Databases 101 for Clinical Pharmacologists: What you need to know about

PharmGKB

The Pharmacogenomics Knowledgebase

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ASCPT March 17, 2017

Content

- PharmGKB background
- Example: phenytoin

- Other related resources
  - CPIC website
  - ClinVar
  - ClinGen

What is PharmGKB?
What can I get from it?

- Premier resource for curated pharmacogenomic information
- Provides annotated
  - Dosing guidelines
  - Drug labels
  - Literature
- Develops
  - VIP gene summaries
  - Pharmacokinetic and pharmacodynamic drug-centered pathways
  - Genotype-based variant-drug association summaries
- Crosslinks to other drug and gene resources
- Downloadable information

www.pharmgkb.org

www.pharmgkb.org

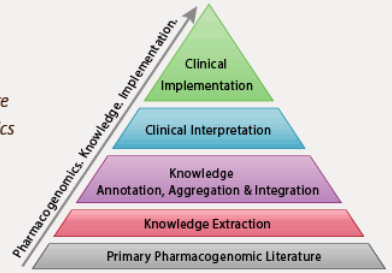
PharmGKB
The Pharmacogenomics Knowledgebase

Search PharmGKB: phenytoin Search

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...

LEARN MORE



Latest News

- Congratulations to Dr. Teri Klein!
- CPIC Guideline Update: CYP2C9/VKORC1/CYP4F2 and Warfarin
- New PharmGKB pathway: macrolide antibiotics pharmacokinetics/pharmacodynamics

Clinically-Relevant PGx

- Selected Pharmacogenomic Associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- PGx gene haplotypes

PGx-Based Drug Dosing Guidelines

- See all CPIC guidelines
- Recent guidelines:
  - TCAs update: amitriptyline / nortriptyline article and supplement
  - CYP2C19/voriconazole article and supplement
- Gene-specific informational tables
- CPIC genes/drugs of interest
- TPP gene tables

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

PGx Research

- VIP: Very Important PGx gene summaries
- PharmGKB pathways
- Annotated SNPs by gene
- Drugs with genetic information
- Cancer PGx

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CHEMICAL: DRUG
phenytoin

Available Prescribing Info

Dosing Guidelines
1. CPIC Guideline for phenytoin and CYP2C9,HLA-B
2. DPWG Guideline for phenytoin and CYP2C9

Rx Annotations
1. Individualized phenytoin therapy for Japanese pediatric patients with epilepsy based on CYP2C9 and CYP2C19 genotypes

1. CPIC Guideline for phenytoin and CYP2C9,HLA-B

last updated 08/05/2014

Summary

Phenytoin is contraindicated in individuals with the HLA-B*15:02 variant allele ("HLA-B*15:02-positive") due to significantly increased risk of phenytoin-induced cutaneous adverse reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Additionally, patients with the CYP2C9 poor metabolizer phenotype may require reduced doses of phenytoin.

Specify a genotype for specific annotations

Help with allele options

Alleles not present in the pull-down menus have no CPIC recommendation.

Pick alleles for **CYP2C9**: -- --

Pick alleles for **HLA-B**: -- --

Annotation

November 2014

Accepted article preview online August 2014; Advance online publication September 2014

- Guidelines regarding the use of pharmacogenomic tests in dosing for phenytoin have been published in Clinical Pharmacology and Therapeutics by the Clinical Pharmacogenetics Implementation Consortium (CPIC).
- Excerpt from the 2014 phenytoin dosing guidelines:
  - "[A]t least a 25% reduction of the recommended starting maintenance dose may be considered for CYP2C9 intermediate metabolizers with subsequent maintenance doses adjusted based on therapeutic drug monitoring and response. For CYP2C9 poor metabolizers, consider at least a 50% reduction of starting maintenance dose with subsequent maintenance doses adjusted based on therapeutic drug monitoring or response."
  - "[R]egardless of the CYP2C9 genotype and individual's ancestry or age, if the HLA-B*15:02 test result is positive, the recommendation is to consider using an anticonvulsant other than carbamazepine and phenytoin unless the benefits of treating the underlying disease clearly outweigh the risks... Alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the HLA-B*15:02 allele and thus caution should be used in choosing alternatives to phenytoin."
- Download and read:
  - Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C9 and HLA-B Genotype and Phenytoin Dosing

Dutch Pharmacogenetics Working Group (DPWG) guideline information for phenytoin and CYP2C9

last updated 08/10/2011

Summary

Use the standard starting dose of phenytoin and reduce the maintenance dose based on CYP2C9 genotype; monitor response and serum concentrations and be aware of ADEs.

Annotation

The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group has evaluated therapeutic dose recommendations for phenytoin based on CYP2C9 genotype [Article:21412232].

Genotype	Therapeutic Dose Recommendation	Level of Evidence	Clinical Relevance
CYP2C9 *1/*2	Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, sedation)	Published controlled studies of good quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints.	Minor clinical effect (S): QTc prolongation (<450 ms females, <470 ms males); INR increase < 4.5Kinetic effect (S)
CYP2C9 *2/*2	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, sedation)	Published controlled studies of good quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints.	Minor clinical effect (S): QTc prolongation (<450 ms females, <470 ms males); INR increase < 4.5Kinetic effect (S)
CYP2C9 *1/*3	Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, sedation)	Published controlled studies of good quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints.	Clinical effect (S): long-standing discomfort (> 168 hr), permanent symptom or invalidating injury e.g. failure of prophylaxis of atrial fibrillation; venous thromboembolism; decreased effect of clopidogrel on inhibition of platelet aggregation; ADE resulting from increased bioavailability of phenytoin; INR > 6.0; neutropenia 0.5-1.0x10^9/l; leucopenia 1.0-2.0x10^9/l; thrombocytopenia 25-50x10^9/l; severe diarrhea
CYP2C9 *2/*3	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, sedation)	Published controlled studies of good quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints.	Minor clinical effect (S): QTc prolongation (<450 ms females, <470 ms males); INR increase < 4.5Kinetic effect (S)
CYP2C9	Standard loading dose. Reduce	Published controlled studies of	Clinical effect (S): long-standing discomfort (> 168 hr), permanent symptom

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline information for phenytoin and CYP2C9, HLA-B

last updated 08/05/2014

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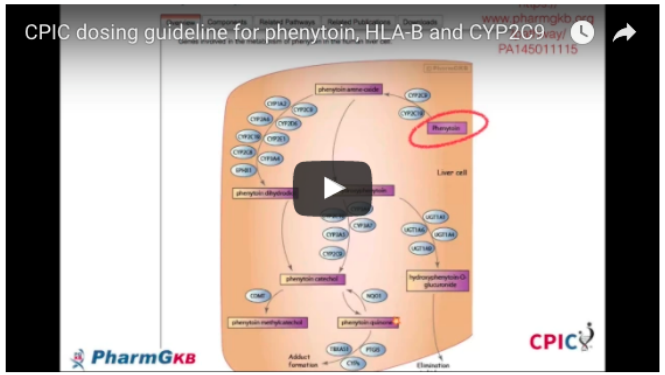

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Gene-specific Information Tables for CYP2C9

This page contains reference files created by PharmGKB and CPIC. The files support CPIC guidelines, but are also general resources for CYP2C9.

- **CYP2C9 Allele Definition Table**
  - Information about what variants define star (*) alleles
  - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides rsIDs, if available
  - Allele functionality using CPIC standardized terms
- **CYP29 Allele Functionality Table**
  - References for the allele functionality provided in the Allele Definition Table
- **CYP2C9 Frequency Table**
  - Population-based allele frequency reported by references
  - Calculated allele frequency by major ethnic groups based on frequencies reported by references
    - Worldwide race/ethnic designations based on the Human Genome Diversity Project - Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) [Articles:16355252, 12493913], with the addition of the African American category
  - Calculated diplotype frequency
  - Calculated phenotype frequency
- **CYP2C9 Diplotype-Phenotype Table**
  - Mapping of each diplotype to possible phenotype
  - Mapping of possible phenotype to EHR priority result notation and consultation text
  - Possible implementation workflow diagram
- **CYP2C9 Gene Resource Mappings**
  - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

See all genes with information tables

Clinical Pharmacogenetics Implementation Consortium (CPIC)

www.cpicpgx.org

CPIC open meeting on 3/15/2017 in Washington DC – more details on the meetings page

What is CPIC?

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN). CPIC guidelines are peer-reviewed and published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to PharmGKB with supplemental information/data and updates. Anyone with clinical interests in pharmacogenetics is eligible for membership. CPIC's goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice.

Background

One barrier to clinical implementation of pharmacogenetics is the lack of freely available, peer-reviewed, updatable, and detailed gene/drug clinical practice guidelines. CPIC provides guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs. The guidelines can center on genes (e.g. thiopurine methyltransferase and its implications for thiopurines) or around drugs (e.g. warfarin and CYP2C9 and VKORC1). Priority is given to genotyping tests that are already offered in CLIA-approved clinical settings.

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.

Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The CPIC authorship guidelines were updated in June 2014.

Search:

DRUGS	GENES	GUIDELINES
abacavir	HLA-B	*guideline*
allopurinol	HLA-B	*guideline*
amitriptyline	CYP2C19 CYP2D6	*guideline*
atazanavir	UGT1A1	*guideline*
azathioprine	TPMT	*guideline*

Genes-Drugs

last updated 01/5/2017

CPIC assigns CPIC levels to genes/drugs with (1) PharmGKB Clinical Annotation Levels of Evidence of 1A, 1B, 2A and 2B, or (2) a PharmGKB PGx level for FDA-approved drug labels of "actionable pgx", "genetic testing recommended", or "genetic testing required", or (3) based on nomination to CPIC for consideration.

- View CPIC's process for prioritizing genes/drugs
- View CPIC's levels for genes/drugs

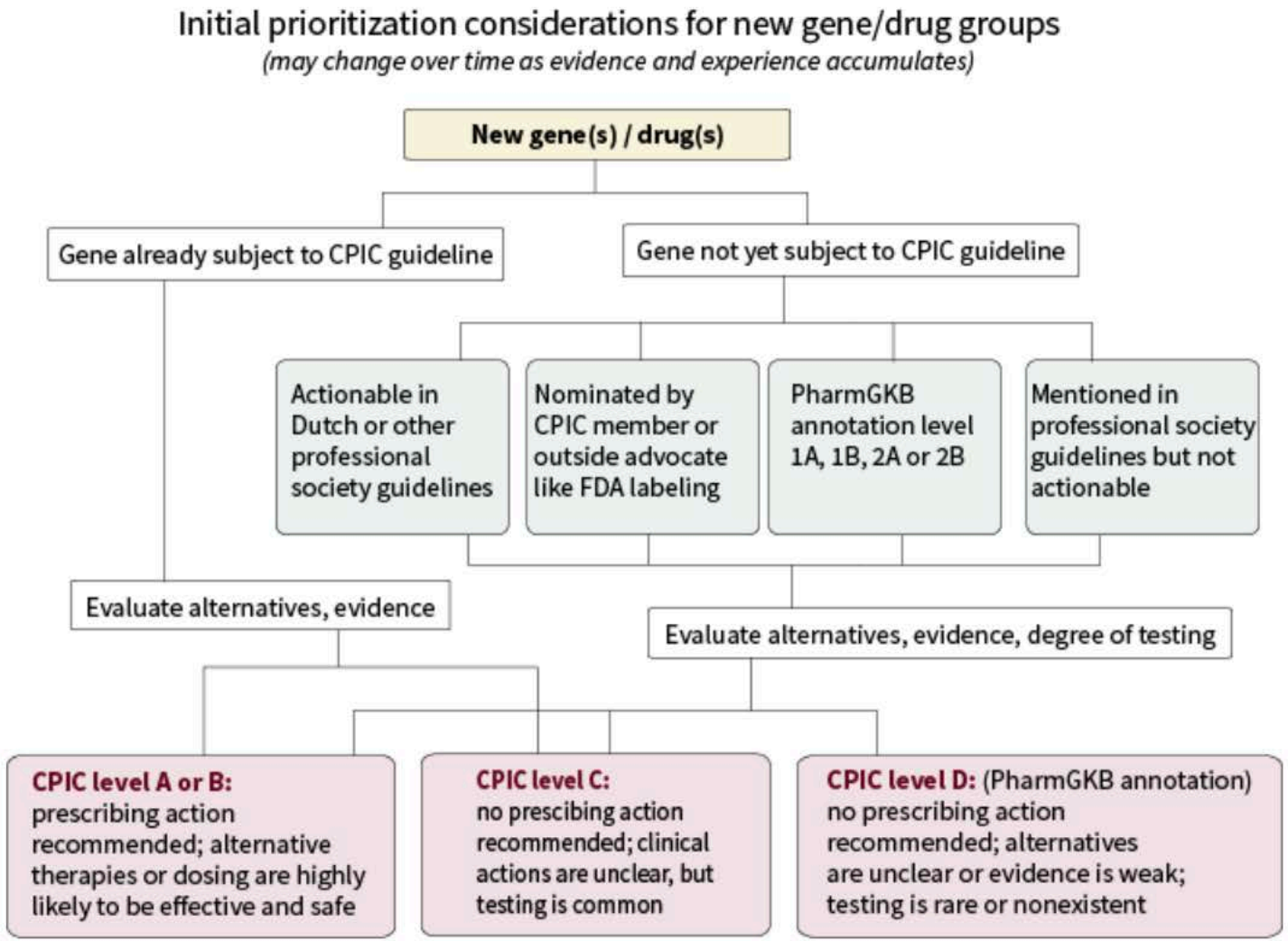
CPIC invites feedback on existing and planned gene/drug guidelines.

Download Table (CSV)

Search:

# (N=329)	GENE (UNIQUE = 123)	DRUG (UNIQUE = 211)	GUIDELINE	CPIC LEVEL	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)
1	HLA-B	abacavir	Guideline	A	1A	Genetic testing required	• 22378157 • 24561393
2	HLA-B	allopurinol	Guideline	A	1A		• 23232549 • 26094938
3	CYP2C19	amitriptyline	Guideline	A	1A		• 23486447 • 27997040

Prioritization of CPIC Genes/Drugs Diagram



CPIC® Guideline for Phenytoin and CYP2C9 and HLA-B

Most Recent Guideline Publication

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C9 and HLA-B Genotype and Phenytoin Dosing (November 2014)

Updates since publication:

No updates on dosing recommendations since publication.

Tables and figure provided in the main manuscript of the guideline

Table 1. Assignment of likely phenotype based on diplotypes
Table 2. Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype
Figure 1. Algorithm for suggested clinical actions based on *HLA-B*15:02* and *CYP2C9* genotypes

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C9 and HLA-B Genotype and Phenytoin Dosing (November 2014)

Tables included in the supplement[a] or referenced in the guideline

Supplemental Table S1. Genotypes that constitute the * alleles for CYP2C9. **For an updated version of this table see the *CYP2C9* Allele Definition Table.**
Supplemental Table S2. Association between *CYP2C9* allelic variants and CYP2C9 function. **For an updated version of this table see the *CYP2C9* Allele Functionality Table.**
Supplemental Table S3. Worldwide Allele Frequencies* of HLA-B*15:02 – Summary by Region
Supplemental Table S4. Worldwide Allele Frequencies of HLA-B*15:02 – Detailed by Sample
Supplemental Table S5. CYP2C9*2 (rs1799853) and *3 (rs1057910) allele frequencies (%) in A) 1000 Genomes populations and B) Populations from International Warfarin Pharmacogenetic Consortium. **For an updated version of this table see the *CYP2C9* Frequency Table.**
Supplemental Table S6. Diplotype frequencies (%) for CYP2C9 alleles in 1000 Genomes populations. **For an updated version of this table see the *CYP2C9* Frequency Table.**
Supplemental Table S7. Regional Diplotype frequencies (%) for CYP2C9 alleles in 1000 Genomes populations. **For an updated version of this table see the *CYP2C9* Frequency Table.**
Supplemental Table S9. Evidence linking CYP2C9 genotype to phenytoin metabolism and/or toxicities
Supplementary Figure S1. Metabolism of phenytoin or see PharmGKB Phenytoin Pathway, Pharmacokinetics
Supplementary Figure S2. Metabolism of fosphenytoin to phenytoin

CHEMICAL: DRUG

phenytoin

Available Prescribing Info

Dosing Guidelines

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Annotation

November 2014

Accepted article preview online August 2014; Advance online publication September 2014

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

Rx Annotation

for phenytoin, CYP2C19, CYP2C9

This study 1) investigated factors that affected target dose of phenytoin in 170 pediatric patients through multiple regression analysis, and 2) compared phenytoin withdrawal rates between 17 patients who received genotype-directed dosing and 139 patients who received conventional dosing in order to evaluate clinical usefulness of genotyping.

Part 1 of the study: Dosing Algorithm

Estimated target dose (mg/kg/d) = 17.63 - 6.94[log(body weight)] - 2.68(CYP2C9*3) - 0.68(CYP2C19*2) - 1.06(CYP2C19*3) - 1.07(sulthiame)

Main findings

This model explained 74% of the interindividual variability of the target dose of phenytoin in 170 pediatric patients

Part 2 of the study: Main findings

There was **NO** significant difference in the total phenytoin withdrawal rate between the pediatric individualized therapy group (23.5%) and the pediatric standard therapy group (33.1%) (p=0.074)Dosing protocol

Dosing protocol

Individualized therapy (n=17)

CYP2C9 Genotype	CYP2C19 Genotype	Initial Dose
*1/*1	*1/*1	6.7+/-1.9
*1/*1	*1/*2 or *1/*3	6.2+/-1.8
*1/*1	*2/*2, *2/*3 or *3/*3	5.2+/-1.5
*1/*3	*1/*1, *1/*2 or *1/*3	3.0+/-0.2

Standard therapy (n=139)

Dosing based on package insert for phenytoin

Additional information

- **Ethnicity:** Japanese (pediatric)
- **Indication:** Epilepsy

Total publications: 1

Reference

1. Individualized phenytoin therapy for Japanese pediatric patients with epilepsy based on CYP2C9 and CYP2C19 genotypes. *Therapeutic drug monitoring.* 2015. Yamamoto Yoshiaki, Takahashi Yukitoshi, Imai Katsumi, Miyakawa Kou, Ikeda Hiroko, Ueda Yuki, Yamaguchi Tokito, Nasu Hirosato, Ohtani Hideyuki, Shigematsu Hideo, Kagawa Yoshiyuki, Inoue Yushi. PubMed

last updated 10/25/2013

U.S. Food and Drug Administration (FDA) label information for phenytoin and CYP2C19, CYP2C9, HLA-B

On FDA Biomarker List

Actionable PGx

Summary

A strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLAB*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

Annotation

Phenytoin sodium is an antiepileptic drug.

Excerpt from the phenytoin sodium (Dilantin) drug label:

> There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference.

> Phenytoin is metabolized by hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

> Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLAB*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

For the complete drug label text with sections containing pharmacogenetic information highlighted, see the Phenytoin sodium (Dilantin) drug label.

*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
More information about drug labels on PharmGKB.

Genes and/or phenotypes found in this label

- Congenital Abnormalities
  - *appears in:*
    - Warnings section
  - *source:* PHONT

Drug Label Information and Legend

FDA: US Food and Drug Administration-approved drug label.

- Information is gathered from the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels" and from FDA-approved labels brought to our attention. Please note that drugs may be removed from or added to the FDA's Table without our knowledge. We periodically check the Table for changes and update PharmGKB accordingly. Drugs listed on the Table to our knowledge are tagged with the Biomarker icon. A drug label that has been removed from the Table will not have the Biomarker icon but will continue to have an annotation on PharmGKB stating the label has been removed from the FDA's Table. We acquire label PDF files from DailyMed and Drugs@FDA.

EMA: European Medicines Agency-approved drug label.

- European Public Assessment Reports (EPARs) that contain PGx information were identified from [Article:24433361] and also by searching for drugs for which we have PGx-containing FDA drug labels.

PMDA: Pharmaceuticals and Medical Devices Agency (Japan)-approved drug label.

- Unless otherwise stated, Japanese drug label annotations were translated through a collaboration with the Japanese Society of Pharmacogenomics and Silicon Valley Tech KK. PMDA package inserts were selected to be examined for PGx information by searching for drugs for which we have PGx-containing FDA, EMA or HCSC labels.

HCSC: Health Canada (Santé Canada)-approved drug label.

- Canadian drug labels (referred to as product monographs) are sourced from Health Canada's Drug Product Database (DPD). Product monographs that contain PGx information were identified by searching for drugs for which we have PGx-containing FDA or EMA labels.

The PharmGKB badge refers to a drug label found on the DailyMed website but the drug label is not approved by the FDA.

The Biomarker badge B refers to a drug label that is found on the FDA's Table of Pharmacogenomic Biomarkers in Drug Labels.

PGx Level

Genetic testing required The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted before using this drug. This requirement may only be for a particular subset of patients. PharmGKB considers labels that state the variant is an indication for the drug, as implying a test requirement. If the label states a test "should be" performed, this is also interpreted as a requirement.

Genetic testing recommended The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., is recommended before using this drug. This recommendation may only be for a particular subset of patients. PharmGKB considers labels that say testing "should be considered" to be recommending testing.

Actionable PGx The label does not discuss genetic or other testing for gene/protein/chromosomal variants, but does contain information about changes in efficacy, dosage or toxicity due to such variants. The label may mention contraindication of the drug in a particular subset of patients but does not require or recommend gene, protein or chromosomal testing.

Informative PGx The label mentions a gene or protein is involved in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes/proteins leads to different response.

Health Canada Santé Canada (HCSC) label information for phenytoin and HLA-B

Genetic testing recommended

Summary

The product monograph for phenytoin (DILANTIN) notes that individuals with the HLA-B*1502 allele have an increased risk of developing Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) when receiving the drug. It further notes that this allele is common in individuals of Asian ancestry, and HLA-B genotyping should be considered as a screening tool in these patients.

Annotation

Phenytoin (DILANTIN) is an anti-epileptic. Excerpts from the phenytoin (DILANTIN) product monograph:

> In studies that included small samples of patients of Asian ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Results of these studies suggest that the presence of the HLA-B*1502 allele may be one of the risk factors for phenytoin-associated SJS/TEN in patients with Asian ancestry.

> ...physicians should consider HLA-B*1502 genotyping as a screening tool in these patients. Until further information is available, the use of phenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele.

> HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management.

For the complete product monograph text with sections containing pharmacogenetic information highlighted, see the phenytoin product monograph.

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

More information about drug labels on PharmGKB.

Genes and/or phenotypes found in this label

No objects specified.

Label History

Date	Event	Comment
No tracked changes		

CHEMICAL: DRUG
phenytoin

Edit Drug | Add Component | update

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

Prescribing Info (3) | Drug Labels (2) | Clinical Annotations (23)

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 CYP2C9*1, CYP2C9*2, CYP2C9*3, phenytoin and Epilepsy (level 1A Toxicity/ADR, Metabolism/PK)

Level of Evidence
Level 1A

Type
Toxicity/ADR, Metabolism/PK

Variant
*1, *2, *3

Genes
CYP2C9

Phenotypes
Epilepsy

OMB Race
Mixed Population

User ID
hodoglugil

***1/*1**	Patients with *1/*1 genotypes may have increased metabolism, decreased plasma concentration, decreased toxicity and decreased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*3, *2/*3 *2/*2 or *3/*3 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
***1/*3**	Patients with *1/*3 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
***2/*2**	Patients with *2/*2 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
***2/*3**	Patients with *2/*3 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
***3/*3**	Patients with *3/*3 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.

View Evidence

Clinical Annotation for HLA-B*15:02:01, phenytoin, Epidermal Necrolysis, Toxic and Stevens-Johnson Syndrome (level 1A Toxicity/ADR)

Level of Evidence
Level 1A

Type
Toxicity/ADR

Variant
*15:02:01

Genes
HLA-B

Phenotypes
Epidermal Necrolysis, Toxic, Stevens-Johnson Syndrome

OMB Race
Asian

***15:02:01**	Patients with one or two copies of the HLA-B*15:02:01 allele may have an increased risk of Severe Cutaneous Adverse Reactions, such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, when treated with phenytoin as compared to patients with no HLA-B*15:02:01 alleles or negative for the HLA-B*15:02:01 test. Other genetic and clinical factors may also influence a patient's risk of phenytoin-induced adverse reactions.

Clinical Annotation for CYP2C9*1, CYP2C9*2, CYP2C9*3, phenytoin and Epilepsy (level 1A Toxicity/ADR, Metabolism/PK)

Level of Evidence
Level 1A

Type
Toxicity/ADR, Metabolism/PK

Variant
*1, *2, *3

Genes
CYP2C9

Phenotypes
Epilepsy

OMB Race
Mixed Population

User ID
hodoglugil

*1/*1	Patients with *1/*1 genotypes may have increased metabolism, decreased plasma concentration, decreased toxicity and decreased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*3, *2/*3 *2/*2 or *3/*3 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
*1/*3	Patients with *1/*3 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
*2/*2	Patients with *2/*2 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
*2/*3	Patients with *2/*3 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.
*3/*3	Patients with *3/*3 genotypes may have decreased metabolism, increased plasma concentration, increased toxicity and increased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*1 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy.

Hide Evidence

1. CYP2C9 *3 is associated with increased risk of Epidermal Necrolysis, Toxic and Stevens-Johnson Syndrome when treated with phenytoin as compared to CYP2C9 *1.
Association is significant using Bonferroni's correction for multiple comparison (18 for HLA-A, 26 for HLA-B, 15 for HLA-C, 2 for CYP2C9). *2 was genotyped but no carriers in either cases or controls identified.
PMID:26928377 Annotation Page

Study Size	Frequency	Race	Population Characteristics	P-value	Ratio	Type
39 / 92		Asian		= 0.0266	OR : 4.3	case/control

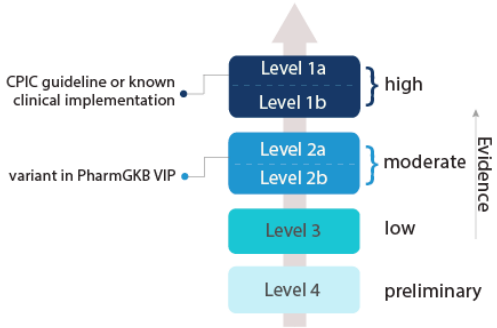
2. CYP2C9 *1/*1 + *1/*2 + *1/*17 are not associated with dose-adjusted trough concentrations of phenytoin in people with Epilepsy.
No significant difference in dose-corrected phenytoin concentrations was seen between the *1/*1 and *1/*2 genotypes (p=0.90), or between the *1/*2 and *1/*17 genotypes (p=0.91). Univariate analysis.
PMID:26122019 Annotation Page

Study Size	Frequency	Race	Population Characteristics	P-value	Ratio	Type
64 /	0.05 *2 / 0.04 *17	Hispanic or Latino		> 0.05		cohort

3. CYP2C9 *3 is associated with increased risk of severe cutaneous adverse reactions when treated with phenytoin.
Multiple cohorts were studied. 1) A GWAS discovery cohort of Taiwanese patients with healthy general population controls, 2) a replication cohort of Taiwanese patients with phenytoin-tolerant controls, 3) a combination of the discovery and replication cohorts of Taiwanese patients (population and tolerant controls combined), 4) in Malaysian patients with healthy general population controls and 5) in a meta-analysis of Taiwanese, Japanese and Malaysian patients with healthy general population controls. Severe cutaneous adverse reactions (SCARs) include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reactions with eosinophilia and systemic symptoms (DRESS).
PMID:25096692 Annotation Page

Study Size	Frequency	Race	Population Characteristics	P-value	Ratio	Type
60 / 412	0.21 *3 / 0.024 *3	Asian	Study Cohort: Taiwanese patients. GWAS Discovery cohort. Healthy general population controls.	= 1.5E-12	OR : 11.0	cohort, GWAS

Clinical Annotation Levels of Evidence



Level 1A

Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.

Level 1B

Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.

Level 2A

Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

Level 2B

Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Level 3

Annotation for a variant-drug combination based on a single significant (not yet replicated) or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.

Level 4

Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.

For more information about clinical annotations and levels of evidence, please refer to *Pharmacogenomics knowledge for personalized medicine.* Clinical pharmacology and therapeutics. 2012. Whirl-Carrillo M, McDonagh E M, Hebert J M, Gong L, Sangkuhl K, Thorn C F, Altman R B, Klein T E. [Article:22992668]

ClinVar

https://www.ncbi.nlm.nih.gov/clinvar/

ClinVar

ClinVar aggregates information about genomic variation and its relationship to human health.

Using ClinVar

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Tools

- ACMG Recommendations for Reporting of Incidental Findings
- ClinVar Submission Portal
- Submissions
- Variation Viewer
- Clinical Remapping - Between assemblies and RefSeqGenes
- RefSeqGene/LRG
- Variation Reporter

Related Sites

- ClinGen
- GeneReviews®
- GTR®
- MedGen
- OMIM®
- Variation

Submitter highlights

We gratefully acknowledge those who have submitted data and provided advice during the development of ClinVar.

Subscribe to our RSS feed and follow us on Twitter to receive announcements of the release of new datasets.

More information about our submitters is available, as well as a list of submitters with the number of records each has submitted.

Disclaimer

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Example: Phenytoin

NCBI Resources How To Sign in to NCBI

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ClinVar

ClinVar aggregates information about genomic variation and its relationship to human health.

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	Variation *Location*	Gene(s)	Condition(s)	Frequency	Clinical significance (Last reviewed)	Review status
1.	NM_021007.2(SCN2A):c.4633A>G (p.Met1545Val) *GRCh37:* Chr2:166243337 *GRCh38:* Chr2:165386827	SCN2A	not provided		Likely pathogenic (Dec 23, 2016)	criteria provided, single submitter
2.	NM_006920.4(SCN1A):c.603-91G>A *GRCh37:* Chr2:166909544 *GRCh38:* Chr2:166053034	SCN1A	Febrile seizures, familial, 3a, carbamazepine response - Dosage, **phenytoin** response - Dosage, antiepileptics response - Efficacy, carbamazepine response - Efficacy	GMAF:0.49340(T)	drug response	reviewed by expert panel
3.	NM_000927.4(ABCB1):c.3435T>C (p.Ile1145=) *GRCh37:* Chr7:87138645 *GRCh38:* Chr7:87509329	ABCB1	Non-small cell lung cancer, MDR1 POLYMORPHISM, digoxin response - Other, fentanyl response - Dosage, methadone response - Dosage, morphine response - Dosage, opioids response - Dosage, oxycodone response - Dosage, tramadol response - Dosage, ondansetron response - Efficacy, methotrexate response - Toxicity/ADRnevirapine response - Toxicity/ADR, ...see more	GMAF:0.39520(A)	drug response	reviewed by expert panel
4.	NM_000083.2(CLCN1):c.2680C>T (p.Arg894Ter) *GRCh37:* Chr7:143048771 *GRCh38:* Chr7:143351678	CLCN1	Congenital myotonia, autosomal recessive form, Congenital myotonia, autosomal dominant form, Myotonia congenita, not provided	GO-ESP:0.00085(T) GMAF:0.00160(T) GO-ESP:0.00287(T)	Conflicting interpretations of pathogenicity (Jan 3, 2017)	criteria provided, conflicting interpretations
5.	NM_000771.3(CYP2C9):c.[430C=;1075A>C] *GRCh37:* Chr10:96741053 Chr10:96702047 *GRCh38:* Chr10:94981296 Chr10:94942290	CYP2C9	Warfarin response	GO-ESP:0.04844(C) GMAF:0.04850(C) GO-ESP:0.06371(C) GMAF:0.04790(T)	drug response (Nov 20, 2006)	no assertion criteria provided
6.	NM_000771.3(CYP2C9):c.1075A>C (p.Ile359Leu) *GRCh37:* Chr10:96741053 *GRCh38:* Chr10:94981296	CYP2C9	Tolbutamide response, **Phenytoin** response, Glipizide poor metabolizer, Warfarin response, not provided, acenocoumarol response - Dosage, Toxicity/ADR, Antiinflammatory agents, non-steroids response -	GO-ESP:0.04844(C) GMAF:0.04850(C) GO-ESP:0.06371(C)	drug response	reviewed by expert panel

NM_000771.3(CYP2C9):c.1075A>C (p.Ile359Leu)

Variation ID: 8408

Review status: ★ ★ ★ ☆ reviewed by expert panel

Interpretation

Go to:

Clinical significance: drug response

Number of submission(s): 11

Condition(s):

- Tolbutamide response [MedGen]
- Phenytoin response [MedGen]
- Glipizide poor metabolizer [MedGen]
- Warfarin response [MedGen - OMIM]
- acenocoumarol response - Dosage, Toxicity/ADR [MedGen]
- Antiinflammatory agents, non-steroids response - Toxicity/ADR [MedGen]
- celecoxib response - Dosage [MedGen]
- celecoxib response - Toxicity/ADR [MedGen]
- diclofenac response - Toxicity/ADR [MedGen]
- warfarin response - Dosage, Toxicity/ADR [MedGen]

See supporting ClinVar records

Allele(s)

Go to:

NM_000771.3(CYP2C9):c.1075A>C (p.Ile359Leu)

Allele ID: 23447

Variant type: single nucleotide variant

Cytogenetic location: 10q23.3

Genomic location:
- Chr10: 94981296 (on Assembly GRCh38)
- Chr10: 96741053 (on Assembly GRCh37)

Other names:
- CYP2C9, ILE359LEU (rs1057910)
- CYP2C9*3

Protein change: I359L

HGVS:
- NG_008385.1:g.47639A>C
- NM_000771.3:c.1075A>C

...more

Links:
- PharmGKB Clinical Annotation: 655384720
- PharmGKB Clinical Annotation: 769181841
- PharmGKB Clinical Annotation: 827862258
- PharmGKB Clinical Annotation: 981238437
- UniProtKB: P11712#VAR_008345

Assertions for related alleles

NM_000771.3(CYP2C9):c.[430C=;1075A>C] Hel

Clinical significance: drug response

Review status: ☆ ☆ ☆ ☆ (0/4)

Number of submission(s): 1

Condition(s)

Warfarin response [MedGen - OMIM]

See supporting ClinVar records

1 Affected gene

cytochrome P450 family 2 subfamily C member 9 (CYP2C9) [Gene - OMIM - Variation Viewer]

Search ClinVar for variants within CYP2C9

Search ClinVar for variants including CYP2C9

Variant frequency in dbGaP

NM_000771.3(CYP2C9):c.1075A>C (p.Ile359Leu)
GRCh37 Chr10:96741053

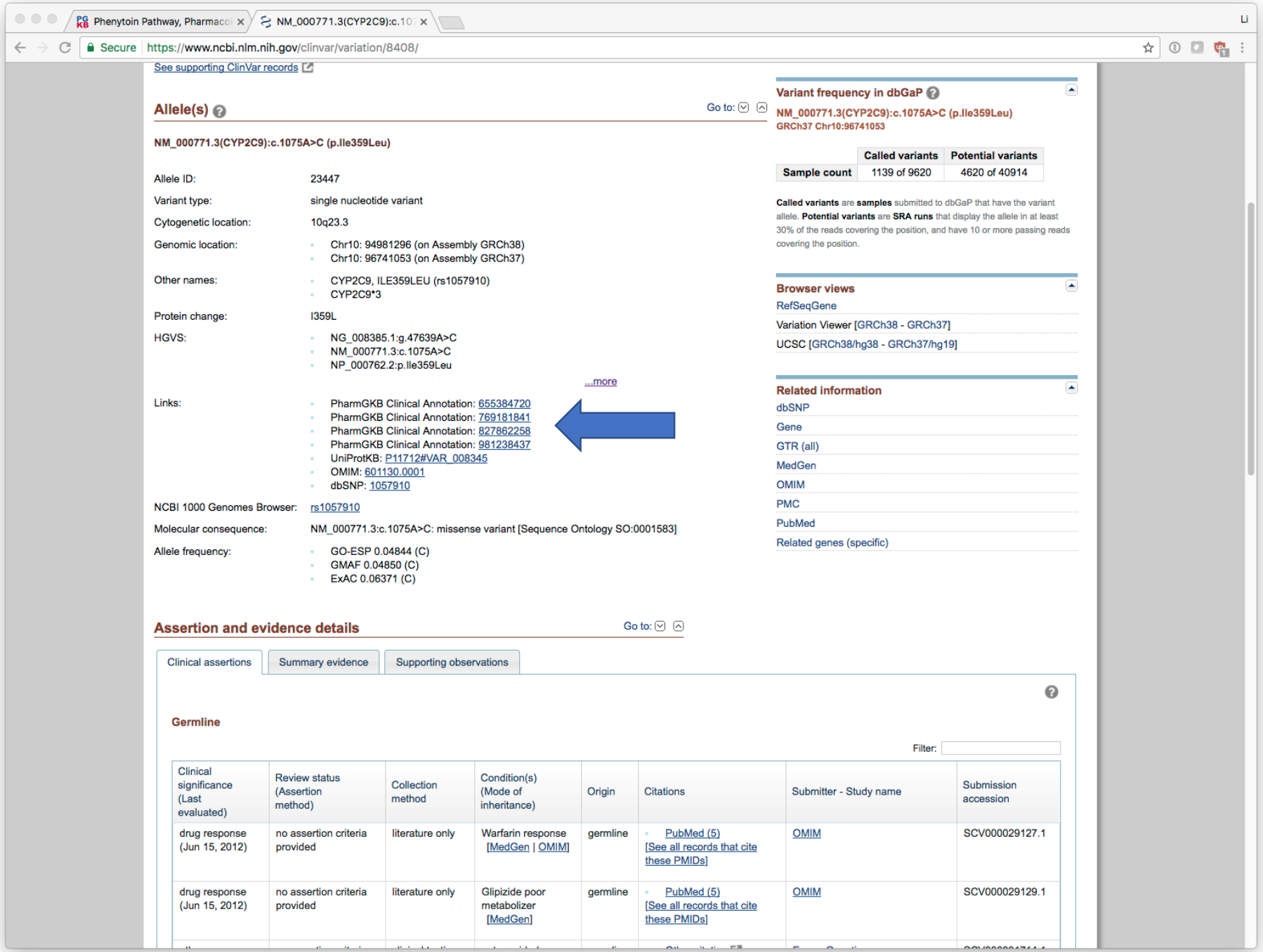
	Called variants	Potential variants
Sample count	1139 of 9620	4620 of 40914

Called variants are **samples** submitted to dbGaP that have the variant allele. **Potential variants** are **SRA runs** that display the allele in at least 30% of the reads covering the position, and have 10 or more passing reads covering the position.

Browser views

RefSeqGene

Variation Viewer [GRCh38 - GRCh37]


Phenytoin Pathway, Pharmacol
NM_000771.3(CYP2C9):c.107
Secure https://www.ncbi.nlm.nih.gov/clinvar/variation/8408/
See supporting ClinVar records
Allele(s)
Go to:
NM_000771.3(CYP2C9):c.1075A>C (p.Ile359Leu)
Allele ID: 23447
Variant type: single nucleotide variant
Cytogenetic location: 10q23.3
Genomic location: Chr10: 94981296 (on Assembly GRCh38)
Chr10: 96741053 (on Assembly GRCh37)
Other names: CYP2C9, ILE359LEU (rs1057910)
CYP2C9*3
Protein change: I359L
HGVS: NG_008385.1:g.47639A>C
NM_000771.3:c.1075A>C
NP_000762.2:p.Ile359Leu
...more
Links: PharmGKB Clinical Annotation: 655384720
PharmGKB Clinical Annotation: 769181841
PharmGKB Clinical Annotation: 827862258
PharmGKB Clinical Annotation: 981238437
UniProtKB: P11712#VAR_008345
OMIM: 601130.0001
dbSNP: 1057910
NCBI 1000 Genomes Browser: rs1057910
Molecular consequence: NM_000771.3:c.1075A>C: missense variant [Sequence Ontology SO:0001583]
Allele frequency: GO-ESP 0.04844 (C)
GMAF 0.04850 (C)
ExAC 0.06371 (C)
Variant frequency in dbGaP
NM_000771.3(CYP2C9):c.1075A>C (p.Ile359Leu)
GRCh37 Chr10:96741053
Called variants
Potential variants
Sample count
1139 of 9620
4620 of 40914
Called variants are samples submitted to dbGaP that have the variant allele. Potential variants are SRA runs that display the allele in at least 30% of the reads covering the position, and have 10 or more passing reads covering the position.
Browser views
RefSeqGene
Variation Viewer [GRCh38 - GRCh37]
UCSC [GRCh38/hg38 - GRCh37/hg19]
Related information
dbSNP
Gene
GTR (all)
MedGen
OMIM
PMC
PubMed
Related genes (specific)
Assertion and evidence details
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Germline
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Review status (Assertion method)
Collection method
Condition(s) (Mode of inheritance)
Origin
Citations
Submitter - Study name
Submission accession
drug response (Jun 15, 2012)
no assertion criteria provided
literature only
Warfarin response [MedGen | OMIM]
germline
PubMed (5) [See all records that cite these PMIDs]
OMIM
SCV000029127.1
drug response (Jun 15, 2012)
no assertion criteria provided
literature only
Glipizide poor metabolizer [MedGen]
germline
PubMed (5) [See all records that cite these PMIDs]
OMIM
SCV000029129.1

Assertion and evidence details

Go to:

Clinical assertions | Summary evidence | Supporting observations

Germline

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
drug response (Jun 15, 2012)	no assertion criteria provided	literature only	Warfarin response [MedGen | OMIM]	germline	PubMed (5) [See all records that cite these PMIDs]	OMIM	SCV000029127.1
drug response (Jun 15, 2012)	no assertion criteria provided	literature only	Glipizide poor metabolizer [MedGen]	germline	PubMed (5) [See all records that cite these PMIDs]	OMIM	SCV000029129.1
other (Jul 10, 2015)	no assertion criteria provided	clinical testing	not provided [MedGen]	germline	Other citation	Emory Genetics Laboratory,Emory University	SCV000331714.1

PGx

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Subm acces
drug response	reviewed by expert panel Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (3) [See all records that cite these PMIDs] Other citation	PharmGKB	SCV
drug response	reviewed by expert panel Pharmacogenomics knowledge for personalized	literature only	Condition: warfarin response - Dosage, Toxicity/ADR Drug reported used for: Atrial fibrillation [MedGen]	germline	PubMed (32) [See all records that cite	PharmGKB	SCV

PGx

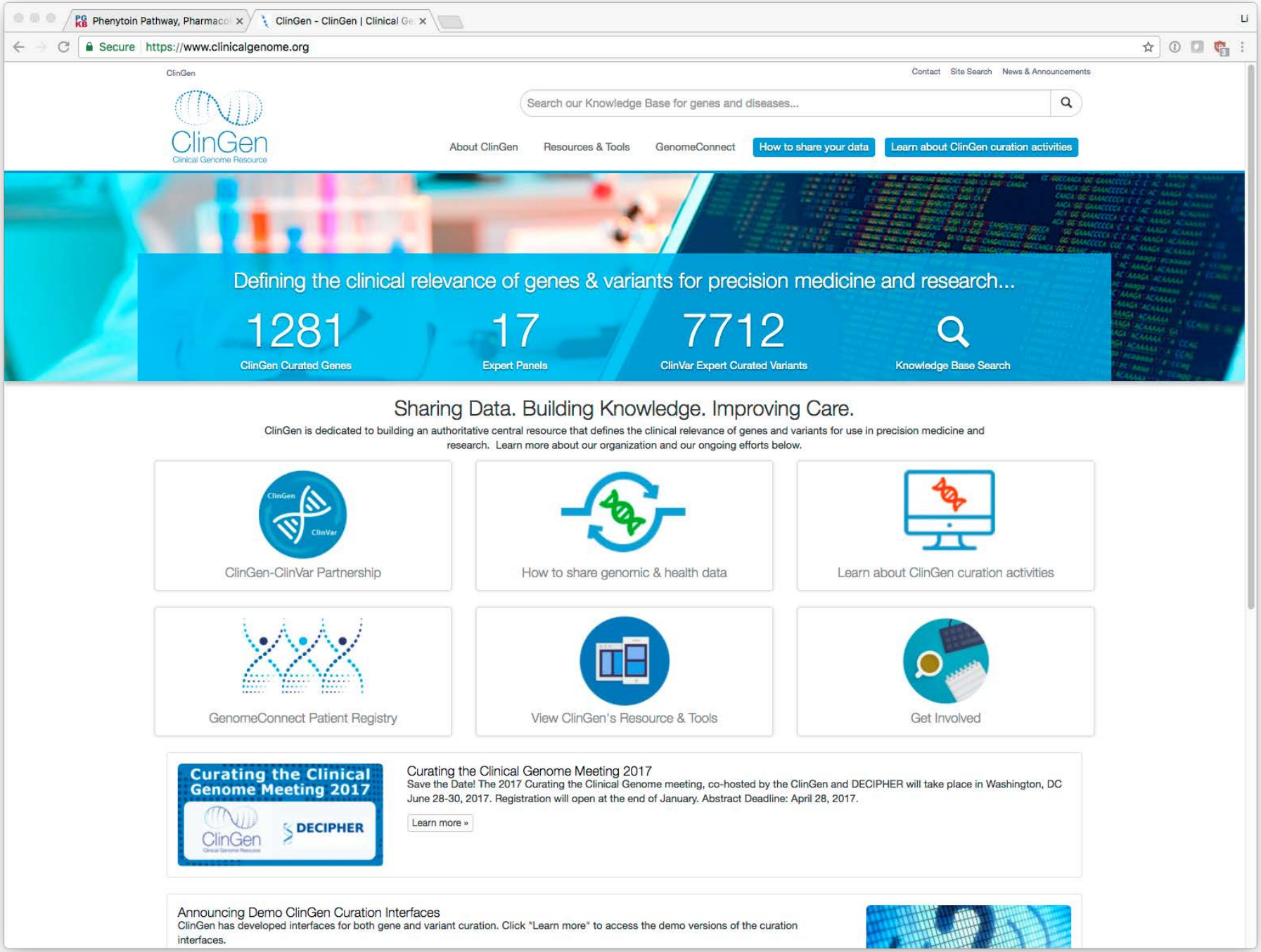
Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (3) [See all records that cite these PMIDs] Other • citation	PharmGKB	SCV000268147.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: warfarin response - Dosage, Toxicity/ADR Drug reported used for: Atrial fibrillation [MedGen] Drug reported used for: Atrial Fibrillation;Pulmonary Embolism;Stroke;Venous Thrombosis	germline	PubMed (32) [See all records that cite these PMIDs] Other • citation	PharmGKB	SCV000268152.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (4) [See all records that cite these PMIDs] Other • citation	PharmGKB	SCV000268153.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (2) [See all records that cite these PMIDs] Other • citation	PharmGKB	SCV000268154.2
drug response	reviewed by expert panel • Pharmacogenomics	literature only	Condition: not provided	germline	PubMed (2)	PharmGKB	SCV000268155.2

drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (2) [See all records that cite these PMIDs] Other • citation	PharmGKB	SCV000268154.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (2) [See all records that cite these PMIDs] Other • citation	PharmGKB	SCV000268155.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (2) [See all records that cite these PMIDs] Other • citation	PharmGKB	SCV000268156.2
drug response (Dec 30, 2010)	no assertion criteria provided	literature only	Condition: not provided	germline	PubMed (5) [See all records that cite these PMIDs]	OMIM	SCV000029126.1
drug response (Jun 15, 2012)	no assertion criteria provided	literature only	Condition: not provided	germline	PubMed (5) [See all records that cite these PMIDs]	OMIM	SCV000029128.1

ClinGen: Clinical Genome Resource

https://www.clinicalgenome.org


Phenytoin Pathway, Pharmacol
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Secure https://www.clinicalgenome.org
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17
Expert Panels
7712
ClinVar Expert Curated Variants
Knowledge Base Search
Sharing Data. Building Knowledge. Improving Care.
ClinGen is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. Learn more about our organization and our ongoing efforts below.
ClinGen-ClinVar Partnership
How to share genomic & health data
Learn about ClinGen curation activities
GenomeConnect Patient Registry
View ClinGen's Resource & Tools
Get Involved
Curating the Clinical Genome Meeting 2017
ClinGen
DECIPHER
Curating the Clinical Genome Meeting 2017
Save the Date! The 2017 Curating the Clinical Genome meeting, co-hosted by the ClinGen and DECIPHER will take place in Washington, DC June 28-30, 2017. Registration will open at the end of January. Abstract Deadline: April 28, 2017.
Learn more »
Announcing Demo ClinGen Curation Interfaces
ClinGen has developed interfaces for both gene and variant curation. Click "Learn more" to access the demo versions of the curation interfaces.

ClinVar

ClinVar is a a freely accessible, public archive of reports of the relationships among human variations and phenotypes hosted by the National Center for Biotechnology Information (NCBI) and funded by intramural National Institutes of Health (NIH) funding. ClinGen investigators work closely with NCBI regarding the development and functionality of ClinVar and to support data deposition from many sources; ClinGen curation efforts will constantly improve the data within ClinVar.

Visit the ClinVar site today to search for information on genomic variants! Not sure how to use ClinVar? Check out the links below for selected "how-to" resources from the ClinVar team. Always check the ClinVar site for the most up-to-date information regarding resource utilization. For instructions and guidance on submitting to ClinVar, visit the ClinVar Submission page and ClinGen's Data Sharing Guidance page.

ClinGen Community ClinVar Call

Beginning in January 2016, the ClinGen Community ClinVar call on the 4th Friday of each month will bring together members of ClinGen and any interested user of ClinVar to suggest and discuss topics about using or submitting to ClinVar. If you would like to join the mailing list to receive call information and a monthly reminder please email us. If you have a topic you would like to add to the agenda, please use our topic request form.

About the ClinGen and ClinVar Partnership

Learn more about ClinVar and ClinGen's partnership to improve our knowledge of clinically relevant genomic variation.

more »

Submitting to ClinVar as an Expert Panel

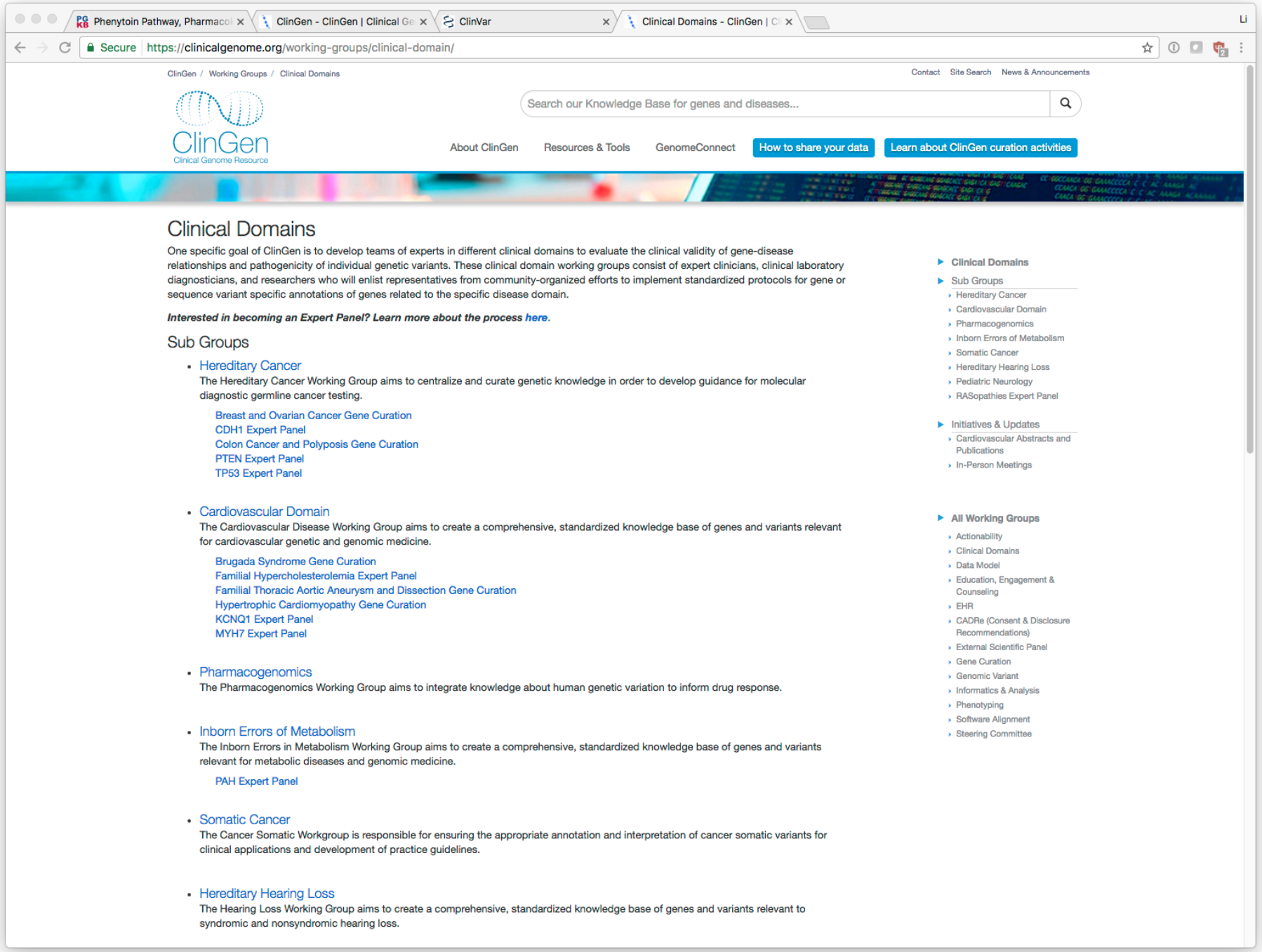
ClinVar uses a rating system to help users assess the quality and consistency of submitted variant interpretations. Click here to learn more about how to apply for Expert Panel and Practice Guideline status

more »

Selected ClinVar FAQs

Click here for a quick look at some of the most frequently asked questions about ClinVar.

more »


Phenytoin Pathway, Pharmacol
ClinGen - ClinGen | Clinical Ge
ClinVar
Clinical Domains - ClinGen | Cl
Secure https://clinicalgenome.org/working-groups/clinical-domain/
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Clinical Genome Resource
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Resources & Tools
GenomeConnect
How to share your data
Learn about ClinGen curation activities
Clinical Domains
One specific goal of ClinGen is to develop teams of experts in different clinical domains to evaluate the clinical validity of gene-disease relationships and pathogenicity of individual genetic variants. These clinical domain working groups consist of expert clinicians, clinical laboratory diagnosticians, and researchers who will enlist representatives from community-organized efforts to implement standardized protocols for gene or sequence variant specific annotations of genes related to the specific disease domain.
Interested in becoming an Expert Panel? Learn more about the process here.
Sub Groups
Hereditary Cancer
The Hereditary Cancer Working Group aims to centralize and curate genetic knowledge in order to develop guidance for molecular diagnostic germline cancer testing.
Breast and Ovarian Cancer Gene Curation
CDH1 Expert Panel
Colon Cancer and Polyposis Gene Curation
PTEN Expert Panel
TP53 Expert Panel
Cardiovascular Domain
The Cardiovascular Disease Working Group aims to create a comprehensive, standardized knowledge base of genes and variants relevant for cardiovascular genetic and genomic medicine.
Brugada Syndrome Gene Curation
Familial Hypercholesterolemia Expert Panel
Familial Thoracic Aortic Aneurysm and Dissection Gene Curation
Hypertrophic Cardiomyopathy Gene Curation
KCNQ1 Expert Panel
MYH7 Expert Panel
Pharmacogenomics
The Pharmacogenomics Working Group aims to integrate knowledge about human genetic variation to inform drug response.
Inborn Errors of Metabolism
The Inborn Errors in Metabolism Working Group aims to create a comprehensive, standardized knowledge base of genes and variants relevant for metabolic diseases and genomic medicine.
PAH Expert Panel
Somatic Cancer
The Cancer Somatic Workgroup is responsible for ensuring the appropriate annotation and interpretation of cancer somatic variants for clinical applications and development of practice guidelines.
Hereditary Hearing Loss
The Hearing Loss Working Group aims to create a comprehensive, standardized knowledge base of genes and variants relevant to syndromic and nonsyndromic hearing loss.
Clinical Domains
Sub Groups
Hereditary Cancer
Cardiovascular Domain
Pharmacogenomics
Inborn Errors of Metabolism
Somatic Cancer
Hereditary Hearing Loss
Pediatric Neurology
RASopathies Expert Panel
Initiatives & Updates
Cardiovascular Abstracts and Publications
In-Person Meetings
All Working Groups
Actionability
Clinical Domains
Data Model
Education, Engagement & Counseling
EHR
CADRe (Consent & Disclosure Recommendations)
External Scientific Panel
Gene Curation
Genomic Variant
Informatics & Analysis
Phenotyping
Software Alignment
Steering Committee

Pharmacogenomics

Sub group of Clinical Domains

The Pharmacogenomics Working Group aims to integrate knowledge about human genetic variation to inform drug response.

Goals:

1. Evaluate PGx genes, their impact on drugs, and provide additional annotation that supplements existing pharmacogenetic guidelines.
2. Develop systematic methods for representing and depositing knowledge from the Pharmacogenomics (PGx) Working Group, Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmGKB into ClinGen and ClinVar on a regular schedule.
3. Participate in discussions on the reconciliation of disparate nomenclatures in pharmacogenetics, including:
    - Build working relationships with CPIC to develop standardized terminology for functional status and allele definitions, and, engage genetic testing laboratories to consistently apply these standardized definitions.
    - Work with the American College of Medical Genetics and Genomics (ACMG) to develop a nomenclature appropriate for PGx variants similar to that of disease variants for pathogenicity.
    - Support the development with the Center for Disease Control (CDC) Nomenclature group for standards for PGx assays such that it is clear what is being tested on a specific gene (e.g., CYP2D6 star system means what actual SNPs were tested).
4. Interact with other ClinGen WGs to harmonize the final contributions to the ClinGen resource.

Chairs

Teri E. Klein, PhD, FACMI, FACMG

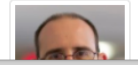
Marylyn D. Ritchie, PhD

Coordinator

E. Andy Rivera M.

Members

Gillian Bell, PharmD



Jonathan Berg, MD, PhD
Principal Investigator, "A Knowledge Base for

▸ Clinical Domains
▸ Sub Groups
› Hereditary Cancer
› Cardiovascular Domain
› Pharmacogenomics
› Inborn Errors of Metabolism
› Somatic Cancer
› Hereditary Hearing Loss
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ClinGen
Clinical Genome Resource

The ClinVar database is hosted by NCBI and currently focuses on sharing variant-centric information. As part of the submission process, the entity submitting information is asked to provide an assertion with regard to "Clinical Significance".

In order for users of ClinVar to have additional information with regard to the level of review of the submissions, ClinVar has developed a four star rating system, representing the "Review Status" of each submission. By default, ClinVar submissions have the review status "single submitter - criteria not provided". However, submissions may obtain the statuses of "single submitter - criteria provided", "expert panel" and "practice guidelines" according to the descriptions below. Full implementation is scheduled for June 2015.

Single submitter - criteria provided – one star

The one star review status refers to "single submitter - criteria provided" assertions. For a submission to achieve this status, the submitter must:

1. Document that the allele or genotype was classified according to a comprehensive review of evidence consistent with, or more thorough than, current practice guidelines (*e.g.* review of case data, genetic data and functional evidence from the literature and analysis of population frequency and computational predictions)
2. Include a clinical significance assertion using a variant scoring system with a minimum of three levels for monogenic disease variants (pathogenic, uncertain significance, benign) or appropriate terms for other types of variation.
3. Provide a publication or other electronic document (such as a PDF) that describes the variant assessment terms used (*e.g.* pathogenic, uncertain significance, benign or appropriate terms for other types of variation) and the criteria required to assign a variant to each category. This document will be available to ClinVar users via the ClinVar website (link provided for all submitted assertions).
4. Submit available supporting evidence or rationale for classification (*e.g.* literature citations, total number of case observations, descriptive summary of evidence, web link to site with additional data, *etc.*) or be willing to be contacted by ClinVar users to provide supporting evidence. In other words, contact information for one person on the submission must be submitted as "public".

ClinVar will not review the details of the variant scoring criteria accompanying a submission. Instructions for completing a submission to meet these requirements will provided on our submission forms. Note that if a submission includes multiple records, designations for each can differ, namely either 'single submitter - criteria provided' or 'single submitter - no criteria provided'.

Expert panel – three stars

The three star review status refers to "expert panel" assertions. Groups seeking expert panel designation should submit the information described below using this form:

ClinVar Expert Panel request form (maximum of 3 pages)

and send to clinvar@ncbi.nlm.nih.gov.

The information provided on the expert panel request form will be posted on the ClinVar website to provide users information about the groups obtaining this status.

For submitted variants to be assigned Expert Panel criteria level, the submitter must meet all requirements for "Single submitter, criteria provided" as well as the additional requirements described below. Applications for Expert Panel status must be reviewed and approved by the Clinical Genome Resource (ClinGen) program.

Panel Membership

- A membership list must be provided for review when requesting Expert Panel status for submissions.
- It is recommended that the expert panel include medical professionals caring for patients relevant to the disease gene in question, medical geneticists, clinical laboratory diagnosticians and/or molecular pathologists who report such findings and appropriate researchers relevant to the disease, gene, functional assays and statistical analyses.
- It is expected that the individuals comprising the expert panel process represent multiple institutions.
- It is expected that the individuals comprising the expert panel should be international in scope, and are considered by the community to be experts in the field based on publications and long-standing scope of work.
- ClinGen hopes that there is only one expert panel per gene and that the panel is inclusive of known experts in the field. Therefore, if you have expertise in a gene that is already evaluated by an expert panel, please consider joining efforts with the existing panel or provide justification for the necessity of an additional panel.
- We encourage newly forming expert panels to contact ClinGen (clingen@clinicalgenome.org) early in the process to discuss the formation of the panel.

Conflict of Interest

Information should be provided with regard to any potential financial conflicts of interest of the panel members and how conflicts are managed.

Practice guideline - four stars

The four star review status refers to "practice guideline" assertions. Groups seeking practice guideline designation should submit the information described below using this form:

ClinVar Practice Guideline request form (maximum of 3 pages)

and send to clinvar@ncbi.nlm.nih.gov. This information will be reviewed by the ClinGen Steering Committee to make the determination of practice guideline status for clinical assertions in ClinVar.

The information provided on the practice guideline request form will be posted on the ClinVar website to provide users information about the groups obtaining this status.

Please make note of the following points:

1. The submitter must meet all requirements for single submitter - criteria provided and expert panel designation as well as the additional requirements described below.
2. A description of the **rating system for strength of evidence** utilized, unless already included in the variant assessment method.
3. A description of the **external review process** for determining the clinical relevance of variants prior to publication

GENETICS IN MEDICINE | ORIGINAL RESEARCH ARTICLE OPEN

Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Kelly E. Caudle PharmD, PhD, Henry M. Dunnenberger PharmD, Robert R. Freimuth PhD, Josh F. Peterson MD, Jonathan D. Burlison PhD, Michelle Whirl-Carrillo PhD, Stuart A. Scott PhD, Heidi L. Rehm PhD, Marc S. Williams MD, Teri E. Klein PhD, Mary V. Relling PharmD & James M. Hoffman PharmD, MS

Affiliations | Corresponding author

Genetics in Medicine (2017) **19**, 215–223 | doi:10.1038/gim.2016.87

Received 29 January 2016 | Accepted 17 May 2016 | Published online 21 July 2016

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Abstract

Introduction:
Reporting and sharing pharmacogenetic test results across clinical laboratories and electronic health records is a crucial step toward the implementation of clinical pharmacogenetics, but allele function and phenotype terms are not standardized. Our goal was to develop terms that can be broadly applied to characterize pharmacogenetic allele function and inferred phenotypes.

Materials and methods:
Terms currently used by genetic testing laboratories and in the literature were identified. The Clinical Pharmacogenetics Implementation Consortium (CPIC) used the Delphi method to obtain a consensus and agree on uniform terms among pharmacogenetic experts.

Results:
Experts with diverse involvement in at least one area of pharmacogenetics (clinicians

Most read

Beta-thalassemia
Genetics in Medicine | 21 January 2010

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology
Genetics in Medicine | 05 March 2015

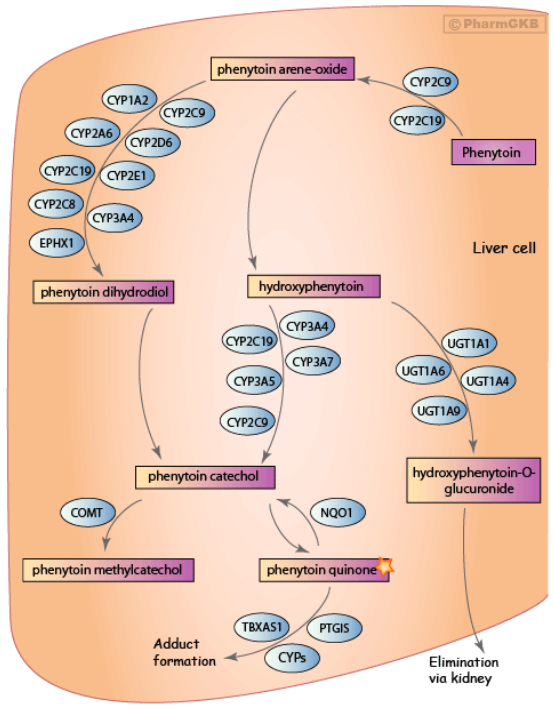
Factor V Leiden thrombophilia
Genetics in Medicine | 14 November 2010

PATHWAY

Phenytoin Pathway, Pharmacokinetics

Overview | Components | Related Pathways | Related Publications | Downloads

Genes involved in the metabolism of phenytoin in the human liver cell.



- Legend
- Pathway diagram
- Pathway diagram (Illustrator)
- How to cite this pathway?
- All PharmGKB pathways

Click icons in pathway for more info
gene | drug | pathway

Description

Background

Phenytoin is one of the most widely-prescribed antiepileptic drugs (AEDs) in the USA (approximately 52% of AED prescriptions compared to 19% for valproic acid, 11% carbamazepine and 7% phenobarbital) [Article:19855097]. It has a narrow therapeutic range and wide inter-individual variability in clearance and as such, therapeutic drug monitoring is often necessary. Adverse effects of phenytoin range from minor (eg. gingival hyperplasia) to severe and life threatening (eg. Stevens-Johnson Syndrome, SJS, and Toxic Epidermal Necrolysis, TEN) and teratogenic (eg. birth defects).

Pharmacokinetics

Metabolizing enzymes

PATHWAY

Phenytoin Pathway, Pharmacokinetics

Entities in the Pathway

Genes (20)

COMT, CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP3A7, EPHX1, NQO1, PTGIS, TBXAS1, UGT1A1, UGT1A4, UGT1A6, UGT1A9

Drugs/Drug Classes (1)

phenytoin

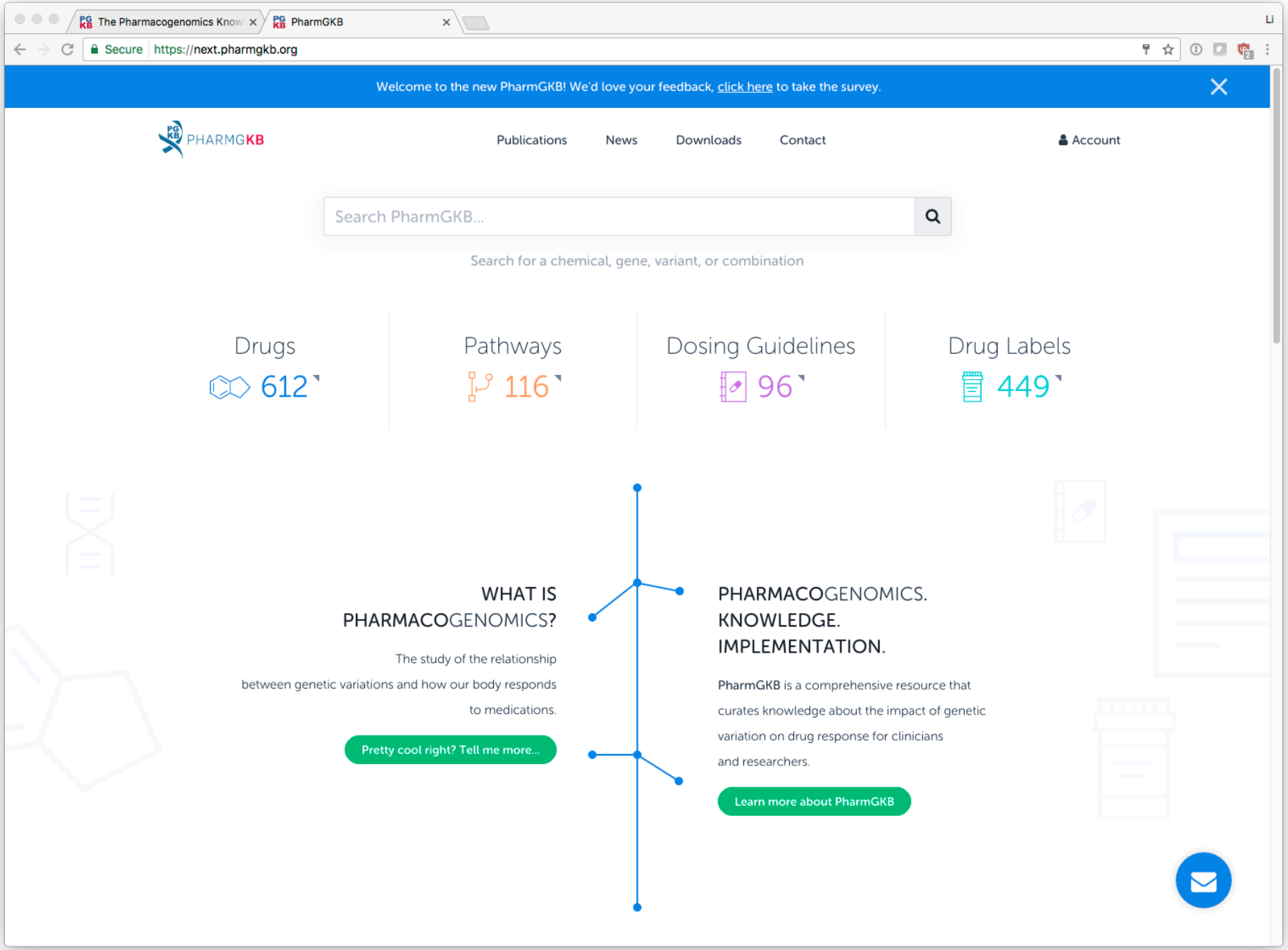
Relationships in the Pathway

Arrow From	Arrow To	Controllers	PMID
hydroxyphenytoin	hydroxyphenytoin-O-glucuronide	UGT1A1, UGT1A4, UGT1A6, UGT1A9	12386132, 15855726, 17576806
hydroxyphenytoin	phenytoin catechol	CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP3A7	10901705, 11038165, 16359177
phenytoin arene-oxide	hydroxyphenytoin		16815679
phenytoin arene-oxide	phenytoin dihydrodiol	CYP1A2, CYP2A6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4, EPHX1	11038165, 9798756
phenytoin catechol	phenytoin methylcatechol	COMT	9798756
phenytoin catechol	phenytoin quinone	NQO1	9798756
phenytoin dihydrodiol	phenytoin catechol		9798756
phenytoin	phenytoin arene-oxide	CYP2C19, CYP2C9	9798756

Download data in TSV format . Other formats are available on the Downloads/LinkOuts tab.

New PharmGKB Website

https://next.pharmgkb.org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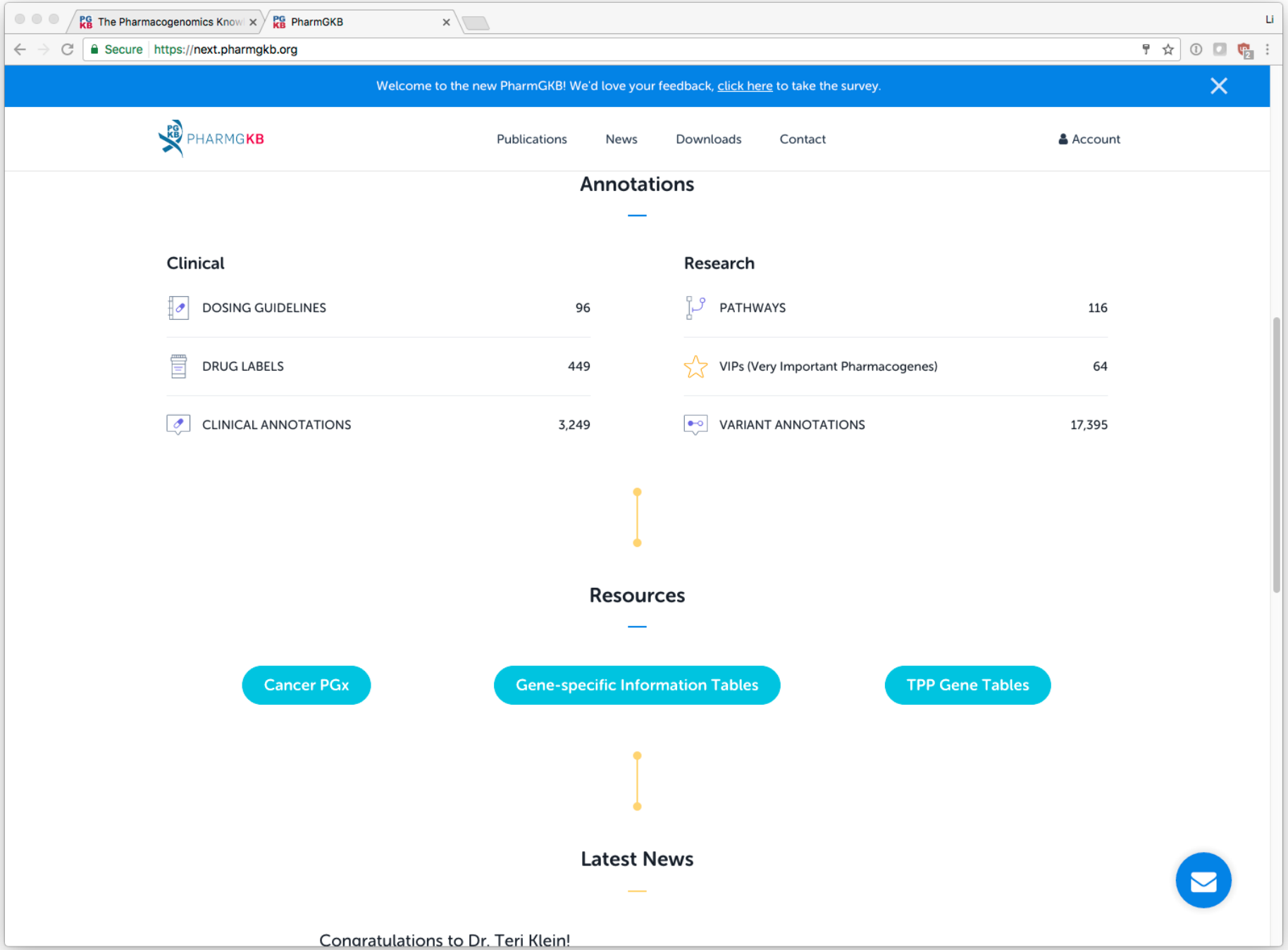
Dosing Guidelines
96
Drug Labels
449
WHAT IS PHARMACOGENOMICS?
The study of the relationship between genetic variations and how our body responds to medications.
Pretty cool right? Tell me more...
PHARMACOGENOMICS. KNOWLEDGE. IMPLEMENTATION.
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.
Learn more about PharmGKB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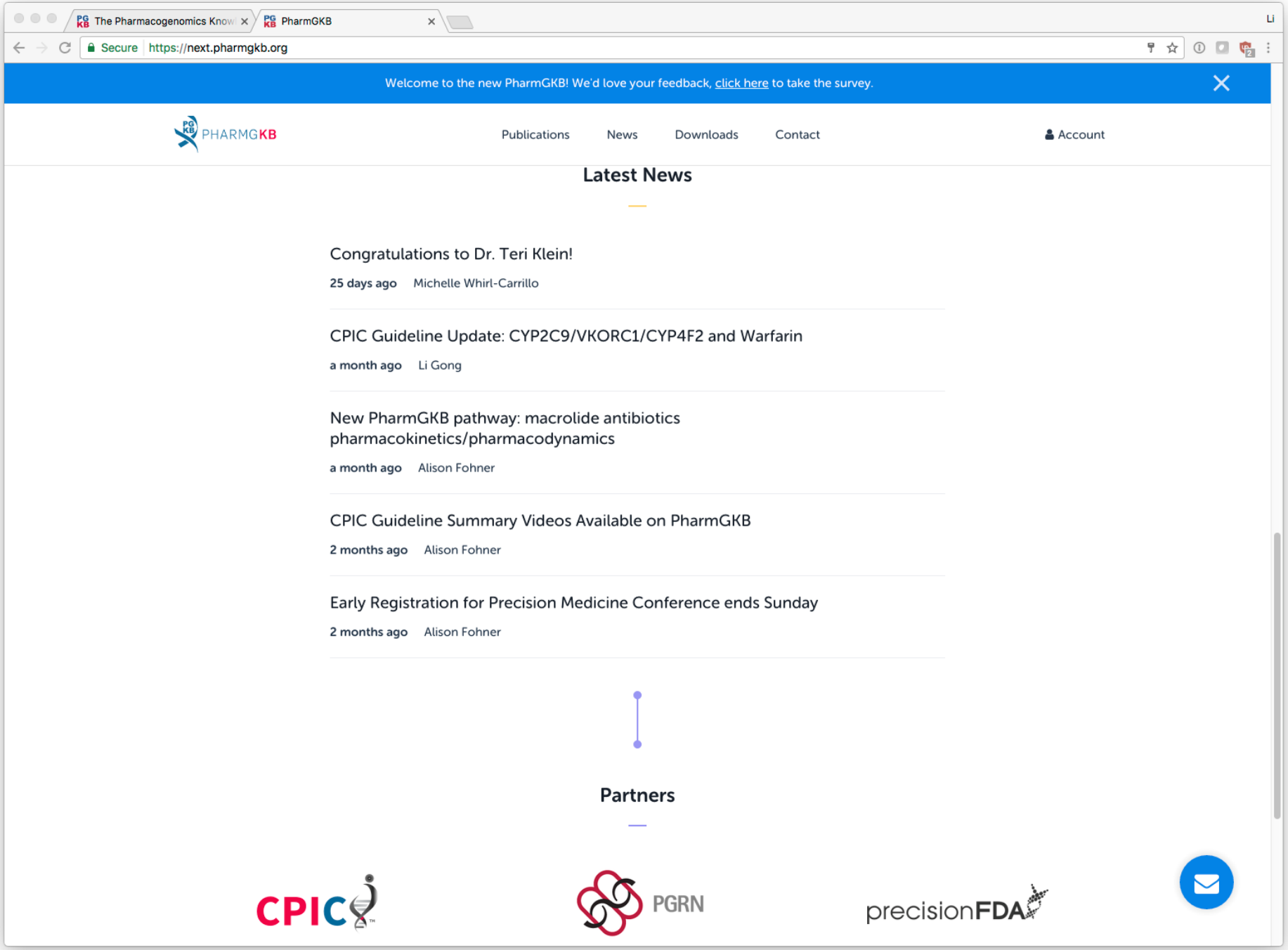
Cancer PGx
Gene-specific Information Tables
TPP Gene Tables
Latest News
Congratulations to Dr. Teri Klein!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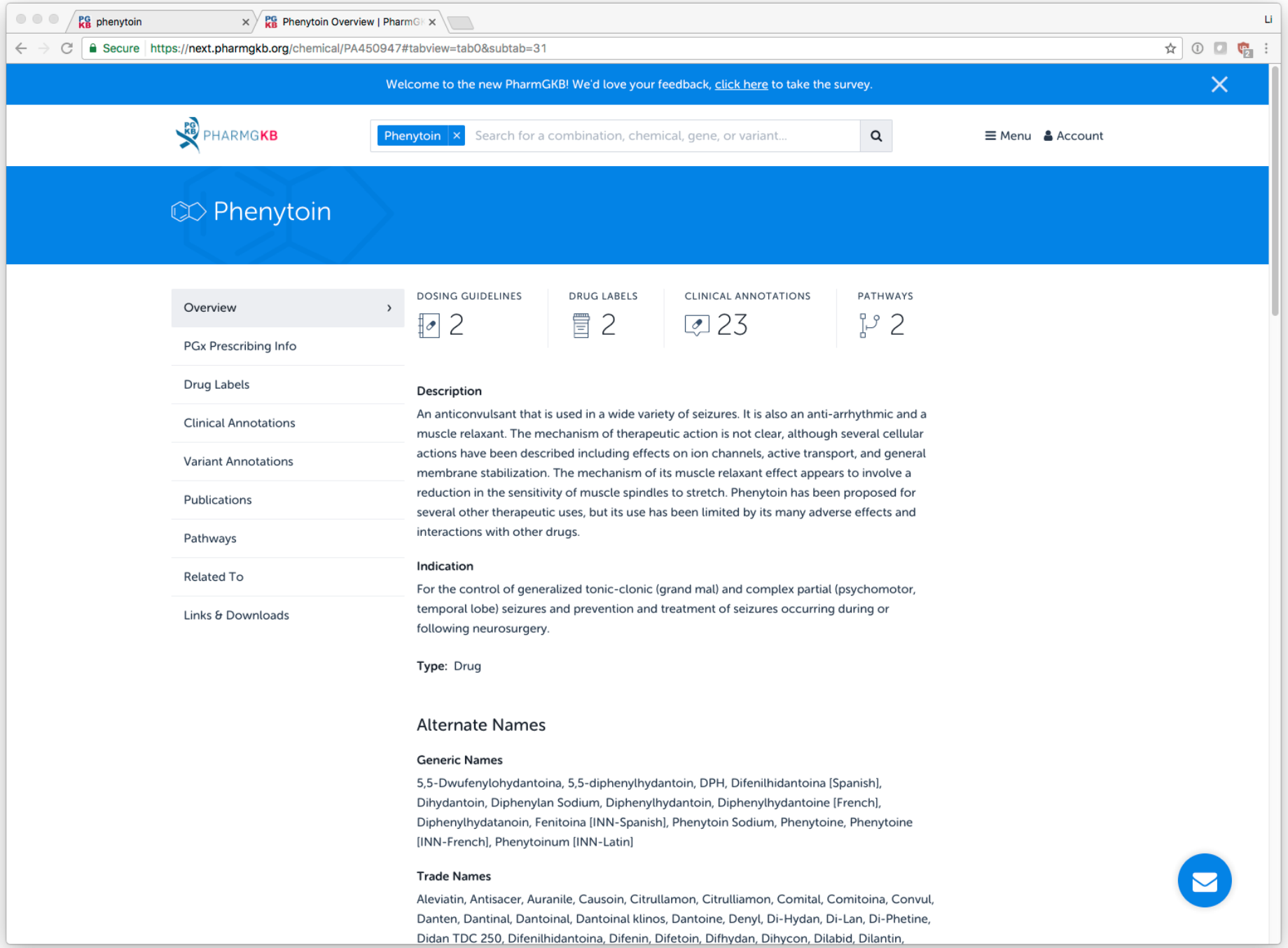
Latest News
Congratulations to Dr. Teri Klein!
25 days ago Michelle Whirl-Carrillo
CPIC Guideline Update: CYP2C9/VKORC1/CYP4F2 and Warfarin
a month ago Li Gong
New PharmGKB pathway: macrolide antibiotics pharmacokinetics/pharmacodynamics
a month ago Alison Fohner
CPIC Guideline Summary Videos Available on PharmGKB
2 months ago Alison Fohner
Early Registration for Precision Medicine Conference ends Sunday
2 months ago Alison Fohner
Partners
CPIC
PGRN
precisionFDA


phenytoin
Phenytoin Overview | PharmG
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Variant Annotations
Publications
Pathways
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2
DRUG LABELS
2
CLINICAL ANNOTATIONS
23
PATHWAYS
2
Description
An anticonvulsant that is used in a wide variety of seizures. It is also an anti-arrhythmic and a muscle relaxant. The mechanism of therapeutic action is not clear, although several cellular actions have been described including effects on ion channels, active transport, and general membrane stabilization. The mechanism of its muscle relaxant effect appears to involve a reduction in the sensitivity of muscle spindles to stretch. Phenytoin has been proposed for several other therapeutic uses, but its use has been limited by its many adverse effects and interactions with other drugs.
Indication
For the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.
Type: Drug
Alternate Names
Generic Names
5,5-Dwufenylohydantoina, 5,5-diphenylhydantoin, DPH, Difenilhidantoina [Spanish], Dihydantoin, Diphenylan Sodium, Diphenylhydantoin, Diphenylhydantoine [French], Diphenylhydatanoin, Fenitoina [INN-Spanish], Phenytoin Sodium, Phenytoine, Phenytoine [INN-French], Phenytoinum [INN-Latin]
Trade Names
Aleviatin, Antisacer, Auranile, Causoin, Citrullamon, Citrulliamon, Comital, Comitoina, Convul, Danten, Dantinal, Dantoinal, Dantoinal klinos, Dantoine, Denyl, Di-Hydan, Di-Lan, Di-Phetine, Didan TDC 250, Difenilhidantoina, Difenin, Difetoin, Difhydan, Dihycon, Dilabid, Dilantin,

Acknowledgments

- Pis: Russ Altman and Teri Klein

- The PharmGKB team:
  - Julia Barbarino, Lester Carter, Matt Devlin, Alie Fohner, Li Gong, Tiffany Murray, Katrin Sangkuhl, Caroline Thor

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