PharmGKB

and

CPIC™

Clinical Pharmacogenetics Implementation Consortium

Resources for PGx Implementation

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and Teri Klein, Stanford University

Overview of the PharmGKB

The PharmGKB is a pharmacogenomics knowledge resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships. PharmGKB collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses through the following activities:

- Annotate genetic variants and gene-drug-disease relationships via literature reviews
- Summarize important pharmacogenomic genes, associations between genetic variants and drugs, and drug pathways
- Curate FDA drug labels containing pharmacogenomic information
- Enable consortia examining important questions in pharmacogenomics
- Curate and participate in writing pharmacogenomic-based drug dosing guidelines
- Contribute to clinical implementation projects for pharmacogenomics through collaborations
- Publish pharmacogenomic-based drug dosing guidelines, very important pharmacogene summaries and drug-centered pathways
- Display all information on the website and provide comprehensive downloads

PharmGKB offers information as:

- Variant Annotations (Research-level annotations of individual publications describing the relationship between genetic variants and drugs; these are created on a paper-by-paper basis)
- Drug-Centered Pathway
- Very Important Pharmacogene Summaries
- Clinical Annotations (Genotype-based pharmacogenomic relationships summarizing all variant annotations regarding the same genetic variant-drug association)
- Pharmacogenomics-Based Drug-Dosing Guidelines
- Drug Labels with Pharmacogenomic Information

The PharmGKB Knowledge Pyramid

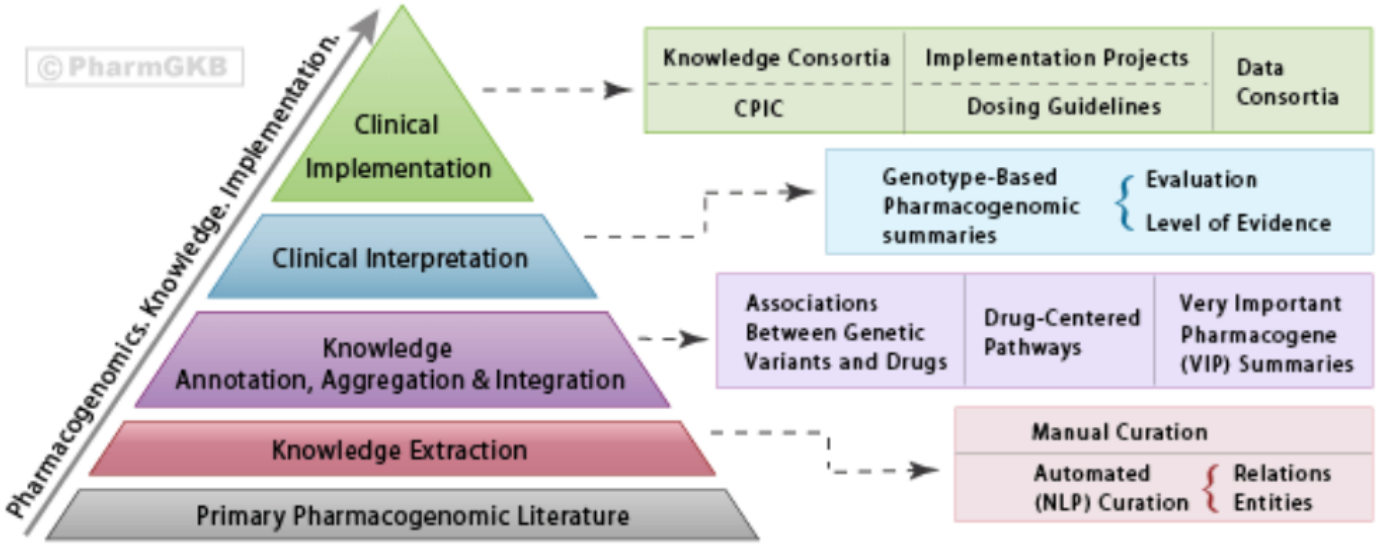
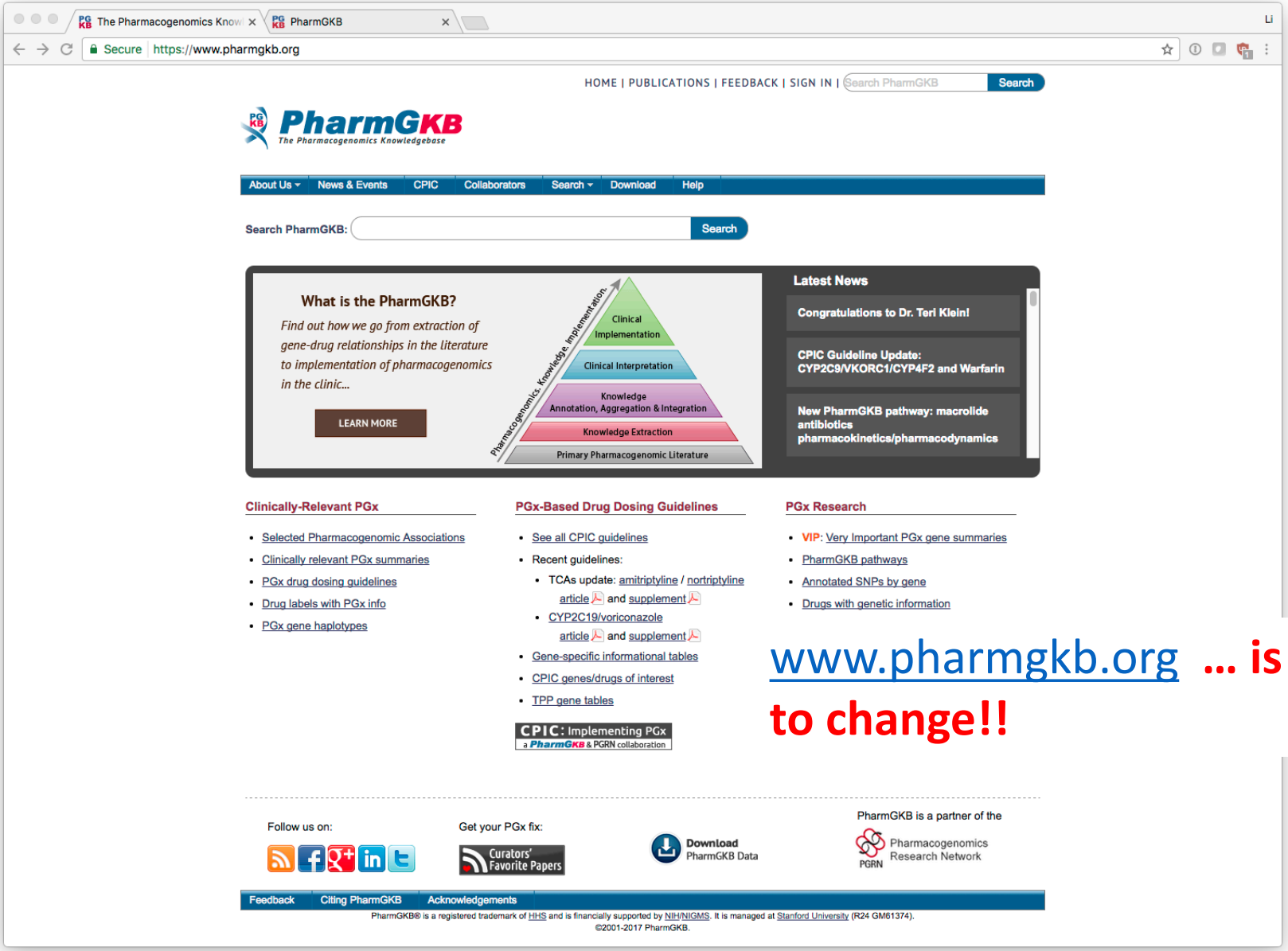


Figure 1: The PharmGKB Knowledge Pyramid. A visual representation of the information available at www.pharmgkb.org and the research by the PharmGKB team.



www.pharmgkb.org **… is about to change!!**

Annotations

Clinical

DOSING GUIDELINES	96
DRUG LABELS	449
CLINICAL ANNOTATIONS	3,249

Research

PATHWAYS	116
VIPs (Very Important Pharmacogenes)	64
VARIANT ANNOTATIONS	17,395

Resources

Cancer PGx

Gene-specific Information Tables

TPP Gene Tables

Latest News

Drug Labels

PharmGKB annotates drug labels containing pharmacogenetic information approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency, Japan (PMDA), and Health Canada (Santé Canada) (HCSC). PharmGKB annotations provide a brief summary of the PGx in the label, an excerpt from the label and a downloadable highlighted label PDF file. A list of genes and phenotypes found within the label is mapped to label section headers and listed at the end of each annotation. PharmGKB also attempts to interpret the level of action implied in each label with the "PGx Level" tag.

See the legend for more information about drug label sources and PGx Levels.

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

☐ B Only FDA Biomarker drugs ☐ Only labels with dosing info Filter

DRUG		FDA	EMA	PMDA	HCSC
Abacavir	B	Genetic testing required	Genetic testing required	Informative PGx	Genetic testing required
Abiraterone		Informative PGx			
Acetaminophen					Actionable PGx
Afatinib	B	Genetic testing required	Genetic testing required		Genetic testing required
Afutuzumab	B	Informative PGx			Informative PGx
Alectinib	B	Genetic testing required			
Alirocumab	B	Actionable PGx			
Aliskiren			Informative PGx		Informative PGx
Allopurinol				Actionable PGx	
Amitriptyline	B	Actionable PGx			
Anastrozole	B	Genetic testing required			Genetic testing required

Pathways | Pathways | PharmGKB

Secure https://next.pharmgkb.org/pathways

Welcome to the new PharmGKB! We'd love your feedback, click here to take the survey.

PHARMGKB

Search for a combination, chemical, gene, or variant...

Menu Account

PharmGKB Pathways

PharmGKB pathways are evidence-based diagrams depicting the pharmacokinetics (PK) and/or pharmacodynamics (PD) of a drug with relevant (or potential) pharmacogenetic (PGx) associations. Drugs featured in PharmGKB pathways are chosen through extensive review of a variety of sources, including, but not limited to, the U.S. Food and Drug Administration (FDA) biomarker list and Clinical Pharmacogenetics Implementation Consortium (CPIC) nominations.

PharmGKB pathways are accompanied by a written summary of the PK and/or PD pathway, as well as other important PGx related information. Interactions within each pathway are supported by manually curated evidence from published literature and specific information for each arrow in the pathway is found on the "Components" tab. Information contained within each pathway is available for download in TSV, BioPAX and GPML formats. The pathway graphic is available for download in PDF file format. PharmGKB pathways are often published in the journal Pharmacogenetics and Genomics.

CATEGORY

- Anti-infective agents (11)
- Anticancer agents (34)
- Cardiovascular and hematology agents (17)
- Endocrine and Metabolic Disease agents (6)
- Gastrointestinal agents (2)
- Musculoskeletal agents (7)
- Neurological agents (20)
- Pain, anti-inflammatory and immunomodulating agents (12)
- Physiological mechanisms (5)
- Respiratory agents (6)

Filter:

Pathway
Abacavir Pathway, Pharmacokinetics/Pharmacodynamics
Anti-infective agents - Schematic representation of abacavir metabolism and mechanism of action. The potential mechanism of an abacavir hypersensitivity reaction is also shown.

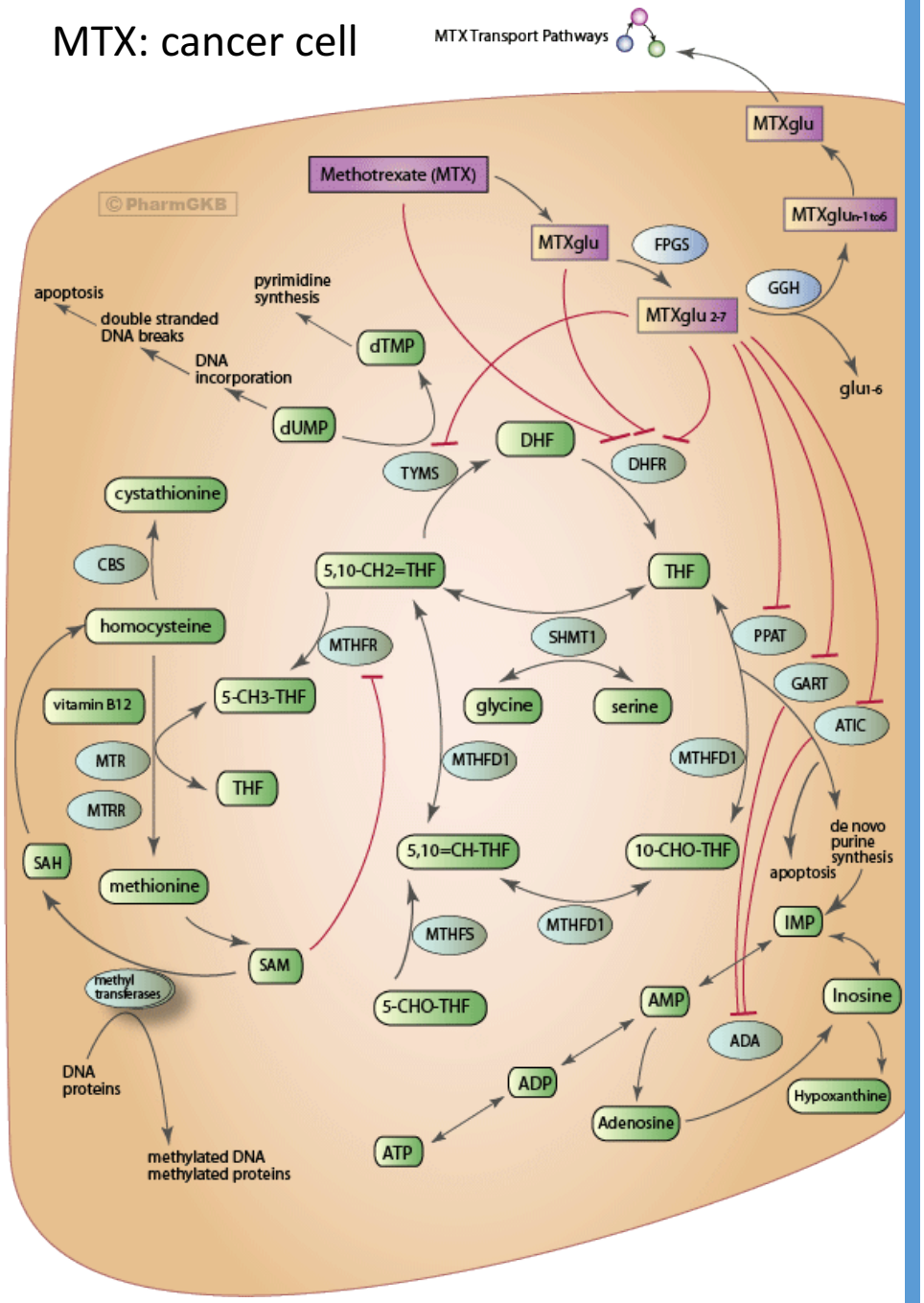
Pathway
ACE Inhibitor Pathway, Pharmacodynamics
Cardiovascular and hematology agents - Model, non-tissue-specific cell displaying genes which may be involved in the ACE inhibitor pathway

Pathway
Acetaminophen Pathway (therapeutic doses), Pharmacokinetics
Pain, anti-inflammatory and immunomodulating agents - Stylized diagram showing acetaminophen metabolism and transport in the liver.

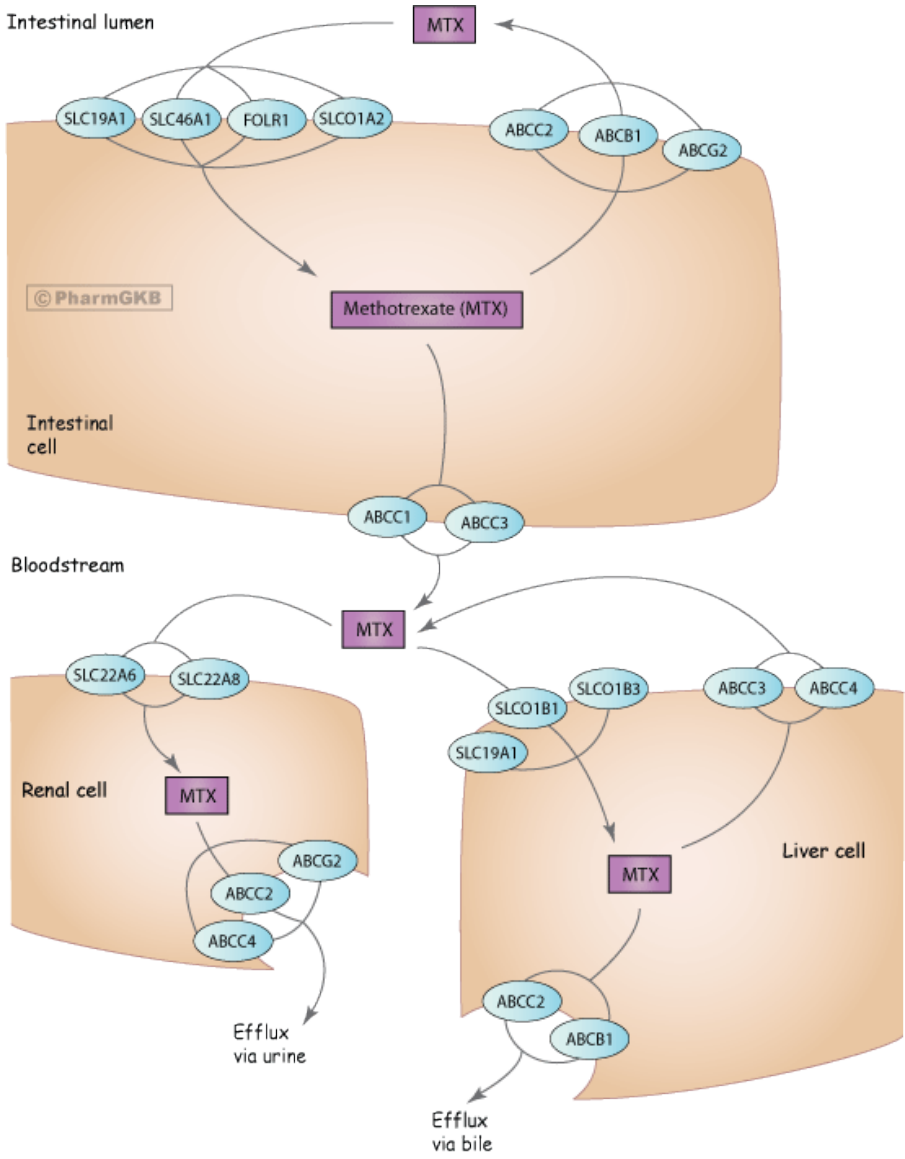
Pathway
Acetaminophen Pathway (toxic doses), Pharmacokinetics
Pain, anti-inflammatory and immunomodulating agents - Stylized diagram showing acetaminophen metabolism at higher acetaminophen doses (toxic doses) in the liver

Pathway

MTX: cancer cell



MTX: Pharmacokinetics



Phenytoin

Overview
PGx Prescribing Info
Drug Labels
Clinical Annotations
Variant Annotations
Publications
Pathways
Related To
Links & Downloads

DOSING GUIDELINES 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,

Phenytoin

Overview
PGx Prescribing Info
Drug Labels
Clinical Annotations ›
Variant Annotations
Publications
Pathways
Related To
Links & Downloads

Clinical Annotations

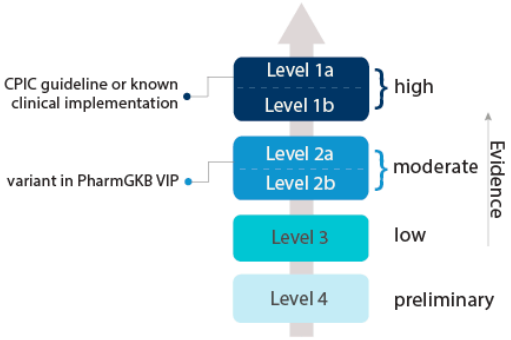
PharmGKB clinical annotations provide information about variant-drug pairs based on variant annotations in the database. Scientific Curators manually review variant annotations and create genotype-based summaries describing the phenotypic impact of the variant.

Read more about Clinical Annotations | Read more about Variant Annotations

Show Fullscreen | Edit Columns | Filter

	LEVEL	VARIANT	GENE	MOLECULE	TYPE	PHENOTYPE
Read Now	Level 1A	CYP2C9*1, CYP2C9*2, CYP2C9*3	CYP2C9	Phenytoin	toxicity/pk	Epilepsy
Read Now	Level 1A	HLA-B*15:02:01	HLA-B	Phenytoin	toxicity	Epidermal Necrolysis, Toxic, Stevens-Johnson Syndrome
Read Now	Level 2B	rs3812718	SCN1A	Phenytoin	dosage	Epilepsy
Read Now	Level 3	rs2606345	CYP1A1	Carbamazepine, Phenobarbital, Phenytoin, Valproic acid	efficacy	Epilepsy
Read Now	Level 3	rs1045642	ABCB1	Phenytoin	dosage	
Read Now	Level 3	rs1045642	ABCB1	Phenytoin	efficacy	Epilepsy
Read Now	Level 3	rs2304016	SCN2A	Antiepileptics, Carbamazepine, Lamotrigine, Oxcarbazepine, Phenytoin, Topiramate	efficacy	Epilepsy
Read Now	Level 3	rs2279020	GABRA1	Carbamazepine, Phenytoin, Valproic acid	efficacy	Epilepsy

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

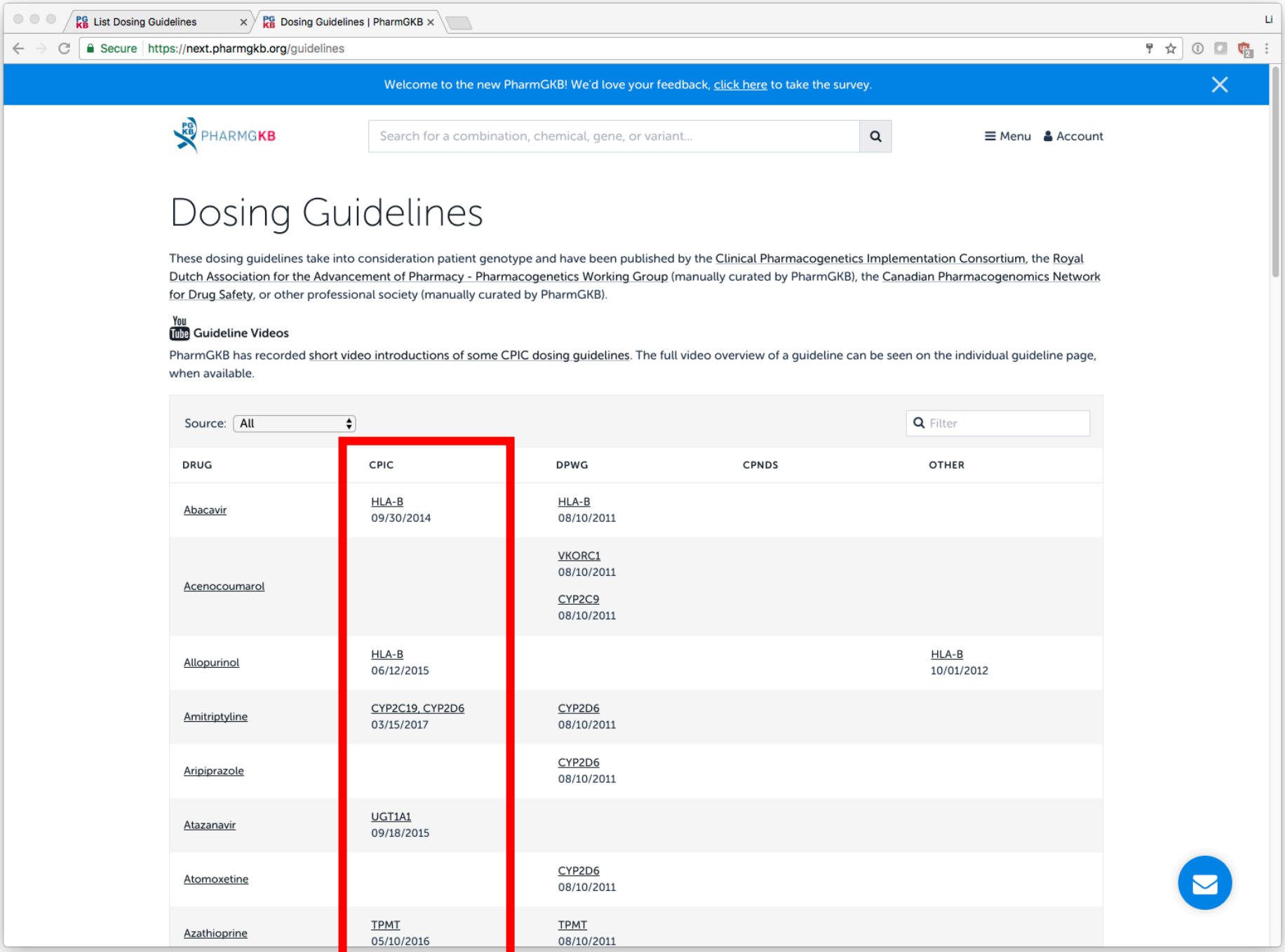
Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.

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


List Dosing Guidelines
Dosing Guidelines | PharmGKB
Secure https://next.pharmgkb.org/guidelines
Welcome to the new PharmGKB! We'd love your feedback, click here to take the survey.
PHARMGKB
Search for a combination, chemical, gene, or variant...
Menu
Account
Dosing Guidelines
These dosing guidelines take into consideration patient genotype and have been published by the Clinical Pharmacogenetics Implementation Consortium, the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (manually curated by PharmGKB), the Canadian Pharmacogenomics Network for Drug Safety, or other professional society (manually curated by PharmGKB).
Guideline Videos
PharmGKB has recorded short video introductions of some CPIC dosing guidelines. The full video overview of a guideline can be seen on the individual guideline page, when available.
Source: All
Filter
DRUG
CPIC
DPWG
CPNDS
OTHER
Abacavir
HLA-B 09/30/2014
HLA-B 08/10/2011
Acenocoumarol
VKORC1 08/10/2011
CYP2C9 08/10/2011
Allopurinol
HLA-B 06/12/2015
HLA-B 10/01/2012
Amitriptyline
CYP2C19, CYP2D6 03/15/2017
CYP2D6 08/10/2011
Aripiprazole
CYP2D6 08/10/2011
Atazanavir
UGT1A1 09/18/2015
Atomoxetine
CYP2D6 08/10/2011
Azathioprine
TPMT 05/10/2016
TPMT 08/10/2011

2009/2010 (&2014) Survey of pgen "experts" (PGRN and ASCPT): top 3 challenges to implementing pharmacogenetics in the clinic

- 95% of respondents selected: "process required to translate genetic information into clinical actions"
- Next 2 responses
  - Genotype test interpretation (e.g. using genotype information to assign phenotype)
  - Providing recommendations for selecting the drug/gene pairs to implement

Clin Pharmacol Ther. 2011 89:464-7.

- CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
  - Not WHETHER tests should be ordered.
- Key Assumption:
  - Clinical high-throughput and pre-emptive genotyping will become more widespread.
  - Clinicians will be faced with having patients' genotypes available even if they did not order test with drug in mind.

Specific Aims for CPIC

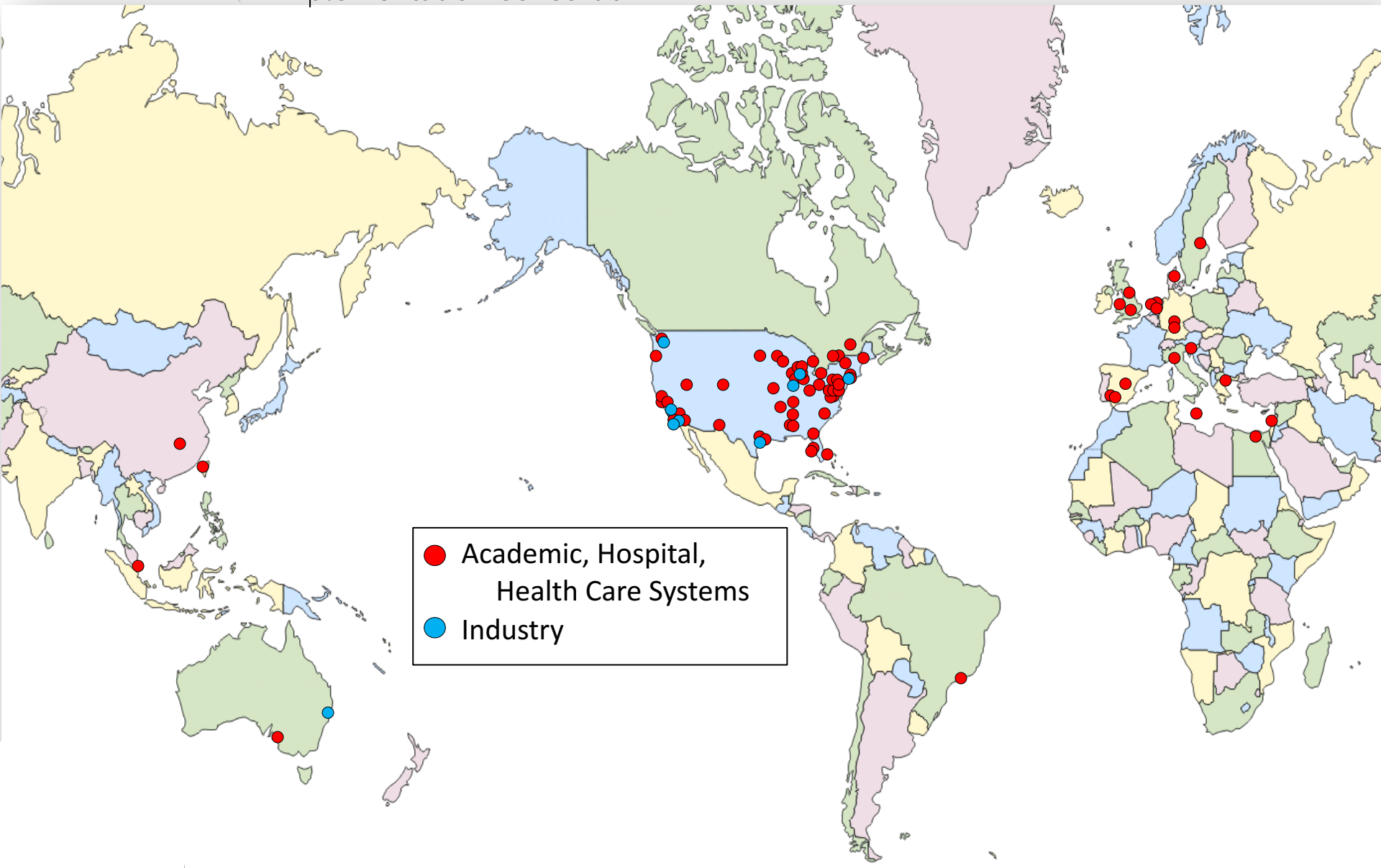
1. Create, curate, and update freely available, peer-reviewed CPIC gene/drug guidelines
2. Enhance access to and input into guidelines by external groups such as NIH's Pharmacogenomics PGRN, NIH's Genomic Medicine Working group, AHRQ's www.guidelines.gov, NIH's Genetic Test Registry, PubMed, FDA, ClinGen, IOM's Genomic Medicine roundtable, professional societies, and EHR vendors

CPIC™
Clinical Pharmacogenetics Implementation Consortium

- Posted on cpicpgx.org and capitalize on PharmGKB resources
- Freely available, no limits on use
- Peer reviewed, *CPT* first right of refusal to publish, standardized format, minimum set of elements
- Grading of evidence and of recommendations
- Can be updated on CPIC website ahead of publications
- Authorship, COI policy
- Closely follow IOM practices
  - Curr Drug Metab. 2014 Feb;15(2):209-17

CPIC™
Clinical Pharmacogenetics Implementation Consortium

2017 > 200 Members



Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling[1], EE Gardner[1], WJ Sandborn[2], K Schmiegelow[3,4], C-H Pui[5], SW Yee[6], CM Stein[7], M Carrillo[8], WE Evans[1] and TE Klein[8]

Clinical Pharmacogenetics Implementat Consortium Guidelines for Cytochrome P450-2C19 (*CYP2C19*) Genotype and Clopidogrel Therapy

SA Scott[1], K Sangkuhl[2], EE Gardner[3], CM Stein[4,5], J-S Hulot[6,7], JA Johnson[8,9,10], DM Roden[11,12], TE Klein[2] and AR Shuldiner[13,14]

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1* Genotypes and Warfarin Dosing

JA Johnson[1], L Gong[2], M Whirl-Carrillo[2], BF Gage[3], SA Scott[4], CM Stein[5], JL Anderson[6], SE Kimm MTM Lee[10], M Pirmohamed[11], M Wadelius[12], TE Klein[2] and RB Altman[2,13]

Clinical Pharmacogenetics Implementation Consortium Guidelines for Human Leukocyte Antigen-B Genotype and Allopurinol Dosing

MS Hershfield[1,2], JT Callaghan[3,4,5], W Tassaneeyakul[6], T Mushiroda[7], CF Thorn[8], TE Klein[8] and MTM Lee[9,10,11]

The Clinical Pharmacogenomics Implemen Consortium: CPIC Guideline for *SLCO1B1* and Simvastatin-Induced Myopathy

RA Wilke[1,2], LB Ramsey[3], SG Johnson[4,5], WD Maxwell[6], HL McLeod[7], D Voora[8], RM Krauss[9], DM Roden[1,2], Q Feng[1,2], RM Cooper-DeHoff[10], L Gong[11], TE Klein[11,12], M Wadelius[13] and M Niemi[14]

Clinical Pharmacogenetics Implementat Consortium Guidelines for *HLA-B* Genoty Abacavir Dosing

Clinical Pharmacogenetics Implementation Consortium Guidelines for *HLA-B* Genotype and Carbamazepine Dosing

SG Leckband[1,2], JR Kelsoe[1,2], HM Dunnenberger[3], AL George Jr[4], E Tran[1], R Berger[1], DJ Müller[5,6], M Whirl-Carrillo[7], KE Caudle[3] and M Pirmohamed[8]

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of *Cytochrome P450 2D6 CYP2D6*) Genotype

R Crews[1], A Gaedigk[2], HM Dunnenberger[3], TE Klein[4], DD Shen[5,6], JT Callaghan[7,8], ED Kharasch[9] nd TC Skaar[7]

Each guideline has a page on www.cpicpgx.org, with most up-to-date information

CPIC® Guideline for Clopidogrel and CYP2C19

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 update (September 2013)

Updates since publication:

March 2017: The FDA-approved label for clopidogrel (Plavix) was recently updated (September 2016) and warns that patients who are CYP2C19 poor metabolizers may have diminished effectiveness of the drug as compared to patients with normal CYP2C19 function. The drug label suggests that a different platelet P2Y12 inhibitor be used in patients identified as CYP2C19 poor metabolizers. **The FDA label change does not alter the recommendation from the authors that based on available evidence, the CPIC guideline is most applicable to ACS/PCI patients.**

Tables and figure in the main manuscript of the guideline:

Table 1. Assignment of likely CYP2C19 phenotypes based on genotypes

CPIC® Guideline for Tricyclic Antidepressants and CYP2D6 and CYP2C19

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update (December 2016)

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 phenotypes based on diplotypes

Table 2. Dosing recommendations for tricyclic antidepressants based on CYP2D6 phenotype

Table 3. Dosing recommendations for the tertiary amines amitriptyline, clomipramine, doxepin, imipramine, and trimipramine based on CYP2C19

CPIC Guidelines Genes-Drugs Alleles Publications Meetings Resources Informatics Members Contact

CPIC® Guideline for Codeine and CYP2D6

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Cytochrome P450 2D6 (CYP2D6) Genotype and Codeine Therapy: 2014 Update (April 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 codeine metabolism phenotypes based on cytochrome P450 2D6 (*CYP2D6*) diplotypes

Table 2. Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Figure 3. Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolism or see PharmGKB Codeine and Morphine Pathway, Pharmacokinetics

CPIC Guidelines Genes-Drugs Alleles Publications Meetings Resources Informatics Members Contact

CPIC® Guideline for Fluoropyrimidines and DPYD

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing (December 2013)

Updates since publication:

May 2014: The CPIC authors recommend that the *DPYD*4*, **5*, **6* and **9A* alleles be categorized as "normal" activity, in part based upon the recent publication Comparative Functional Analysis of DPYD Variants of Potential Clinical Relevance to Dihydropyrimidine Dehydrogenase Activity.

Tables provided in the main manuscript of the guideline:

Table 1. Assignment of likely DPD phenotype based on genotype

Table 2. Recommended dosing of fluoropyrimidines by DPD phenotype

22 guidelines
17 genes

2011

- *TPMT* – thiopurines
- *CYP2C9, VKORC*1 – warfarin

2012

- *CYP2D6* – codeine
- *HLA-B* – abacavir
- *SLCO1B1* – simvastatin

2013

- *HLA-B* – allopurinol
- *CYP2D6, CYP2C19* – TCAs
- *HLA-B* – carbamazepine
- *DPYD* -- 5FU / capecitabine
- *TPMT* – thiopurines—UPDATE
- *CYP2C19* – clopidogrel

2014

- *IL28B* -- PEG interferon α
- *CFTR* -- Ivacaftor
- *G6PD* -- Rasburicase
- *CYP2C9, HLA-B* -- Phenytoin
- *CYP2D6* – codeine--UPDATE
- *HLA-B* – abacavir--UPDATE
- *SLCO1B1* – simvastatin--UPDATE

2015

- *CYP3A5* – tacrolimus
- *CYP2D6*, *CYP2C19*– SSRIs
- *UGT1A1* – atazanavir
- *HLA-B* – allopurinol--UPDATE

2016

- *CYP2C19* – voriconazole
- *CYP2D6* – ondansetron
- *CYP2C9, VKORC1, CYP4F2* – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs--UPDATE

2017

- *CYP2D6* – tamoxifen
- *RYR1*– inhaled anesthetics
- *CYP2B6*—efavirenz
- *TPMT/NUDT15* – thiopurines UPDATE
- *HLA-B* – carbamazepine—UPDATE
- *DPYD* -- 5FU / capecitabine--UPDATE

Current estimate: 17 genes, ~87 drugs with pharmacogenetically-based prescribing

Number of current and planned CPIC genes, drugs and anticipated guidelines.	Genes	Drugs	Anticipated number of unique guidelines
Strong or Moderate prescribing action-CPIC level A	17	40	22 (19 published)
Optional prescribing actions-CPIC level B	4[a]	47	6
No prescribing actions-CPIC level C	16[b]	47	20
[a]all 4 genes are already CPIC level A. [b]several are already CPIC level A or B guidelines for other drugs.			

Apr 2017

Each CPIC guideline has a "Table 2": prescribing recommendations based on genotype-assigned phenotype, backed up by evidence

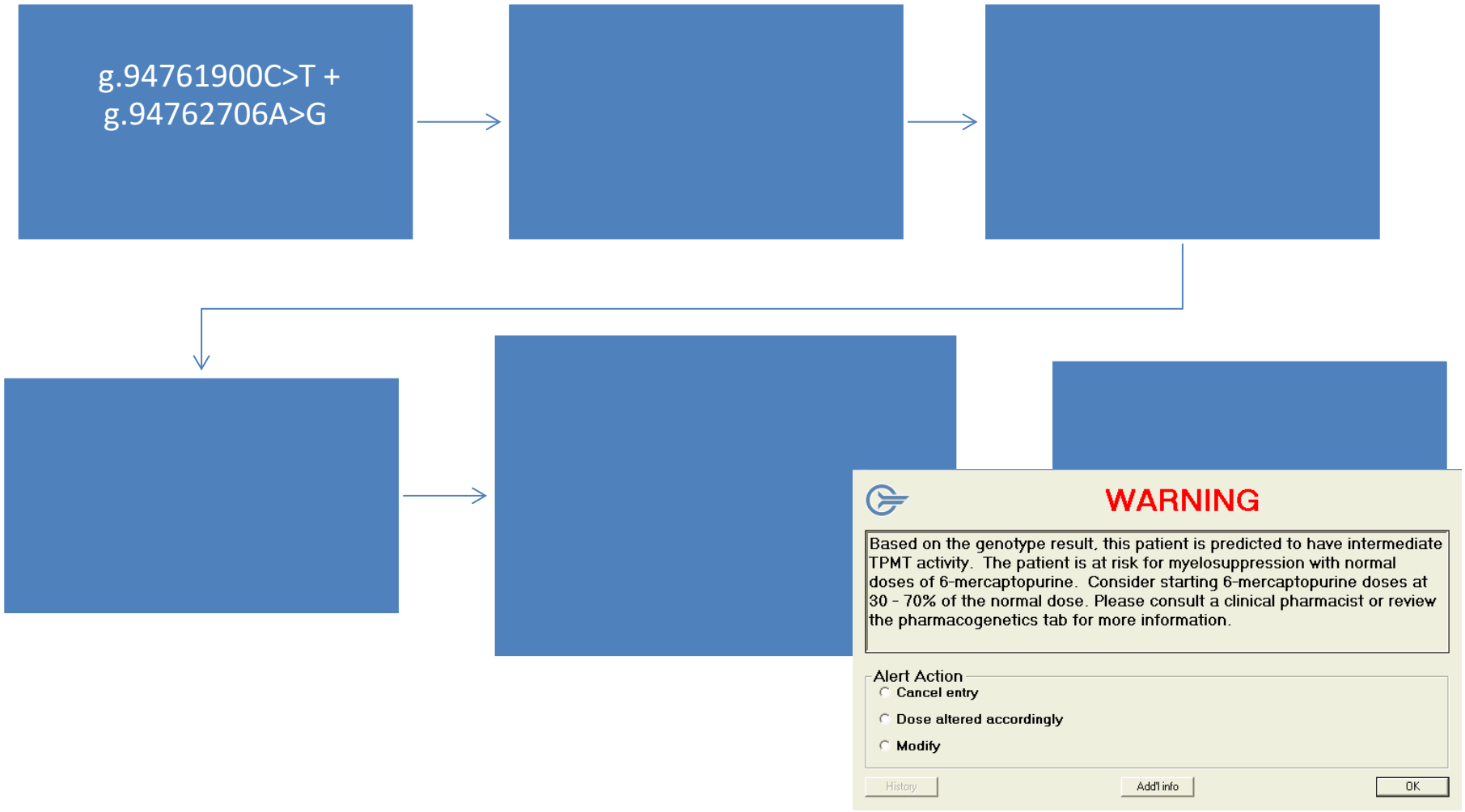
Table 2 Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations[a]
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation[b]	Clopidogrel: label-recommended dosage and administration	Strong
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

[a]See **Supplementary Materials and Methods** (Strength of Therapeutic Recommendations) online. [b]The *CYP2C19*17* allele may be associated with increased bleeding risks (ref. 15). ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

Clinical pharmacology & Therapeutics | VOLUME 94 NUMBER 3 | SEPTEMBER 2013

CPIC provides the resources to get from genotype to prescribing



CPIC® Guideline for Voriconazole and CYP2C19

Most Recent Guideline Publication

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Voriconazole Therapy (December 2016)

Updates since publication: No updates on dosing recommendations since publication.

Tables provided in the main manuscript of the guideline

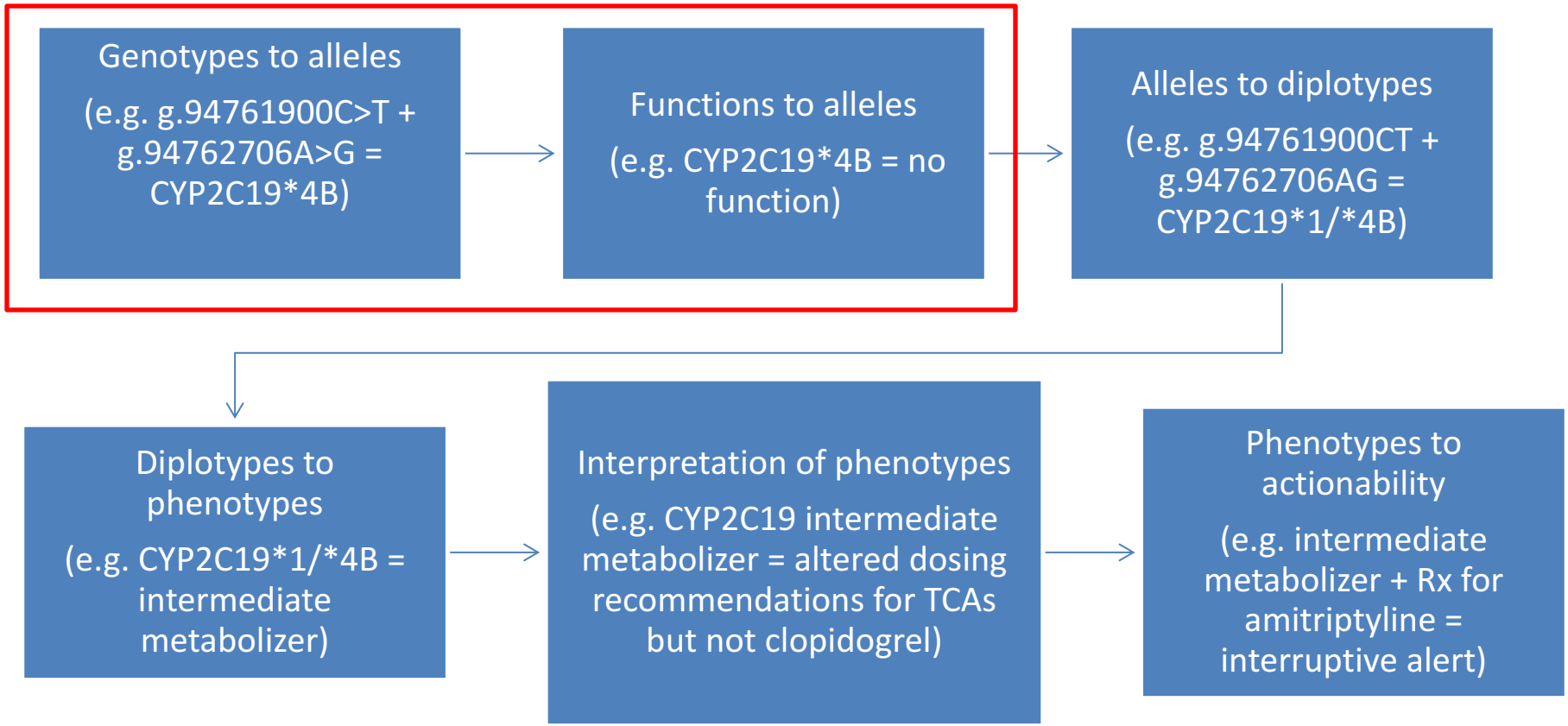
Table 1. Assignment of likely CYP2C29 phenotype based on genotypes
Table 2. Dosing recommendations for voriconazole based on CYP2C19 phenotype for adult patients
Table 3. Dosing recommendations for voriconazole based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Voriconazole Therapy (December 2016)

Tables provided in the guideline publication supplement or referenced in the guideline[a]

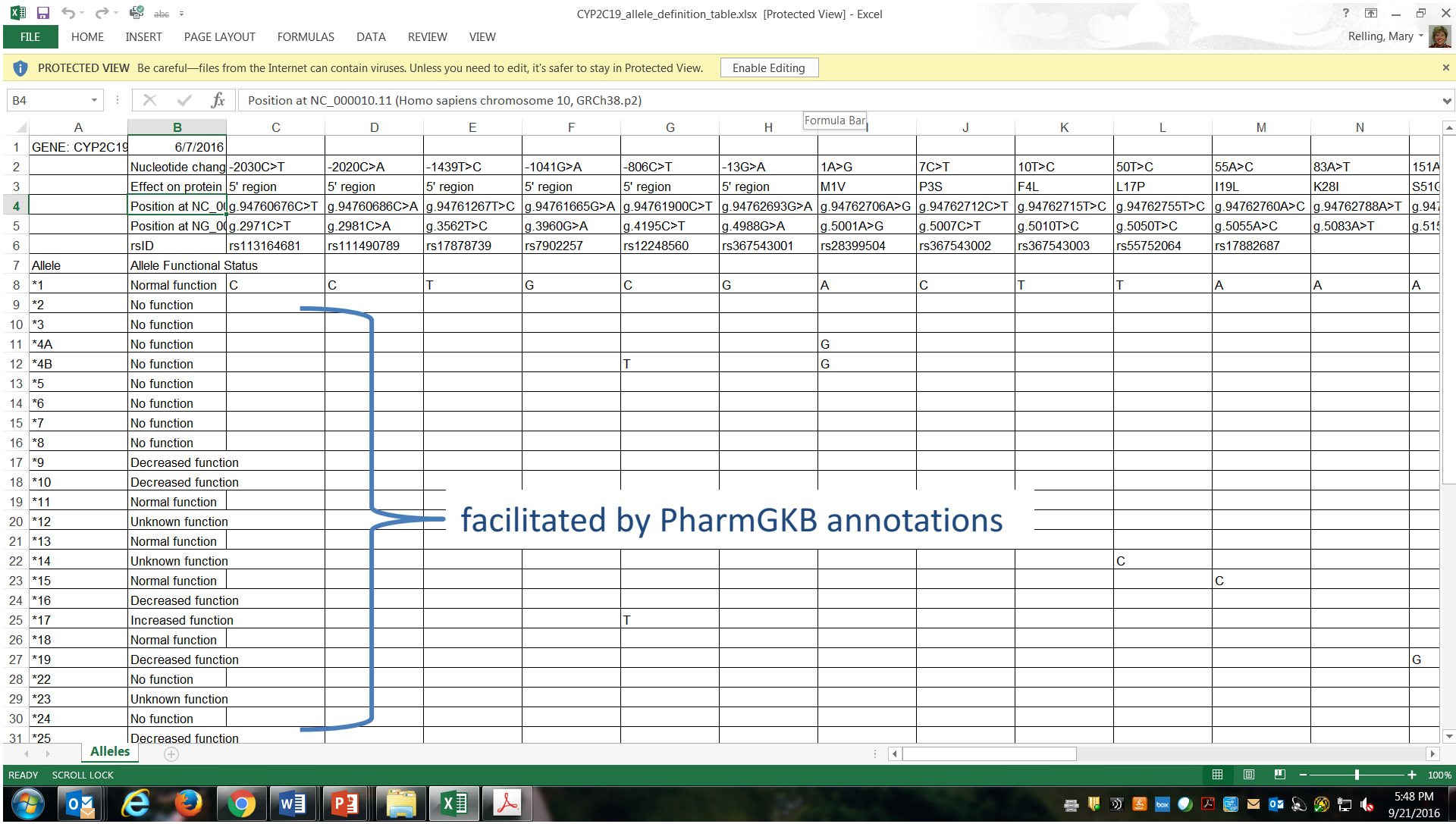
Levels of Evidence Linking Genotype to Phenotype
CYP2C19 Allele Definition Table
CYP2C19 Allele Functionality Table
CYP2C19 Frequency Table
CYP2C19 Diplotype-Phenotype Table
Gene Resource Mapping *CYP2C19* Gene Resource Mappings

CPIC tables allow translation of genetic test results to actionability



https://cpicpgx.org/guidelines/
https://www.pharmgkb.org/page/cyp2c19RefMaterials

CPIC Allele definition table: define variants and assign function



CYP2C19_allele_definition_table.xlsx [Protected View] - Excel

FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW

Relling, Mary

PROTECTED VIEW Be careful—files from the Internet can contain viruses. Unless you need to edit, it's safer to stay in Protected View. Enable Editing

B4 Position at NC_000010.11 (Homo sapiens chromosome 10, GRCh38.p2)

Formula Bar

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	
1	GENE: CYP2C19	6/7/2016													
2		Nucleotide chang	-2030C>T	-2020C>A	-1439T>C	-1041G>A	-806C>T	-13G>A	1A>G	7C>T	10T>C	50T>C	55A>C	83A>T	151A
3		Effect on protein	5' region	5' region	5' region	5' region	5' region	5' region	M1V	P3S	F4L	L17P	I19L	K28I	S51C
4		Position at NC_0(	g.94760676C>T	g.94760686C>A	g.94761267T>C	g.94761665G>A	g.94761900C>T	g.94762693G>A	g.94762706A>G	g.94762712C>T	g.94762715T>C	g.94762755T>C	g.94762760A>C	g.94762788A>T	g.947
5		Position at NG_0(	g.2971C>T	g.2981C>A	g.3562T>C	g.3960G>A	g.4195C>T	g.4988G>A	g.5001A>G	g.5007C>T	g.5010T>C	g.5050T>C	g.5055A>C	g.5083A>T	g.515
6		rsID	rs113164681	rs111490789	rs17878739	rs7902257	rs12248560	rs367543001	rs28399504	rs367543002	rs367543003	rs55752064	rs17882687		
7	Allele	Allele Functional Status													
8	*1	Normal function	C	C	T	G	C	G	A	C	T	T	A	A	A
9	*2	No function													
10	*3	No function													
11	*4A	No function							G						
12	*4B	No function					T		G						
13	*5	No function													
14	*6	No function													
15	*7	No function													
16	*8	No function													
17	*9	Decreased function													
18	*10	Decreased function													
19	*11	Normal function													
20	*12	Unknown function													
21	*13	Normal function													
22	*14	Unknown function										C			
23	*15	Normal function											C		
24	*16	Decreased function													
25	*17	Increased function					T								
26	*18	Normal function													
27	*19	Decreased function													G
28	*22	No function													
29	*23	Unknown function													
30	*24	No function													
31	*25	Decreased function													

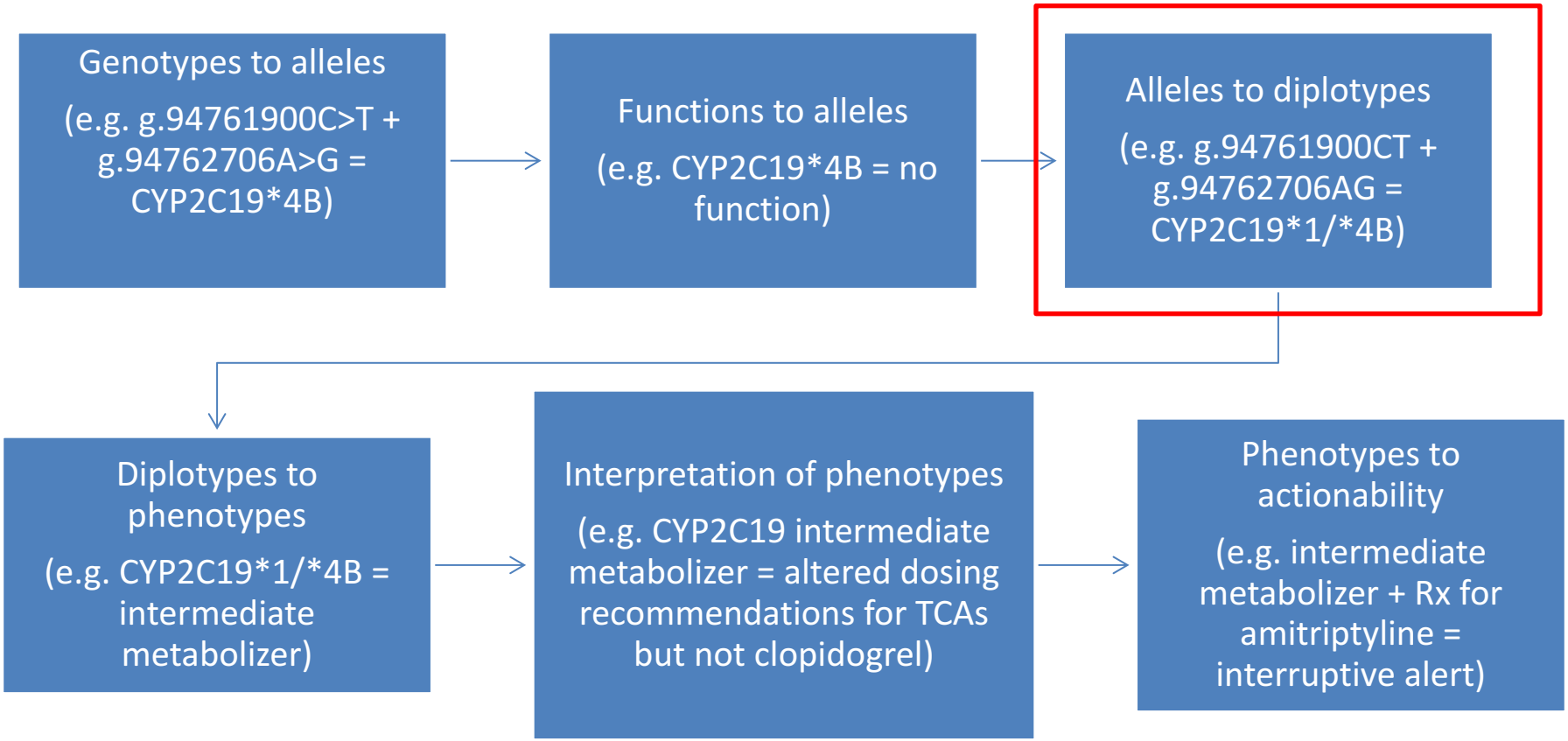
facilitated by PharmGKB annotations

Alleles

READY SCROLL LOCK 100%

5:48 PM 9/21/2016

CPIC tables allow translation of genetic test results to actionability



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https://www.pharmgkb.org/page/cyp2c19RefMaterials

Variants must be phased to assign diplotypes for pharmacogenes

CPIC Gene	Prescribing different for Var/var than var/wt?
TPMT	**Yes**
CYP2C19	**Yes**
CYP2D6	**Yes**
DPYD	**Yes**
CYP2C9	**Yes**
SLCO1B1	**Yes**
HLA-B	No
VKORC1	**Yes**
IL28-B	**Yes**
CFTR	No
G6PD	**Yes**
UGT1A1	**Yes**
CYP3A5	**Yes**

DMET_8170_CYP2D6_translation.txt - Notepad

File Edit Format View Help

```
#SJAccession=08-155-0435B
#PatientName=XXXXX
#DMETfile=DMET_8170.dmet_GT.txt
#TubeNumber=8170
#PatientID=(0000)02XXXX
#SampleType=PGEN DNA
#TranslationFile=DMET_Plus.v1.20101104DRAF
#AnnotationFile=DMET_Plus.v1.20090910.dc_annot.csv
#ReporterBuild=0.8.5
#VerifiedList=VerifiedbyAffy_Nov08 marker list.txt
PharmGKB link    http://www.pharmgkb.org/do/serve?objId=PA128&objCls=Gene
Independent Copy Number 2
Called Interpretation Code        UNIQ+UNK
Called Diplotypes Possible        *1/*41
Called Novel Diplotypes Possible        *2/UNK
Copy Number Corrected Alleles    NA
Number Non-reference Probe Sets 5
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12261        Y       Ch22:40853887   rs16947 C/T     Ref/Var *2,*8,*11,*12,*14A,*14B,*17,*19,*20,*21,*29,*40,*41,*4
AM_12257        Y       Ch22:40853749   rs28371725      G/A     Ref/Var *41     CYP2D6*41_2988G>A(SpliceDefect)
AM_15502        N       Ch22:40858512   rs1080983       G/A     Ref/Var -       CYP2D6_-1770G>A
AM_12277        Y       Ch22:40855076   rs1058164       G/C     Ref/Var -       CYP2D6_1661G>C(V136V)
AM_12247        Y       Ch22:40852557   rs1135840       G/C     Ref/Var S486T   CYP2D6_4180G>C(S486T)
Number Reference only Probe Sets        25
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12285        Y       Ch22:40856638   rs1065852       C/C     Ref/Ref *4,*10,*14A,*56B,*64    CYP2D6_100C>T(P34S)
AM_12284        Y       Ch22:40856614   rs5030862       G/G     Ref/Ref *12     CYP2D6*12_124G>A(G42R)
AM_12283        N       Ch22:40856600   rs72549357      T/T     Ref/Ref *15     CYP2D6*15_137insT
AM_12281        Y       Ch22:40855856   rs5030863       G/G     Ref/Ref *11     CYP2D6*11_883G>C(SpliceDefect)
AM_12280        Y       Ch22:40855716   rs28371706      C/C     Ref/Ref *17,*40,*64     CYP2D6_1023C>T(T107I)
AM_12278        N       Ch22:40855078   rs61736512      G/G     Ref/Ref *29     CYP2D6*29_1659G>A(V136I)
AM_12276        Y       Ch22:40855030   rs5030655       T/T     Ref/Ref *6      CYP2D6*6_1707delT
AM_12275        N       Ch22:40854979,Ch22:40854979     rs5030865       G/G     Ref/Ref *14A,*14B,*8    CYP2D6*14or*8_
AM_12274        Y       Ch22:40854891   rs3892097       G/G     Ref/Ref *4      CYP2D6*4_1846G>A(SpliceDefect)
AM_12272        Y       Ch22:40854873   rs72549356      -/-     Ref/Ref *40     CYP2D6*40_1863ins(TTTCGCCCC)2
AM_12270        Y       Ch22:40854763   rs72549354      -/-     Ref/Ref *20     CYP2D6*20 _1973insG
AM_12268        Y       Ch22:40854195   rs72549353      AACT/AACT       Ref/Ref *19     CYP2D6*19_2539delAACT
AM_12267        Y       Ch22:40854188   rs35742686      A/A     Ref/Ref *3      CYP2D6*3_2549delA
AM_12266        Y       Ch22:40854157   rs72549352      -/-     Ref/Ref *21     CYP2D6*21_2573insC
AM_12265        Y       Ch22:40854147   rs72549351      GACT/GACT       Ref/Ref *38     CYP2D6*38_2587delGACT
AM_12264        Y       Ch22:40854120   rs5030656       AGA/AGA Ref/Ref *9      CYP2D6*9_2615delAAG
AM_12259        Y       Ch22:40853802   rs5030867       A/A     Ref/Ref *7      CYP2D6*7_2935A>C(H324P)
AM_12258        Y       Ch22:40853787   rs72549349      G/G     Ref/Ref *44     CYP2D6*44_2950G>C(SpliceDefect)
AM_12255        Y       Ch22:40853554   rs59421388      G/G     Ref/Ref *29     CYP2D6*29_3183G>A(V338M)
AM_12254        Y       Ch22:40853536   rs72549347      C/C     Ref/Ref *56A,*56B       CYP2D6*56_3201C>T(R344X)
AM_12252        Y       Ch22:40853477   rs72549346      -/-     Ref/Ref *42     CYP2D6*42_3259insGT
AM_12248        Y       Ch22:40852603   rs1135836       T/T     Ref/Ref *18     CYP2D6*18_4125dupGTGCCCACT
AM_15506        N       Ch22:40858920   rs28360521      G/G     Ref/Ref -       CYP2D6_-2178G>A
AM_15503        N       Ch22:40858703,Ch22:40858703     -       C/C     Ref/Ref -       CYP2D6_-1961C>G>A
AM_12291        Y       Ch22:40858326   rs1080985       C/C     Ref/Ref -       CYP2D6_-1584C>G
```

From genotype or sequencing data, call gene-centric **haplotypes and diplotypes**—not just variants

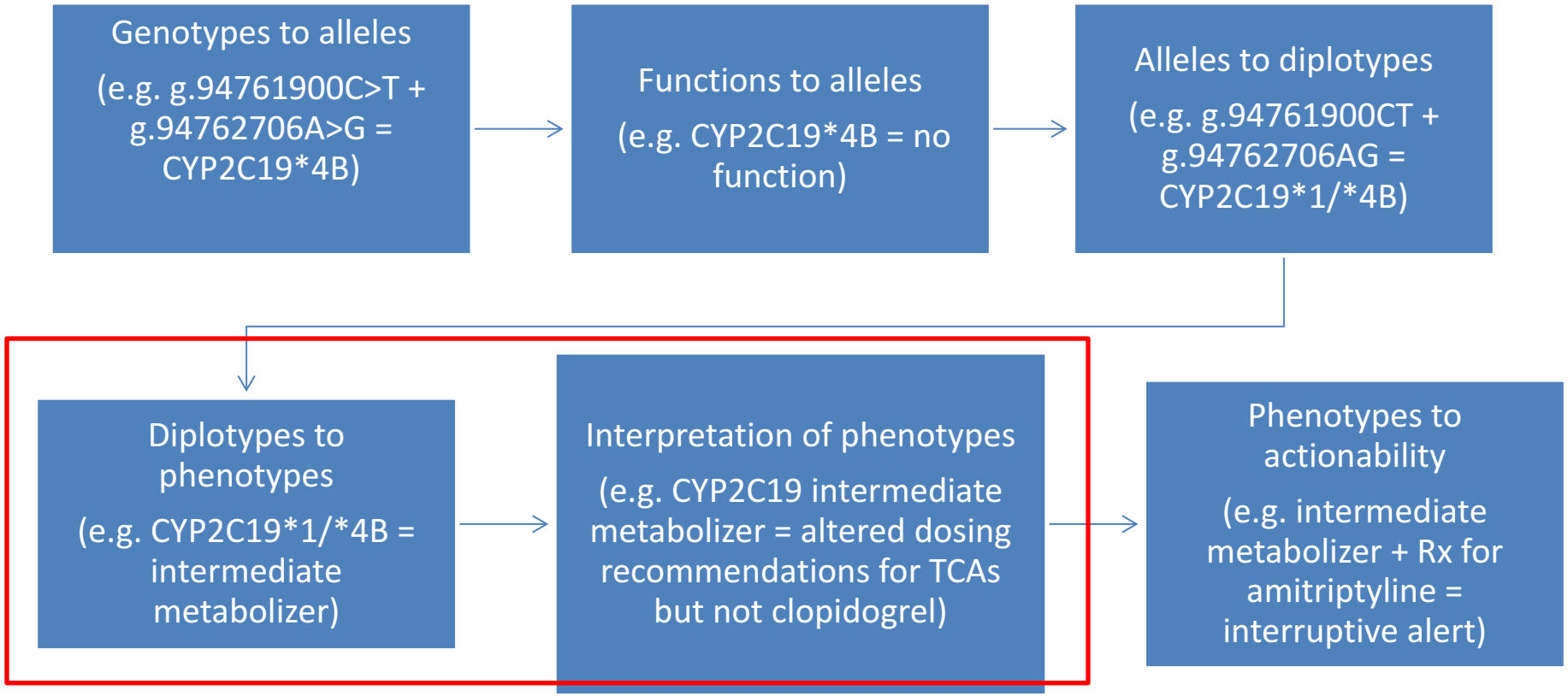
PharmCAT

To automate the annotation of .vcf files with the appropriate haplotypes or diplotypes from the CPIC guideline genes, and generate a report with the corresponding CPIC guideline prescribing recommendations

Geisinger

PharmGKB

CPIC tables allow translation of genetic test results to actionability



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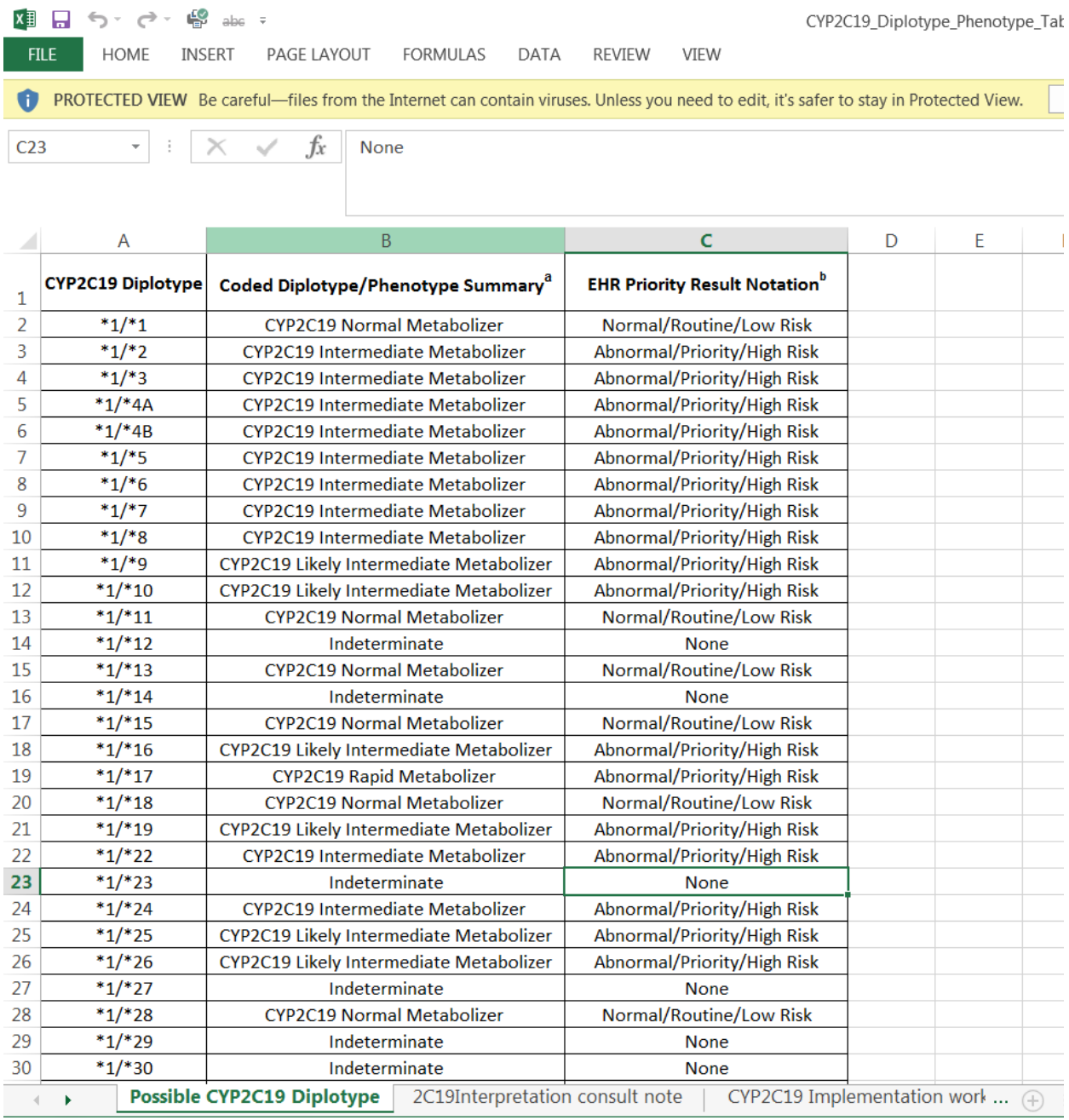
https://www.pharmgkb.org/page/cyp2c19RefMaterials

CYP2C19 diplotype/ phenotype table



	A	B	C	D	E
1	**CYP2C19 Diplotype**	**Coded Diplotype/Phenotype Summary[a]**	**EHR Priority Result Notation[b]**		
2	*1/*1	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
3	*1/*2	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
4	*1/*3	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
5	*1/*4A	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
6	*1/*4B	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
7	*1/*5	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
8	*1/*6	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
9	*1/*7	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
10	*1/*8	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
11	*1/*9	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
12	*1/*10	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
13	*1/*11	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
14	*1/*12	Indeterminate	None		
15	*1/*13	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
16	*1/*14	Indeterminate	None		
17	*1/*15	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
18	*1/*16	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
19	*1/*17	CYP2C19 Rapid Metabolizer	Abnormal/Priority/High Risk		
20	*1/*18	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
21	*1/*19	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
22	*1/*22	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
23	*1/*23	Indeterminate	None		
24	*1/*24	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk		
25	*1/*25	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
26	*1/*26	CYP2C19 Likely Intermediate Metabolizer	Abnormal/Priority/High Risk		
27	*1/*27	Indeterminate	None		
28	*1/*28	CYP2C19 Normal Metabolizer	Normal/Routine/Low Risk		
29	*1/*29	Indeterminate	None		
30	*1/*30	Indeterminate	None		

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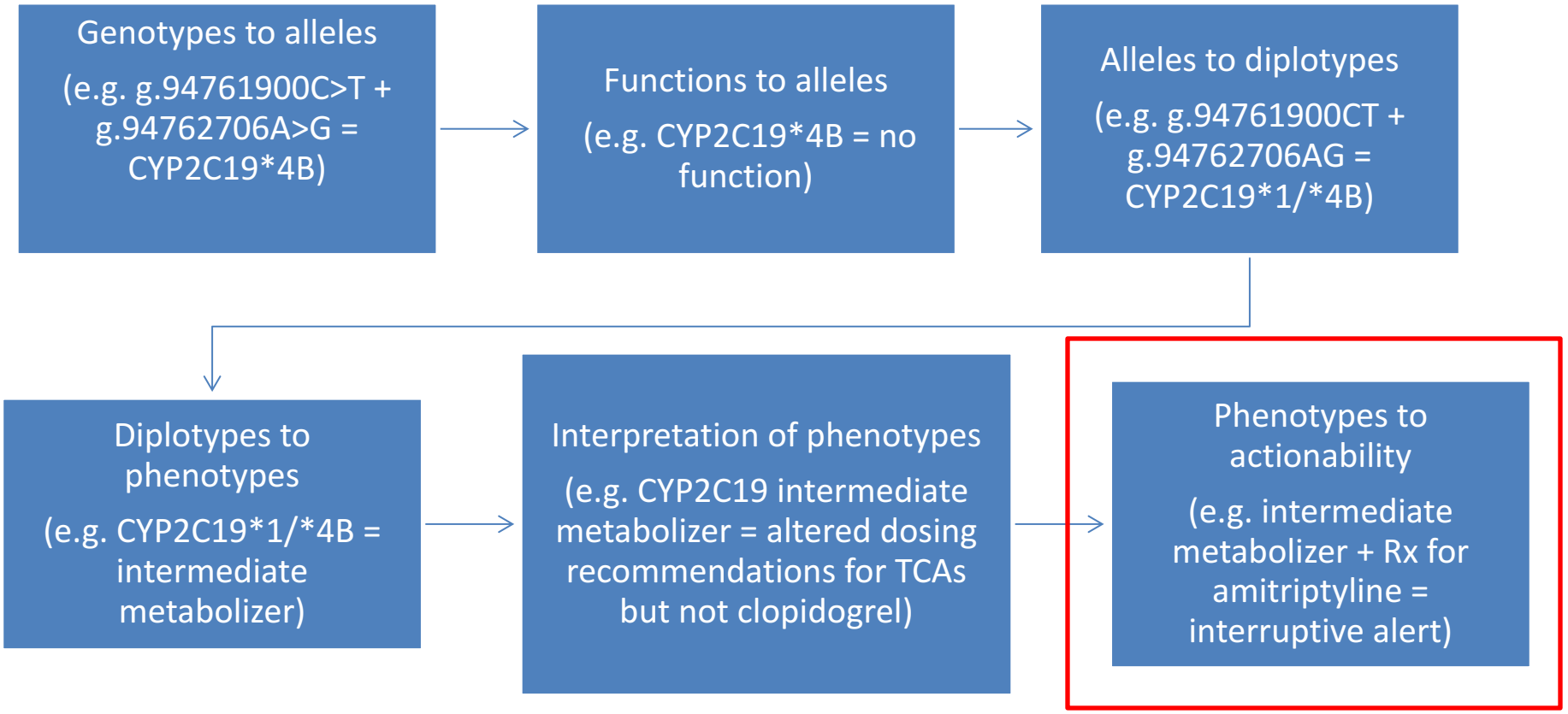
CPIC tables allow translation of genetic test results to actionability



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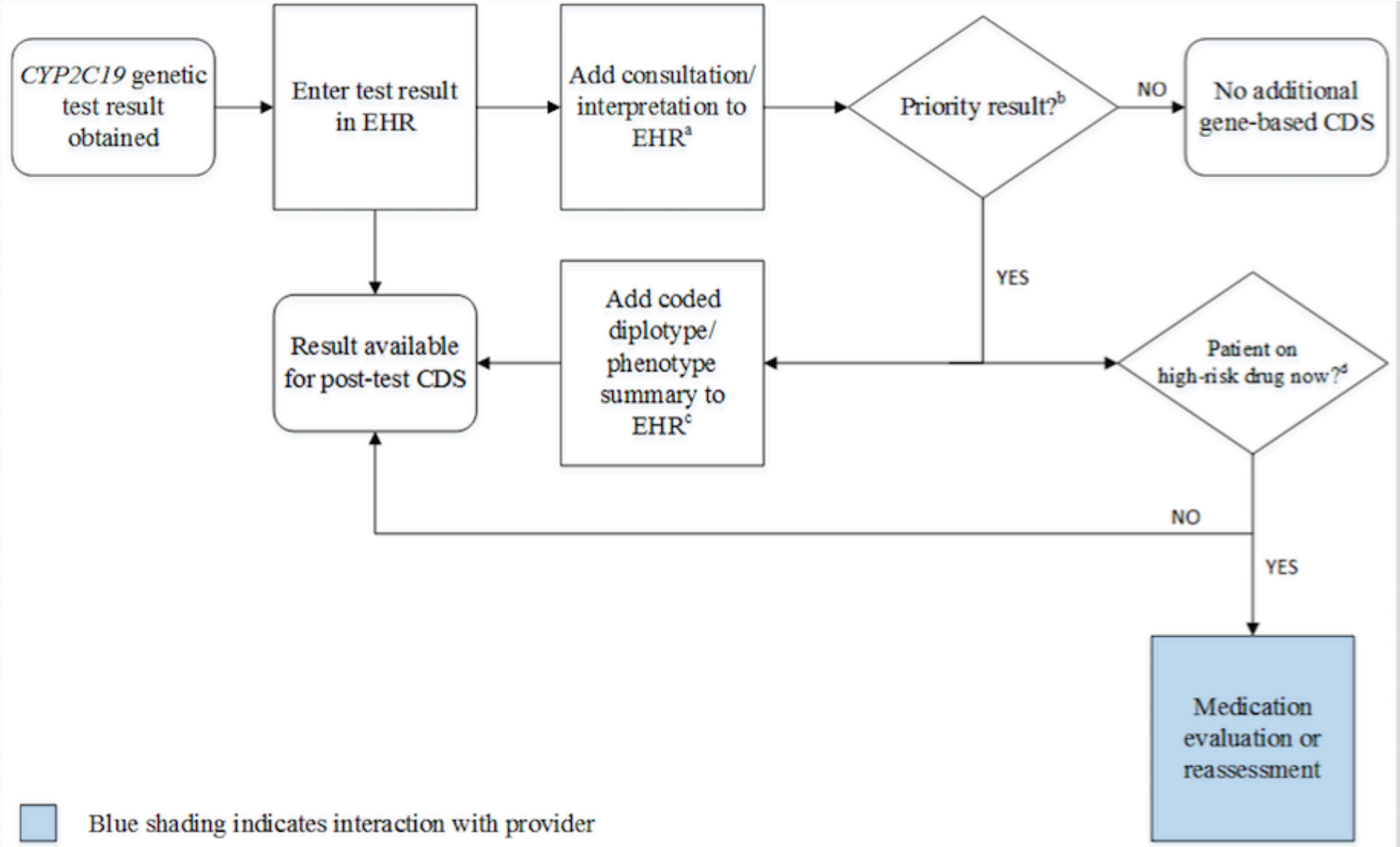
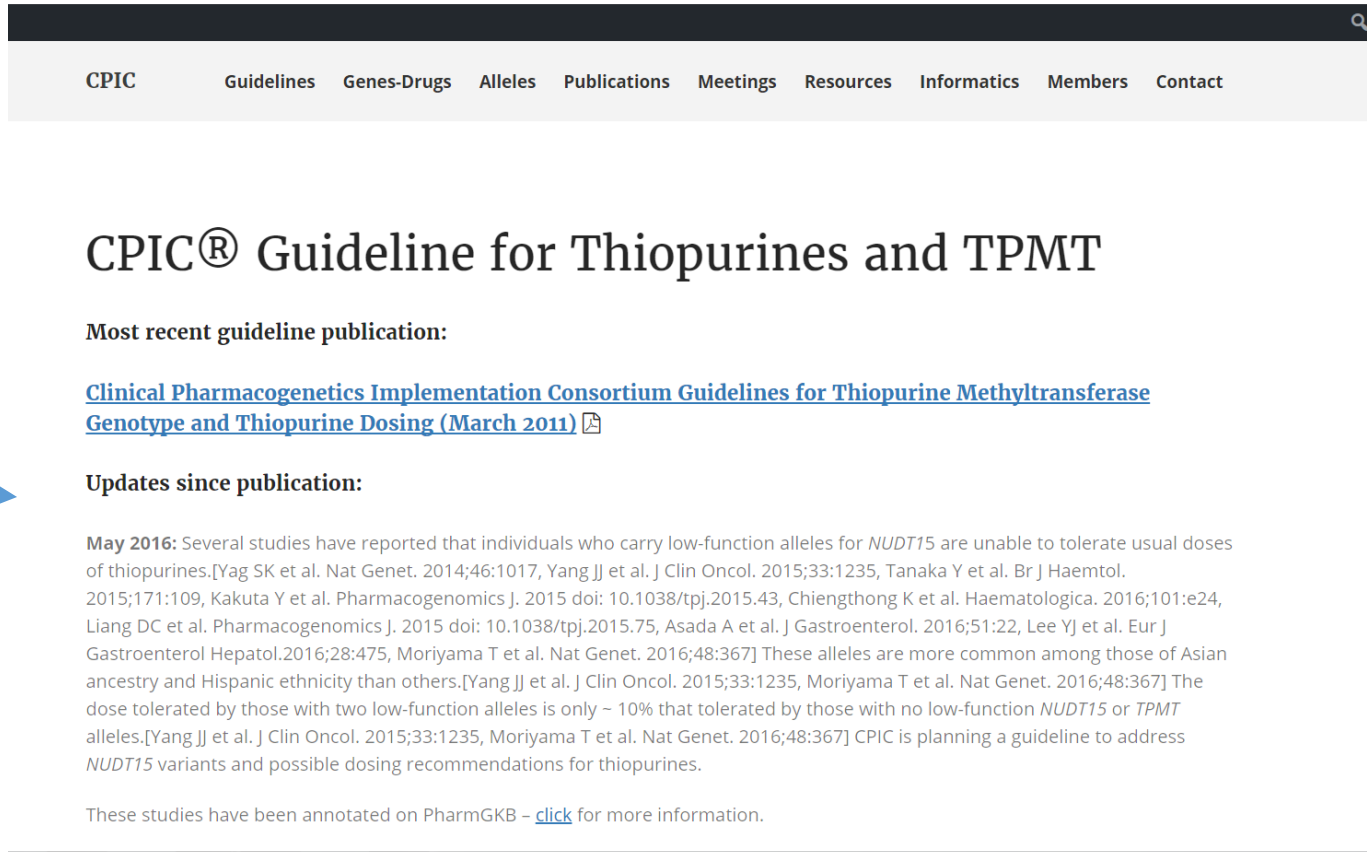
https://www.pharmgkb.org/page/cyp2c19RefMaterials

Coded Genotype/Phenotype Summary[a]	EHR Priority Result Notation[b]	Consultation (Interpretation) Text Provided with Test Result[c]
CYP2C19 Ultrarapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of an increased function allele. Based on the genotype result this patient is predicted to be an ultrarapid metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
CYP2C19 Rapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a normal function allele and one copy of an increased function allele. Based on the genotype result this patient is predicted to be a rapid metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a normal function allele and one copy of a no function allele. Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
CYP2C19 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a no function allele. Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2C19 substrates. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or or alternative therapy may be necessary for medications metabolized by the CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.


CYP2C19 genetic test result obtained
Enter test result in EHR
Add consultation/ interpretation to EHR[a]
Priority result?[b]
NO
No additional gene-based CDS
YES
Add coded diplotype/ phenotype summary to EHR[c]
Result available for post-test CDS
Patient on high-risk drug now?[d]
NO
YES
Medication evaluation or reassessment
Blue shading indicates interaction with provider

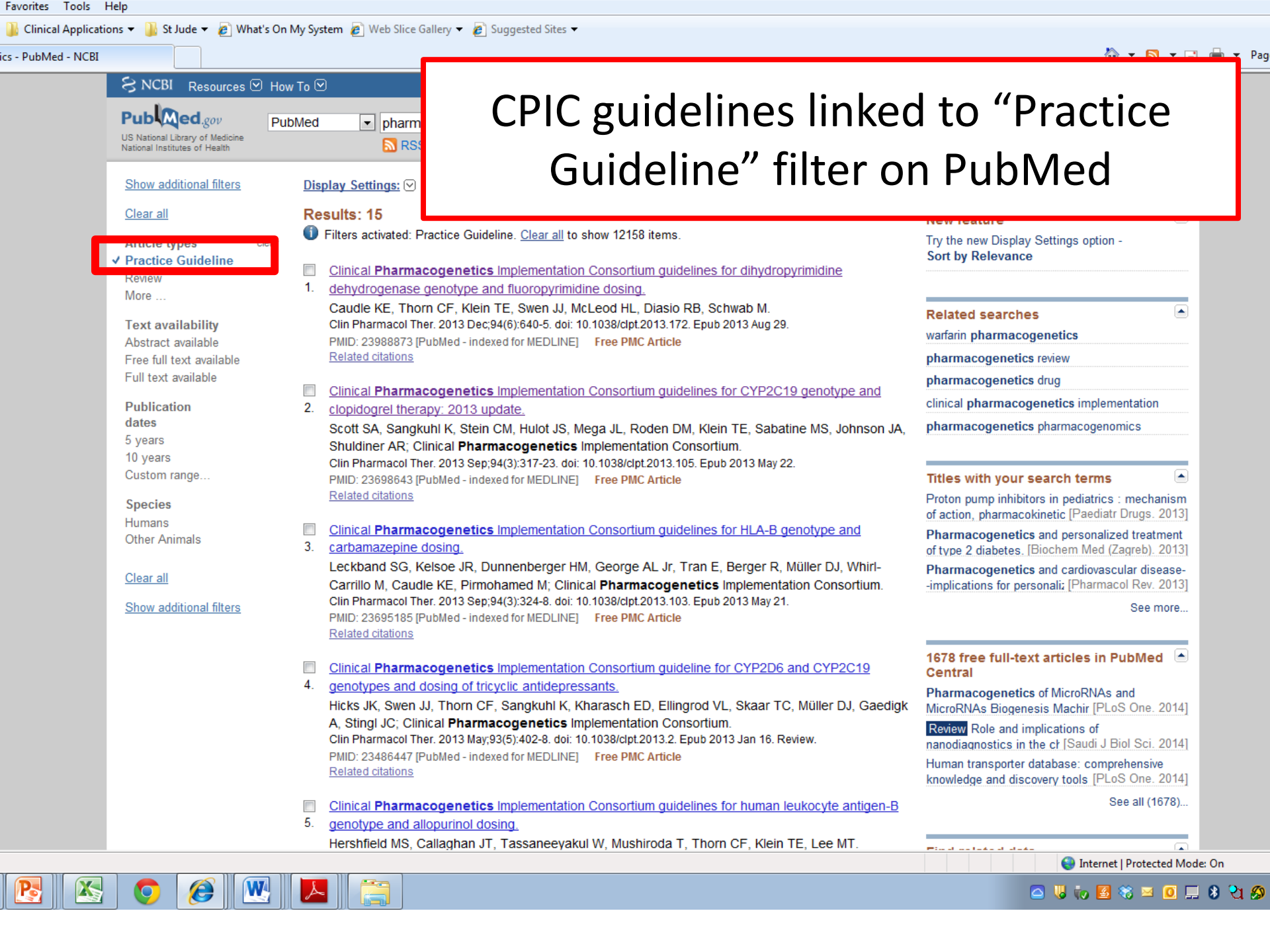
Recent Guideline Updates to cpicpgx.org

- Thiopurines NUDT15
- Clopidogrel/CYP2C19 FDA blackbox update
- Warfarin---GIFT Trial Gage et al—27% decrease in adverse events and death…updated galleys



Specific Aims

1. Create, curate, and update CPIC gene/drug guidelines
2. Enhance access to and input into guidelines by external groups such as NIH's Pharmacogenomics PGRN, NIH's Genomic Medicine Working group, AHRQ's www.guidelines.gov, NIH's Genetic Test Registry, PubMed, FDA, ClinGen, IOM's Genomic Medicine roundtable, professional societies, and EHR vendors


CPIC guidelines linked to “Practice Guideline” filter on PubMed
Favorites Tools Help
Clinical Applications St Jude What's On My System Web Slice Gallery Suggested Sites
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Text availability
Abstract available
Free full text available
Full text available
Publication dates
5 years
10 years
Custom range...
Species
Humans
Other Animals
Clear all
Show additional filters
Display Settings:
Results: 15
Filters activated: Practice Guideline. Clear all to show 12158 items.
1. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing.
Caudle KE, Thorn CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, Schwab M.
Clin Pharmacol Ther. 2013 Dec;94(6):640-5. doi: 10.1038/clpt.2013.172. Epub 2013 Aug 29.
PMID: 23988873 [PubMed - indexed for MEDLINE] Free PMC Article
Related citations
2. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update.
Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR; Clinical Pharmacogenetics Implementation Consortium.
Clin Pharmacol Ther. 2013 Sep;94(3):317-23. doi: 10.1038/clpt.2013.105. Epub 2013 May 22.
PMID: 23698643 [PubMed - indexed for MEDLINE] Free PMC Article
Related citations
3. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing.
Leckband SG, Kelsoe JR, Dunnenberger HM, George AL Jr, Tran E, Berger R, Müller DJ, Whirl-Carrillo M, Caudle KE, Pirmohamed M; Clinical Pharmacogenetics Implementation Consortium.
Clin Pharmacol Ther. 2013 Sep;94(3):324-8. doi: 10.1038/clpt.2013.103. Epub 2013 May 21.
PMID: 23695185 [PubMed - indexed for MEDLINE] Free PMC Article
Related citations
4. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.
Hicks JK, Swen JJ, Thorn CF, Sangkuhl K, Kharasch ED, Ellingrod VL, Skaar TC, Müller DJ, Gaedigk A, Stingl JC; Clinical Pharmacogenetics Implementation Consortium.
Clin Pharmacol Ther. 2013 May;93(5):402-8. doi: 10.1038/clpt.2013.2. Epub 2013 Jan 16. Review.
PMID: 23486447 [PubMed - indexed for MEDLINE] Free PMC Article
Related citations
5. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing.
Hershfield MS, Callaghan JT, Tassaneeyakul W, Mushiroda T, Thorn CF, Klein TE, Lee MT.
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Pharmacogenetics and personalized treatment of type 2 diabetes. [Biochem Med (Zagreb). 2013]
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Human transporter database: comprehensive knowledge and discovery tools [PLoS One. 2014]
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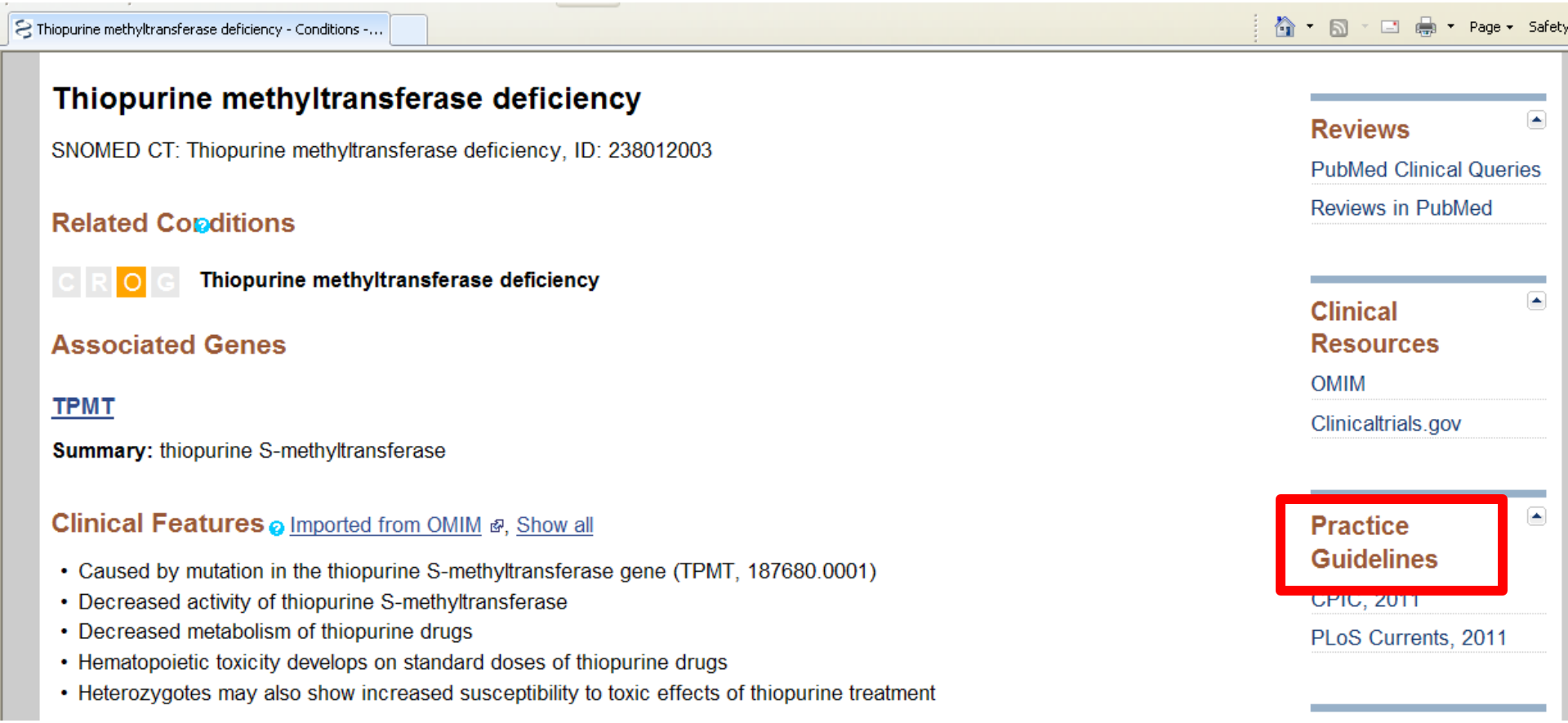
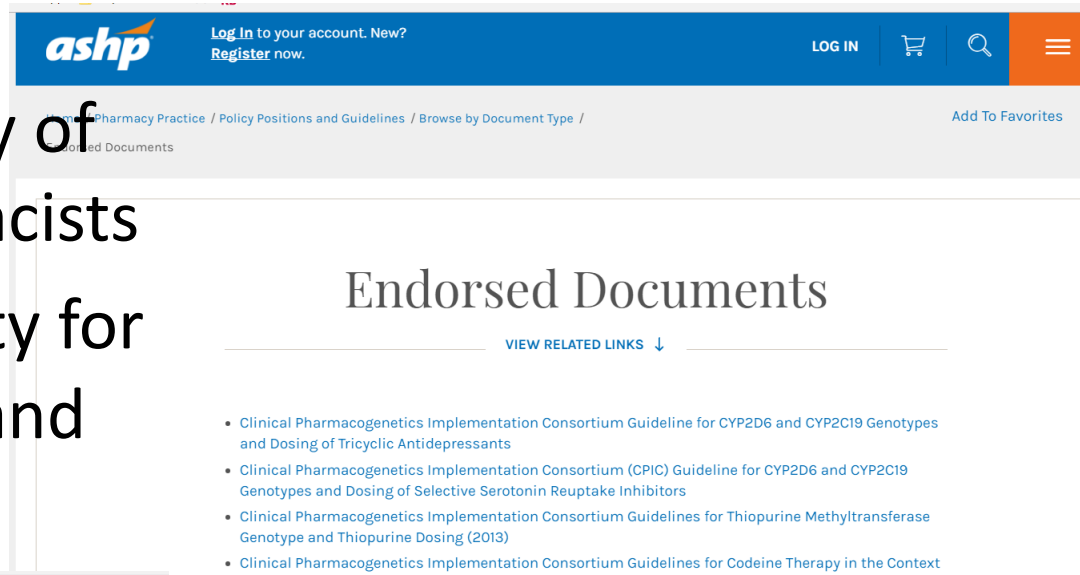
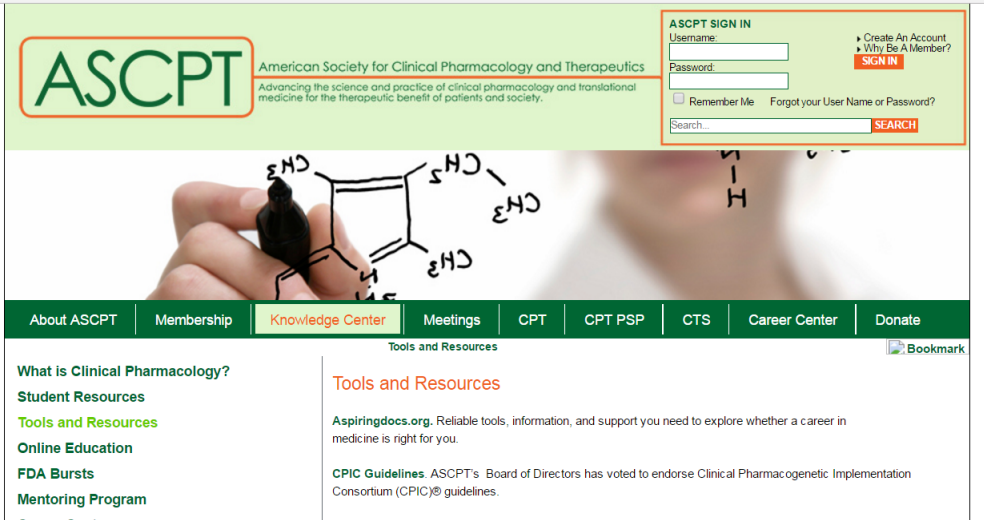
CPIC is cited in NIH's Genetic Test Registry (GTR) for clinical pharmacogenetic tests



Endorsed by professional organizations

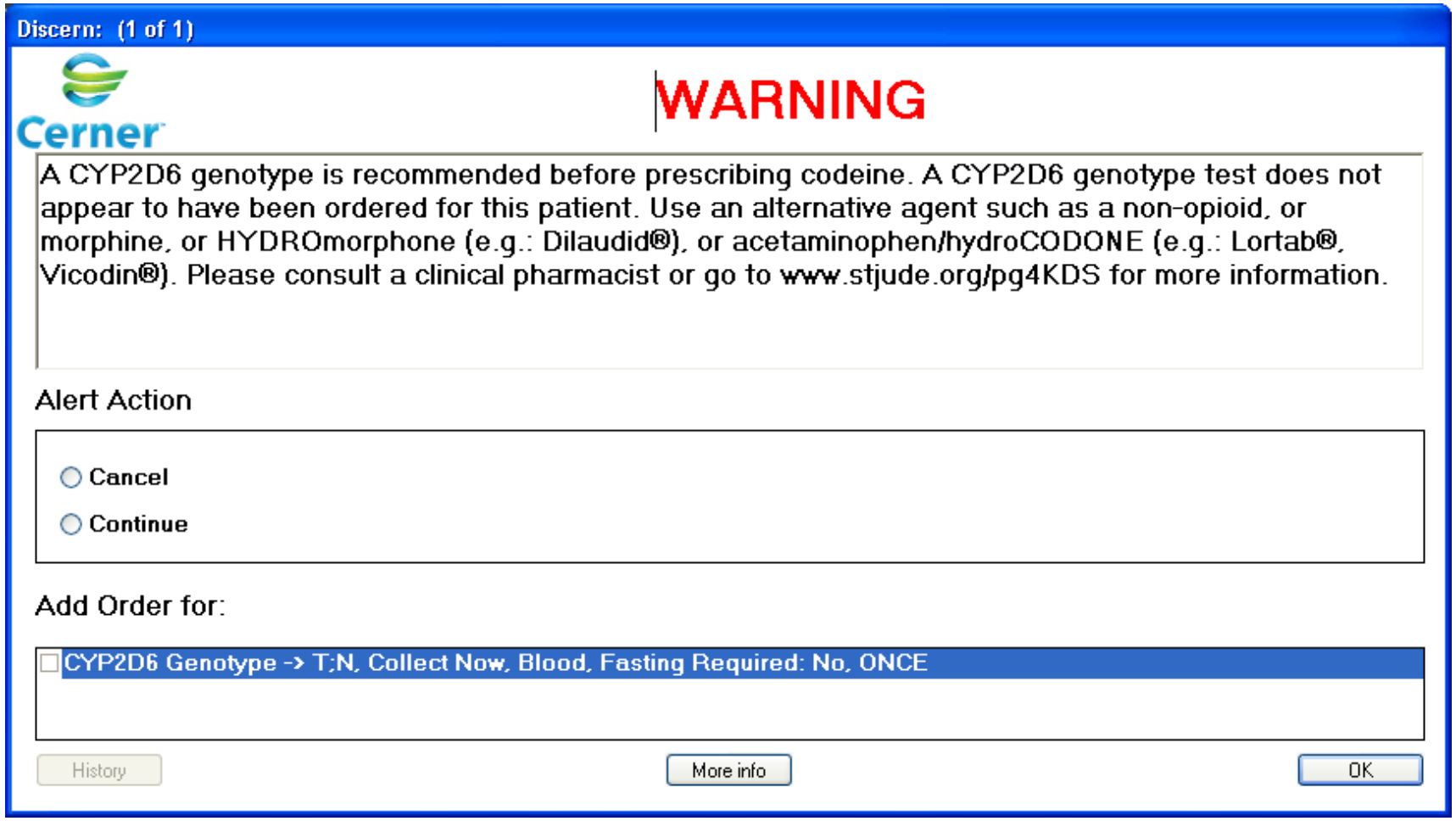
- ASHP: American Society of Health Systems Pharmacists
- ASCPT: American Society for Clinical Pharmacology and Therapeutics



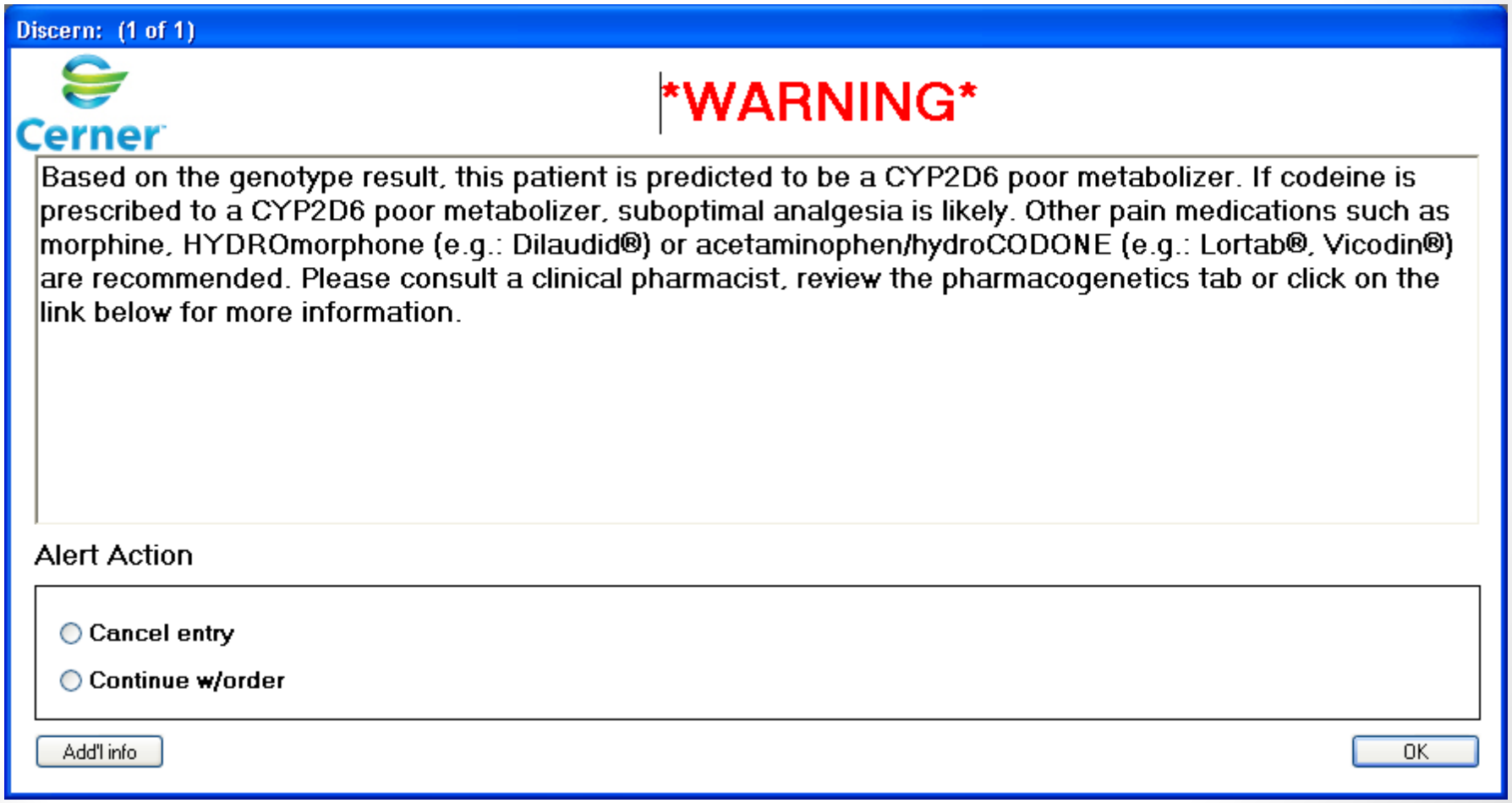


Standardized terms for results are important for clinical actionability

Pre-test alerts contain prescribing and testing recommendations based on the ABSENCE of a test result



Post-test alerts contain prescribing recommendations based on the PRESENCE of a high risk test result



Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

Open

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

Kelly E. Caudle, PharmD, PhD[1], Henry M. Dunnenberger, PharmD[2], Robert R. Freimuth, PhD[3], Josh F. Peterson, MD[4,5], Jonathan D. Burlison, PhD[1], Michelle Whirl-Carrillo, PhD[6], Stuart A. Scott, PhD[7], Heidi L. Rehm, PhD[8], Marc S. Williams, MD[9], Teri E. Klein, PhD[6], Mary V. Relling, PharmD[1], James M. Hoffman, PharmD, MS[1]

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.

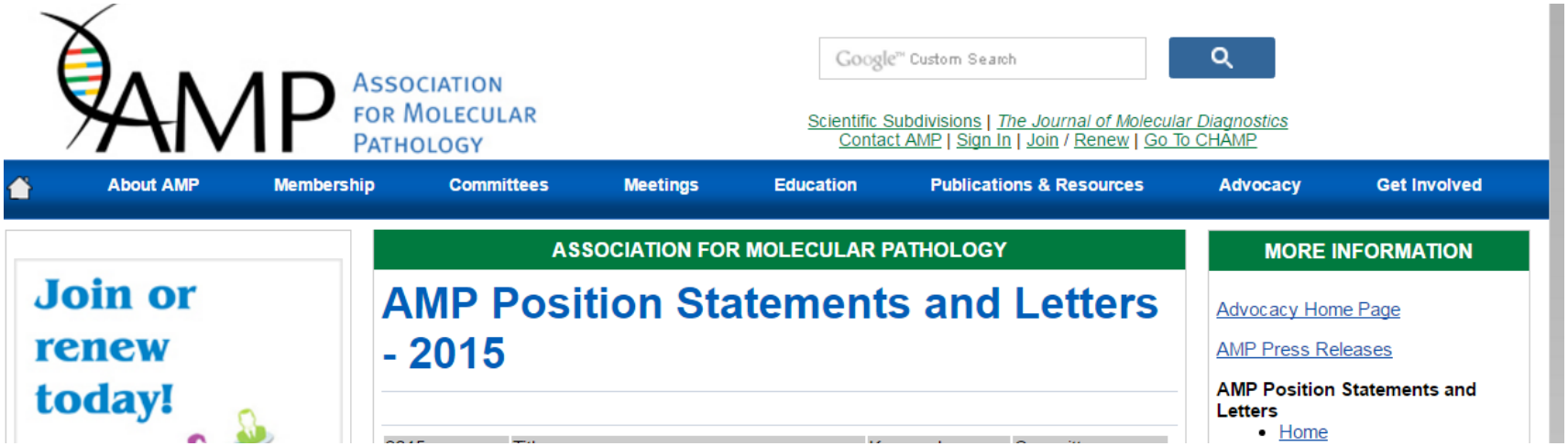
Materials and methods: Terms currently used by genetic testing laboratories and in the literature were identified. The Clinical Pharmacogenetics Implementation Consortium (CPIC) used the Delphi method to obtain a consensus and agree on uniform terms among pharmacogenetic experts.

Results: Experts with diverse involvement in at least one area of pharmacogenetics (clinicians, researchers, genetic testing laboratorians, pharmacogenetics implementers, and clinical informaticians; $n = 58$) participated. After completion of five surveys, a consensus (>70%) was reached with 90% of experts agreeing to the final sets of pharmacogenetic terms.

Discussion: The proposed standardized pharmacogenetic terms will improve the understanding and interpretation of pharmacogenetic tests and reduce confusion by maintaining consistent nomenclature. These standard terms can also facilitate pharmacogenetic data sharing across diverse electronic health care record systems with clinical decision support.

Genet Med advance online publication 21 July 2016

Key Words: CPIC; nomenclature; pharmacogenetics; pharmacogenomics; terminology



	E&C in support of congressional action to ensure a CLIA moderization approach to LDPs	FDA, CMS, CLIA	Relations
October 26	Comments to FDA, CDC, and NLM on Promoting Semantic Interoperability of Laboratory Data	FDA, CDC, NLM, EHR, LOINC, SNOMED-CT	Professional Relations
October 26	**Endorsement of Clinical Pharmacogenetics Implementation Consortium (CPIC) initative to standardize pharmacogenetic nomenclature**	CPIC	Clinical Practice
August 26	Presentation of New Code Crosswalk Recommendations to Advisory Panel on Clinical Diagnostic Laboratory Tests	CMS, CLFS, PAMA, GSP, CPT, CAP	Economic Affairs

CAP

PGX-B

2016
(PGX)

Proficiency testing

Results must be received at the CAP no later than midnight, Central Time by the due date below:

October 4, 2016

CYP2C19 – PGX-04 — PGX-06, cont'd

Clinical Scenario – *CYP2C19*

A 57-year-old Caucasian female with diabetes mellitus, currently on clopidogrel, presents to her primary care physician complaining of easy fatigability and chest pain.

Interpretation (Ungraded)

Exception Code 005 ○ 11 ○ 33

010 PGX-04	020 PGX-05	030 PGX-06
○ 257 This patient is an ultra-rapid metabolizer	○ 257 This patient is an ultra-rapid metabolizer	○ 257 This patient is an ultra-rapid metabolizer
○ 837 This patient is a rapid metabolizer	○ 837 This patient is a rapid metabolizer	○ 837 This patient is a rapid metabolizer
○ 258 This patient is a normal metabolizer	○ 258 This patient is a normal metabolizer	○ 258 This patient is a normal metabolizer
○ 259 This patient is an intermediate metabolizer	○ 259 This patient is an intermediate metabolizer	○ 259 This patient is an intermediate metabolizer
○ 260 This patient is a poor metabolizer	○ 260 This patient is a poor metabolizer	○ 260 This patient is a poor metabolizer
○ 590 Inconclusive	○ 590 Inconclusive	○ 590 Inconclusive

Clinical Management (Ungraded)

Exception Code 035 ○ 11 ○ 33

040 PGX-04 (Select all that apply.)	100 PGX-05 (Select all that apply.)	160 PGX-06 (Select all that apply.)
○ 262 An increased dose should be considered	○ 262 An increased dose should be considered	○ 262 An increased dose should be considered
○ 263 The standard dose should be considered	○ 263 The standard dose should be considered	○ 263 The standard dose should be considered
○ 264 A decreased dose should be considered	○ 264 A decreased dose should be considered	○ 264 A decreased dose should be considered

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)

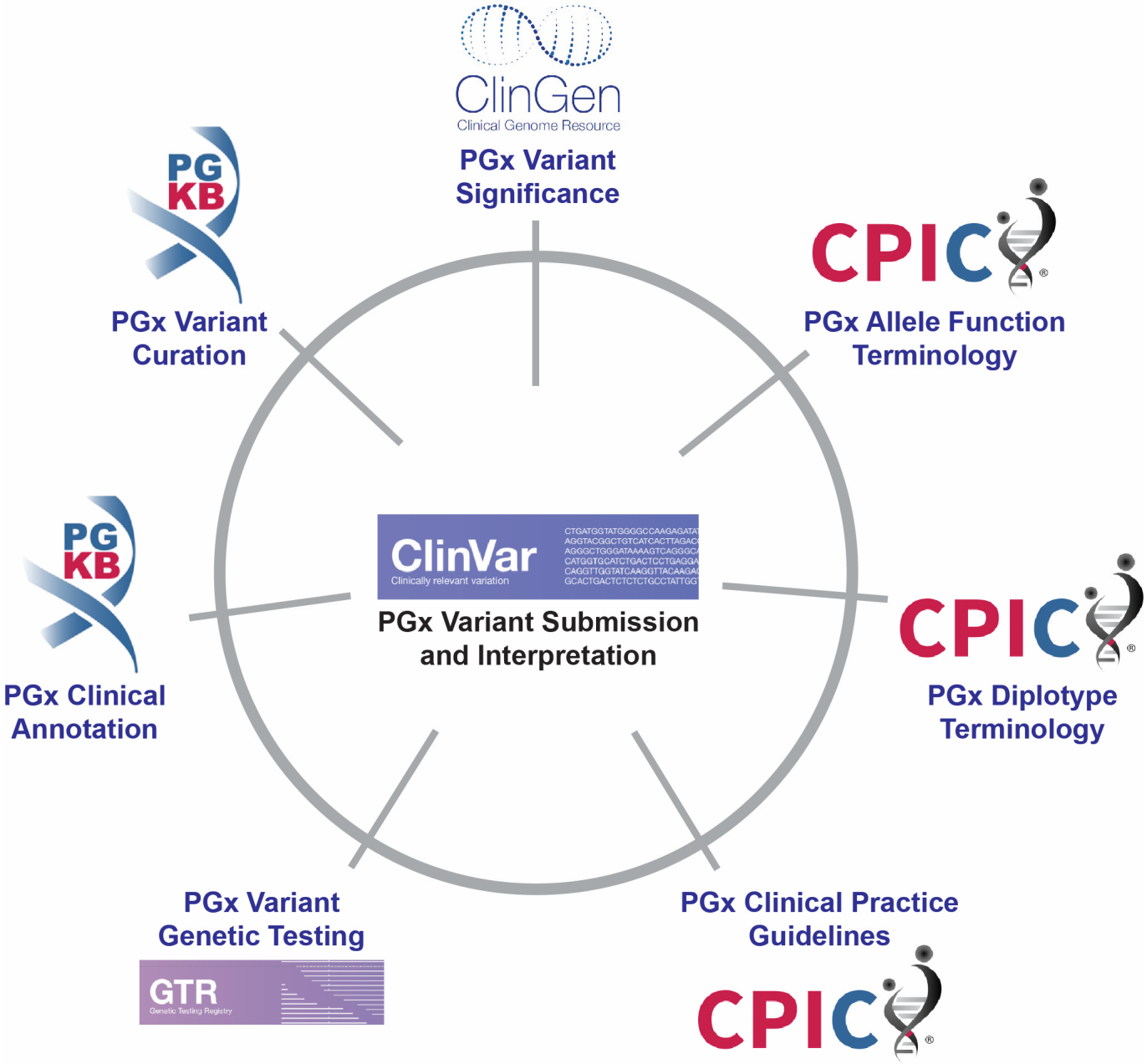
and send to clinvar@ncbi.nlm.nih.gov. This information will be reviewed by the ClinGen Steering Committee to make the determination of practice guideline status for clinical assertions in ClinVar.

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.

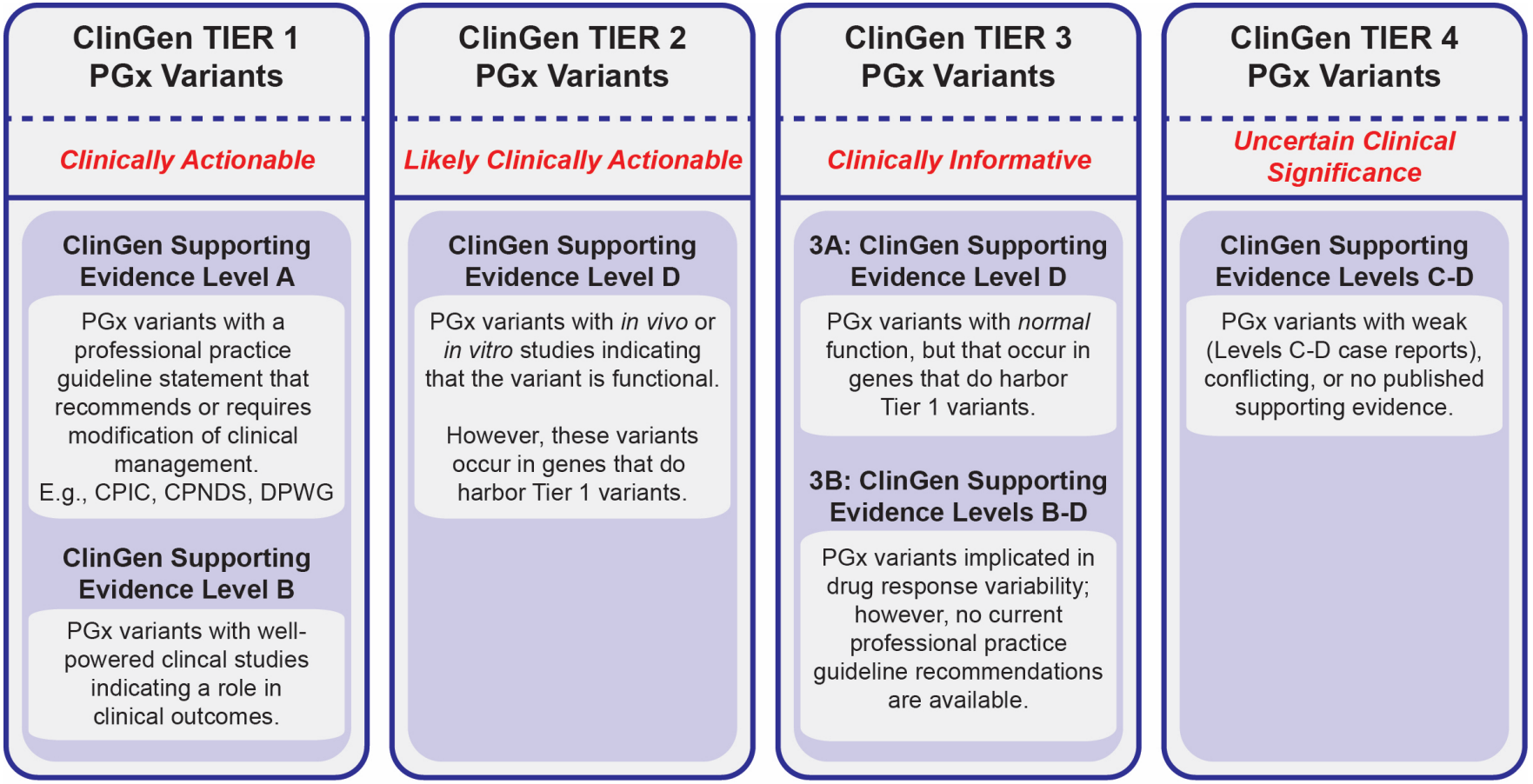
Please make note of the following points:

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

ClinGen/ClinVar relationships with CPIC & PharmGKB



Proposed Classification for "Clinical Significance" of Pharmacogenomic Variants



ClinGen
Clinical Genome Resource

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the nation • Improving health

ABOUT THE IOM | REPORTS | ACTIVITIES | MEETINGS

BROWSE HISTORY

Action Collaboratives

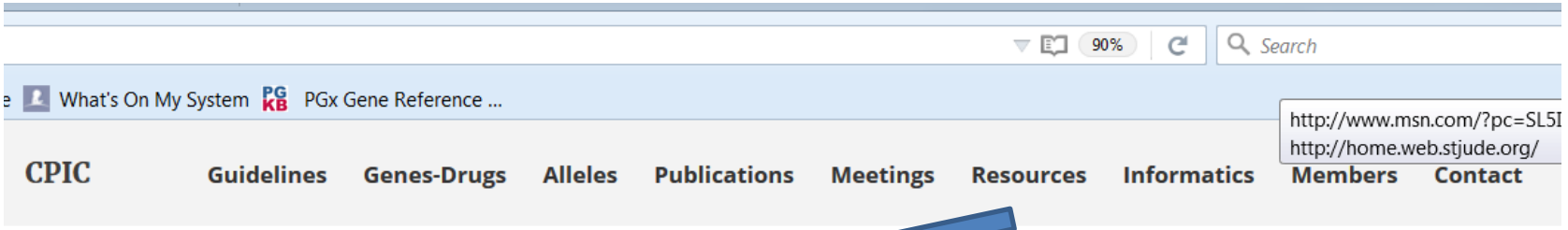
DIGITizE: Displaying and Integrating Genetic Information Through the EHR

Establishing Connectivity and Pharmacogenomic Clinical Decision Support Rules to Protect Patients Carrying HLA-B*57:01 and TPMT Variants

An Implementation Guide

12/1/2015
Displaying and Integrating Genetic Information Through the EHR Action Collaborative (DIGITizE AC)

Version 1.0



Implementation

The following is a list of PGx implementers who are using CPIC guidelines as part of a program to facilitate use of genetic tests to guide prescribing for patients in clinical care settings:

Institution	Website and/or Contact (if available)
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The IGNITE Network	IGNITE

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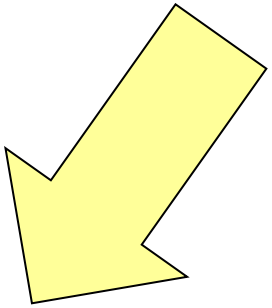
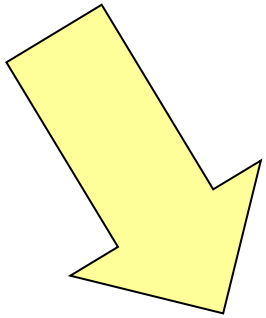
We are approaching implementation on 2 fronts at St. Jude





CPIC
Clinical Pharmacogenetics Implementation Consortium

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

St. Jude Children's Research Hospital
PG4KDS Protocol

STANFORD UNIVERSITY

Long-term goal: preemptive pharmacogenetic testing as the standard of care… for everyone
All CPIC guidelines.
> 4000 pts, 7 genes, 21 drugs

PHARMGKB

Acknowledgements

PIs

Teri Klein

Russ Altman

Associate Director

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Katrin Sangkuhl

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Ryan Whaley

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www.pharmgkb.org

www.pgrn.org/clinical-implementation.html

Bookmarks WhatsApp Imported From IE (1) PGx Gene Reference

PGRN HOME WHAT IS PGRN? MEMBERS TOOLS PGRN RES

PGRN

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Acknowledgements

CPIC™ Clinical Pharmacogenetics Implementation Consortium

CPIC Informatics: Marc Williams, Bob Freimuth, Josh Peterson & others

CPIC guideline authors: volunteers!

NIH: R24GM115264

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Brad Strock, Epic

CDS needed for Clinical actionability of genetic test results

- Interruptive alerts (active CDS):
  - Pre-test situation:
    - Check for genetic test and, if missing, guide prescriber to consider ordering the test
  - Post-test situation:
    - Test result is high-risk and advice for prescribing alternatives should be presented
    - Test result is low-risk and no interruptive alert should be fired
- Interpretations (passive CDS)

But genetic test names, results, phenotypes (problems, diagnoses) are not standardized, making it difficult for EHR vendors to support efforts to build CDS based on genetic tests

Final Standardized Terms: Allele function

Term/Gene Category	Final Term	Functional Definition	Example diplotypes/alleles
Allele Functional Status-all genes	Increased Function	Function greater than normal function	*CYP2C19*17*
	Normal Function	Fully functional/wild-type	*CYP2C19*1*
	Decreased Function	Function less than normal function	*CYP2C19*9*
	No Function	Non-functional	*CYP2C19*2*
	Unknown Function	No literature describing function or the allele is novel	*CYP2C19*29*
	Uncertain Function	Literature supporting function is conflicting or weak	*CYP2C19*12*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

Final Standardized Terms: Phenotype for Drug Metabolizing Enzymes

For example: CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Ultra-rapid Metabolizer	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles, or more than 2 normal function alleles	*CYP2C19*17/*17* *CYP2D6*1/*1XN*
Rapid Metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
Normal Metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
Intermediate Metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
Poor Metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

Final Standardized Terms: Phenotype for Drug Transporters

For example: SLCO1B1

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Increased Function	Increased transporter function compared to normal function	One or more increased function alleles	*SLCO1B1*1/*14*
Normal Function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
Decreased Function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
Poor Function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles	*SLCO1B1*5/*5*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

Final Standardized Terms: (HLA-genes) Phenotype for High-Risk Genotype Status

For example: HLA-B*57:01

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
Negative	High risk-allele not detected	No copies of high-risk allele	

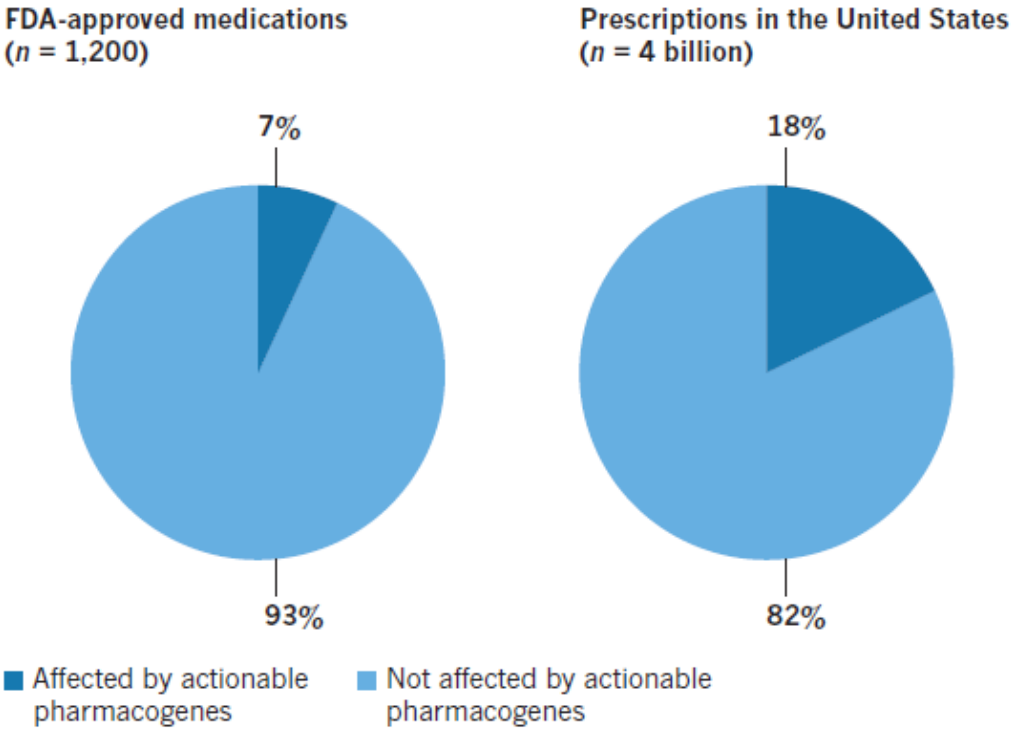
Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

Level Definitions for CPIC Genes/Drugs

CPIC LEVEL	CLINICAL CONTEXT	LEVEL OF EVIDENCE	STRENGTH OF RECOMMENDATION
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended.
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended.
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended.

How many gene/drug pairs should be used in the clinic?

- ~ 1200 chemical entities approved as drugs
- ~ 18,000 genes
- Actionable: ~ 17 genes, ~ 87 drugs (~ 30 guidelines)
  - http://www.pharmgkb.org/page/cpicGeneDrugPairs



Relling & Evans, *Nature*, 2015