	■○○	·	Medium
CYP1A2	rs762551	leflunomide	·	■○■○	·	Medium
PICK1, ENTHD1	rs2076369	methamphetamine	·	○	■■○	Medium
ADORA2A	rs2298383	methotrexate	■○■	○	·	Medium
ABCC1	rs246240	methotrexate	■○■○	·	·	Medium
REN, ETNK2	rs2368564	muraglitazar	■	■○○	·	Medium
CHRNA4	rs2236196	nicotine	○○	■■	·	Medium
MTHFR	rs1801131	nitrous oxide	·	■○■○	·	Medium
HTR2C	rs518147	olanzapine	○■	■	○	Medium
EPHX1	rs1051740	phenytoin	○○	·	■■	Medium
EPHX1	rs1051740	phenytoin	○○	·	■■	Medium
EPHX1	rs2234922	phenytoin	·	○○	■■	Medium
intergenic	rs1695	platinum compounds	■○■○	·	·	Medium

Table S8. Variants associated with drug efficacy

Key: Father, Mother, Brother, Sister =		■○■○	Family members' genotypes as compared to other possible genotypes; not a population-based statistic			
Gene Symbol	SNP	Drug(s)	Drug(s) More Likely to Work	Drug(s) Less Likely to Work	No PGx Action/ Phenotype Unknown	Confidence Level
GRIK4	rs1954787	citalopram	■○○	■	·	High
LTA, TNF	rs1800629	adalimumab, etanercept, infliximab	■○■○	·	·	Medium
VDR	rs1544410	alendronate, bisphosphonates, calcium, clodronate, etidronic acid, raloxifene	·	■○■○	·	Medium
ABCB1	rs2032583	antidepressants	■	■○○	·	Medium
FKBP5	rs3800373	antidepressants	·	■○■○	·	Medium
FKBP5	rs1360780	antidepressants	·	■○■○	·	Medium
HTR2A	rs7997012	antidepressants, citalopram	■○	■○	·	Medium
SERPINE1	rs2227631	antidepressants, citalopram, fluoxetine	○	■○■	·	Medium
NOS3	rs2070744	antihypertensives and diuretics in combination	■○■○	·	·	Medium
PPARA	rs4253778	beta blocking agents	○	■○■	·	Medium
IL1B	rs16944	bisphosphonates, clodronate, etidronic acid, risedronate, tiludronate	■■	○○	·	Medium
COMT	rs165599	bupropion	■○■○	·	·	Medium
HTR3B	rs1800497	bupropion	■○■○	·	·	Medium

Table S10. Variants associated with drug dosing

Key: Father, Mother, Brother, Sister =		n¢n¢	Family members' genotypes as compared to other possible genotypes; not a population-based statistic					
Gene Symbol	SNP Location	Drug(s)	Drug Dose(s) Easy to Predict	Drug Dose(s) Difficult to Predict	Drug Dose(s) Above Average	Drug Dose(s) Below Average	No PGx Action/ Phenotype Unknown	Confidence Level
CYP3A5	rs776746	cyclosporine	·	·	·	■○■○	·	High
CYP4F2	rs2108622	acenocoumarol, warfarin	·	·	·	■○■○	·	Medium
CYP4F2	rs2108622	acenocoumarol, warfarin	·	·	·	■○■○	·	Medium
SCN1A	rs3812718	carbamazepine	·	·	○■○	·	■	Medium
NALCN	rs7992226	methotrexate	·	■○■○	·	·	·	Medium
COMT	rs4680	morphine	·	·	■○■○	·	·	Medium
OPRM1	rs1799971	morphine	·	·	·	■○■○	·	Medium
SCN1A	rs3812718	phenytoin	·	·	○■○	·	■	Medium
EPHX1	rs2292566	warfarin	·	·	■○■○	·	·	Medium
STX4	rs10871454	warfarin	·	·	·	■○■○	·	Medium
VKORC1	rs8050894	warfarin	·	·	·	■○■○	·	Medium
CYP3A4	rs2740574	docetaxel	■○■○	·	·	·	·	Low
ABCB1	rs1045642	fexofenadine	■○○	·	■	·	·	Low
CYP3A4	rs2740574	indinavir	■○■○	·	·	·	·	Low
SLCO1B1	rs4149056	methotrexate	■○■○	·	·	·	·	Low
SLCO1B1	rs2306283	pravastatin	·	■○■○	·	·	·	Low
CYP3A4	rs2740574	tacrolimus	■○■○	·	·	·	·	Low

Take Home from Clinical Annotations of Human Genome Projects

- Pharmacogenomics is a good test bed for whole genome applications
  - strong effects, environment controlled mostly
- PharmGKB has information for individual advice for >100 drugs/individual
- The value for each individual is knowledge about a few key drug response predictions
- Rare variants are important and challenging

Overview:

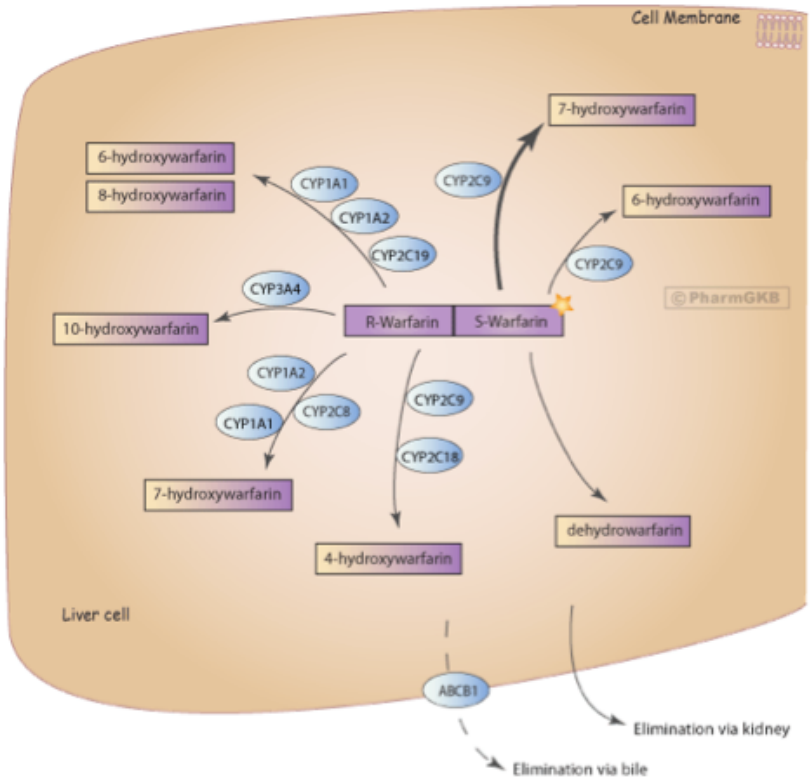
PGx Knowledge → Implementation → Impact

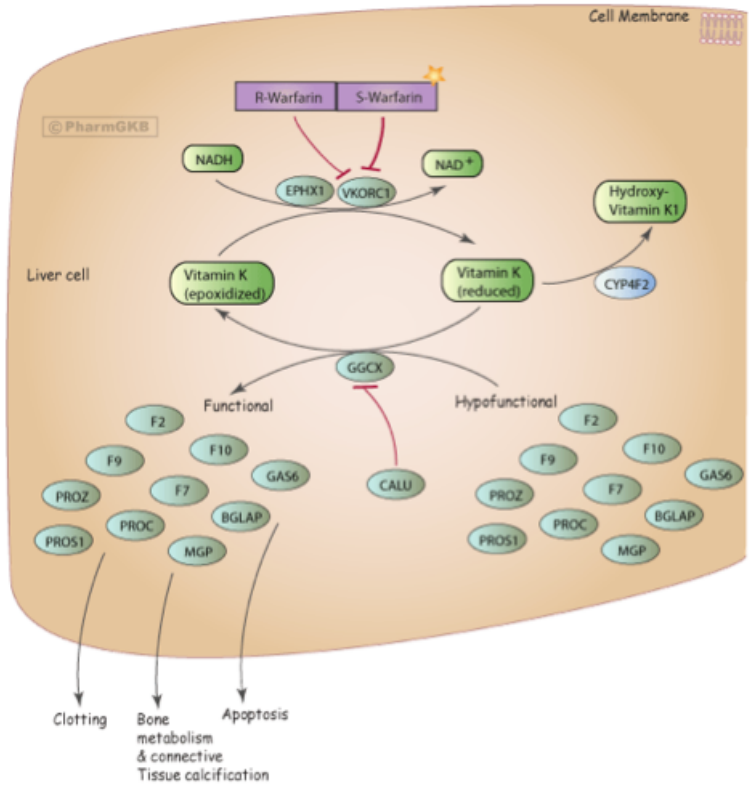
1. PharmGKB and resources for PGx
2. Clinical PGx Implementation
   - Annotation of Human Genomes
   - Dosing Guidelines (CPIC)
3. Does PGx truly have a role in personalized medicine?
   - Warfarin Dosing
   - Narcotics

Case 1: Warfarin Genetics

- Three genes known to affect warfarin dose: CYP2C9, VKORC1 and CYP4F2
- Know variation in CYP2C9 affects PK
- But only accounted for < 15% of variation
- Vitamin K epoxide reductase (VKORC1) affects PD
- Found in rat-poison-resistant rats
- Non-coding SNP explains 35% of variation
- VKORC1: -1639 G>A allele

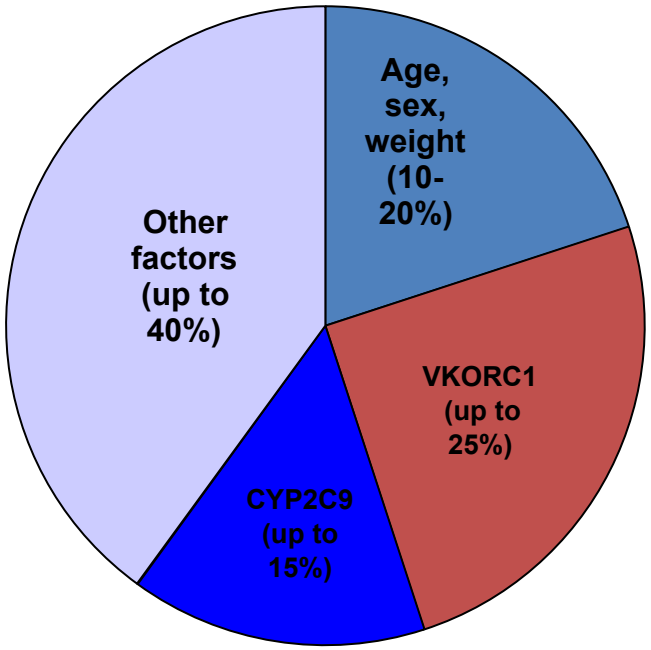
Warfarin PK & PD Pathways





Warfarin Response

- Clinical and environmental factors
  - Age, gender, ethnicity, BMI
  - Co-administered drugs
  - Co-morbidity
  - Food (Vitamin K intake)
  - Smoking
- Genetic factors
  - CYP2C9 and VKORC1



Warfarin Consortium and Recent Results

- IWPC retrospective study – better dose prediction with PGx
- COAG trial – no increase of time in therapeutic range with PGx dosing
- EU-PACT Warfarin trial – PGx group had higher mean percentage of time in therapeutic range
- EU-PACT Acenocoumarol and Phenprocoumon trial – no increase of time in therapeutic range with PGx dosing
- GIFT trial will focus on clinical outcomes with PGx

Warfarin Label Changes for PGx

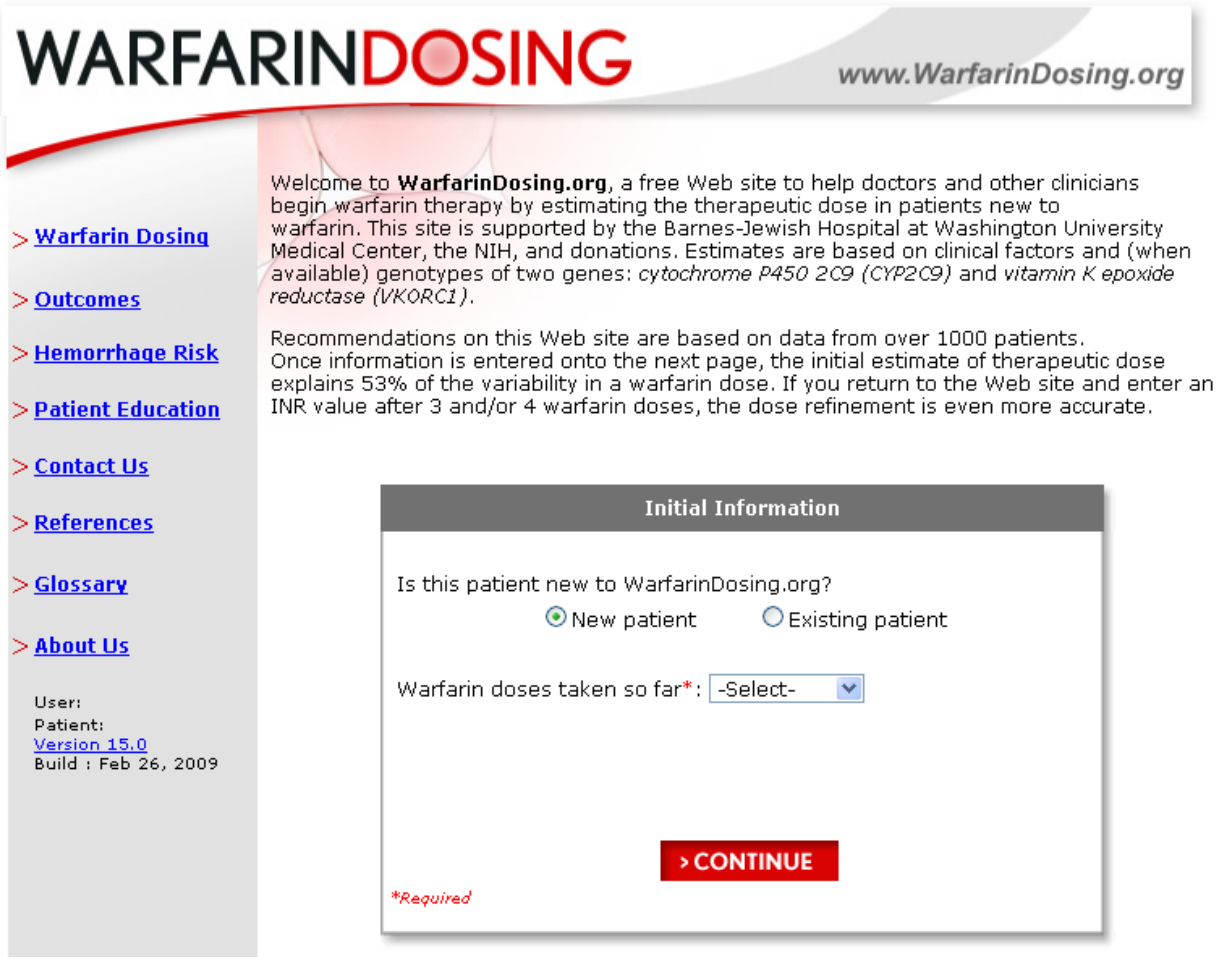
- In 2007 and 2010, FDA updated label
  - a "patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose."
  - provides initial dosage recommendations for different variant combinations

FDA U.S. Food and Drug Administration U.S. Department of Health and Human Services

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Warfarin Dosing Calculator



23andMe, Inc. 11/22/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Nov 22, 2013

Ann Wojcicki
CEO
23andMe, Inc.
1390 Shoreline Way
Mountain View, CA 94043

Document Number: GEN1300666
Re: Personal Genome Service (PGS)

WARNING LETTER

Dear Ms. Wojcicki,

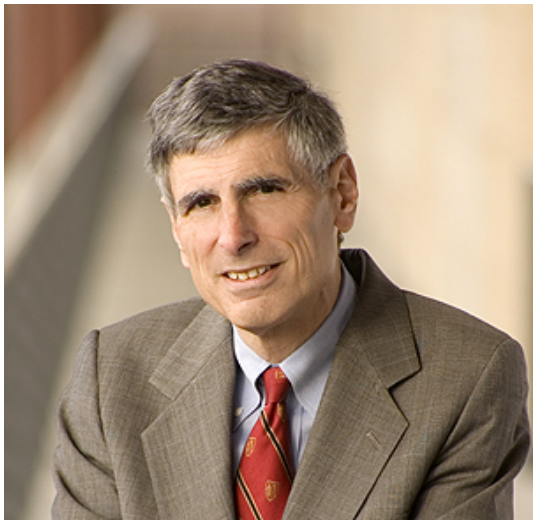
The Food and Drug Administration (FDA) is sending you this letter because you are marketing the 23andMe Saliva Collection Kit and Personal Genome Service (PGS) without marketing clearance or approval in violation of the Federal Food, Drug and Cosmetic Act (the FD&C Act).

This product is a device within the meaning of section 201(h) of the FD&C Act, 21 U.S.C. 321(h), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body. For example, your company's website at www.23andme.com/health (most recently viewed on November 6, 2013) markets the PGS for providing "health reports on 254 diseases and conditions," including categories such as "carrier status," "health risks," and "drug response," and specifically as a "first step in prevention" that enables users to "take steps toward mitigating serious diseases" such as diabetes, coronary heart disease, and breast cancer. Most of the intended uses for PGS listed on your website, a list that has grown over time, are medical device uses under section 201(h) of the FD&C Act. Most of these uses have not been classified and thus require premarket approval or de novo classification, as FDA has explained to you on numerous occasions.

Case 2: An Odyssey With Pain

- Phil Pizzo, former Dean SOM, Stanford
- Chair, IOM panel on pain
- Marathon runner, boundless energy
- Developed chronic pain, 4 negative MRIs
- Compression of a nerve
- Surgery
- Relief from nerve entrapment

within days



BUT….

Adverse Events

- Highly sensitive to opiates
- Two episodes of respiratory depression within days of surgery requiring naloxone reversal and ICU
- PGx an important factor …..

PERSPECTIVE

LESSONS IN PAIN RELIEF

Lessons in Pain Relief — A Personal Postgraduate Experience

Philip A. Pizzo, M.D.

PGx Objectives

- Identify the variation in drug response and associate it with genetic variation
- Evaluate clinical significance (not so easy)
  - Analytic validity, clinical validity, clinical utility
- Develop screening tests
- Individualize drug therapy

Challenges of Translational PGx

- Many published studies but few replications
- Statistical significance ≠ clinical significance
- RCTs are used to show clinical utility but difficult for PGx
- Difficulty controlling for gene-environment, gene-disease and dietary factors

PGx is NOT Routinely Used...

- Analytic validity, clinical validity/utility
- Practical concerns
  - Costs for genotyping and who pays
  - Availability of genotypes/time delay
- Clinician adoption
  - Education
  - Clear, specific guidelines
  - Information delivery mechanisms

…Yet PGx Is Moving Into Practice

- Addressing practical concerns
  - Rapidly decreasing costs and readily available genotyping/ sequencing services
  - Preemptive genotyping results in electronic medical health records
- Addressing clinician adoption
  - Integration into medical training
  - FDA drug labeling
  - Published dosing guidelines
    - Clinical Pharmacogenetics Implementation Consortium (CPIC)
    - "Pharmacogenetics: from bench to byte- an update of guidelines." Swen JJ, et al. Clin Pharmacol Ther. 2011 May; 89(5):662-73.

We MUST be advocates

A fabulous example ….

UF | Department *of* Pharmacotherapy and Translational Research
College *of* Pharmacy

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PharmGKB
Pharmacogenomics Knowledge Base

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

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Thank You