PharmCAT Report

Title	Vanderbilt_CLIA_sample_357_pharmcat_output
Date created	June 12, 2018
Version	unspecified

Pre-release software - For code testing only

This software has not been officially released. You should only be using this software to evaluate whether the PharmCAT executable will compile and run properly on your system. The content of the reporting is not yet complete so **results will change**. The user recognizes they are using PharmCAT at their own risk.

Disclaimer: The PharmCAT report is only able to generate recommendations based on the information imported into the software. The gene and variant information for all reported sections are interpreted directly from the uploaded vcf file. The user recognizes they are using PharmCAT at their own risk. For a detailed disclaimer see section IV.

Sections

Genotype Summary

Genotypes called: 4 / 4

Drugs [a]	Gene	Genotype	Allele Functionality [b]	Phenotype [b]	Missing Variant Input [c]
● trimipramine ● imipramine ● voriconazole ● doxepin ● clomipramine ● sertraline ● clopidogrel ● escitalopram ● citalopram ● amitriptyline	CYP2C19†	*1/*1	Two normal function alleles	Normal Metabolizer	Yes
■ warfarin ● phenytoin	CYP2C9	*1/*1	Two normal function alleles	Normal Metabolizer	Yes
✖ tacrolimus	CYP3A5†	*1/*3	One normal function allele and one no function allele	Intermediate Metabolizer	Yes
● simvastatin	SLCO1B1	*1B/*21 *21/*29	One normal function allele and one unknown or uncertain function allele Two unknown or uncertain function alleles	Indeterminate Indeterminate	Yes

[a] The drugs are colored to indicate whether CPIC recommends a prescribing change based on the given genotype; highlighting is not based on CPIC classification of recommendation. When multiple diplotypes are possible for a gene, the drug is highlighted according to the highest level of prescribing change. ✖ Red indicates a prescribing change is recommended for the given diplotype. That is, the recommendation is different than 'use label recommendation' or 'use recommended starting dose', except for ivacaftor. ⚠ Orange indicates possible prescribing changes depending on additional information, e.g. pediatrics vs. adult, or the specific number of CYP2D6 normal alleles present (copy number). ● Green indicates that there is no CPIC recommended prescribing change for the given diplotype, except for ivacaftor. ■ Blue indicates the specific guideline must be consulted because a CPIC recommended action cannot be provided based solely on diplotype (eg. warfarin and ribavirin/peginterferon).

*[b] Allele functionality and phenotype terms are based on the CPIC term standardization project, PMID:27441996. Guidelines published prior use the term 'extensive' instead of 'normal' metabolizer. CYP2C19*1/*17 is now classified as rapid metabolizer. Guidelines published prior group CYP2C19*1/*17 together with *17/*17 as ultrarapid metabolizer.*

[c] Indicates alleles not considered for the genotype calls due to missing variant information, please see Allele calls section. Alleles that could not be considered due to missing input might change the metabolizer phenotype and possible CPIC recommendation.

† Check the allele call details for this gene for more details about this call.

For a full list of disclaimers and limitations see the Disclaimer section.

CPIC Recommendations

amitriptyline

The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

The official guideline can be found on the CPIC website.

CYP2D6: not called
CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function CYP2D6:Unknown/Unknown
Phenotype	CYP2C19 Normal Metabolizer
Implications	Normal metabolism of tertiary amines
Recommendations	Initiate therapy with recommended starting dose. *Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of amitriptyline for treatment of conditions such as depression.*
Classification of Recommendation	Strong

Classification of recommendation might differ based on the availabilty of CYP2D6 or CYP2C19 genotypes only or a combination of CYP2D6 and CYP2C19 genotypes; see full guideline at cpicpgx.org.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update [PMID:27997040] *Clinical pharmacology and therapeutics*. 2016.
- Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants [PMID:23486447] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.12.14

escitalopram, citalopram

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitors citalopram and escitalopram recommends an alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 ultrarapid metabolizers. For CYP2C19 poor metabolizers, consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.

The official guideline can be found on the CPIC website.

CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function
Phenotype	Normal Metabolizer
Implications	Normal metabolism
Recommendations	Initiate therapy with recommended starting dose.
Classification of Recommendation	Strong

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors [PMID:25974703] *Clinical pharmacology and therapeutics*. 2015.

Guideline annotation last modified: 2015.05.11

clomipramine

Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including clomipramine. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

The official guideline can be found on the CPIC website.

CYP2D6: not called
CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function CYP2D6:Unknown/Unknown
Phenotype	CYP2C19 Normal Metabolizer
Implications	Normal metabolism of tertiary amines
Recommendations	Initiate therapy with recommended starting dose. *Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of amitriptyline for treatment of conditions such as depression.*
Classification of Recommendation	Strong

Classification of recommendation might differ based on the availabilty of CYP2D6 or CYP2C19 genotypes only or a combination of CYP2D6 and CYP2C19 genotypes; see full guideline at cpicpgx.org.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update [PMID:27997040] *Clinical pharmacology and therapeutics*. 2016.
- Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants [PMID:23486447] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.12.14

clopidogrel

The CPIC Dosing Guideline for clopidogrel recommends an alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers if there is no contraindication.

The official guideline can be found on the CPIC website.

CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function
Phenotype	Normal Metabolizer
Implications	Normal platelet inhibition; normal residual platelet aggregation
Recommendations	Clopidogrel - label recommended dosage and administration
Classification of Recommendation	Strong

Antiplatelet therapy recommendations are based on CYP2C19 status when considering clopidogrel for acute coronary syndrome (ACS patients undergoing percutaneous coronary intervention (PCI)). CPIC guidelines reflect the alleles/genotypes known and considered by the guideline authors for inclusion by the time of publication. CPIC guidelines are periodically updated - see

cpicpgx.org.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy: 2013 Update [PMID:23698643] *Clinical pharmacology and therapeutics*. 2013.
- Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy [PMID:21716271] *Clinical pharmacology and therapeutics*. 2011.

Guideline annotation last modified: 2013.05.22

doxepin

Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including doxepin. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

The official guideline can be found on the CPIC website.

CYP2D6: not called
CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function CYP2D6:Unknown/Unknown
Phenotype	CYP2C19 Normal Metabolizer
Implications	Normal metabolism of tertiary amines
Recommendations	Initiate therapy with recommended starting dose. *Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of amitriptyline for treatment of conditions such as depression.*
Classification of Recommendation	Strong

Classification of recommendation might differ based on the availabilty of CYP2D6 or CYP2C19 genotypes only or a combination of CYP2D6 and CYP2C19 genotypes; see full guideline at cpicpgx.org.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update [PMID:27997040] *Clinical pharmacology and therapeutics*. 2016.
- Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants [PMID:23486447] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.12.14

imipramine

Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including imipramine. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

The official guideline can be found on the CPIC website.

CYP2D6: not called
CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function CYP2D6:Unknown/Unknown
Phenotype	CYP2C19 Normal Metabolizer
Implications	Normal metabolism of tertiary amines
Recommendations	Initiate therapy with recommended starting dose. *Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of amitriptyline for treatment of conditions such as depression.*
Classification of Recommendation	Strong

Classification of recommendation might differ based on the availabilty of CYP2D6 or CYP2C19 genotypes only or a combination of CYP2D6 and CYP2C19 genotypes; see full guideline at cpicpgx.org.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update [PMID:27997040] *Clinical pharmacology and therapeutics*. 2016.
- Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants [PMID:23486447] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.12.14

phenytoin

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.

The official guideline can be found on the CPIC website.

CYP2C9: *1/*1
HLA-B: not called

The displayed recommendation for CYP2C9 and phenytoin is ONLY valid for non-carriers of the HLA-B*15:02 high-risk allele. PharmCAT does not interpret HLA carrier status. 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). In HLA-B*15:02 carriers, carbamazepine should not be used as an alternative. 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.

Type	Annotation
Allele Functionality	CYP2C9:Normal Function/Normal Function HLA-B:Absence/Absence
Phenotype	CYP2C9 Normal Metabolizer
Implications	Normal phenytoin metabolism.
Recommendations	Initiate therapy with recommended maintenance dose (based on patient's clinical characteristics).
Classification of Recommendation	Strong

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C9 and HLA-B Genotype and Phenytoin Dosing [PMID:25099164] *Clinical pharmacology and therapeutics*. 2014.

Guideline annotation last modified: 2014.08.05

sertraline

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor sertraline recommends to consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 poor metabolizers.

The official guideline can be found on the CPIC website.

CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function
Phenotype	Normal Metabolizer
Implications	Normal metabolism
Recommendations	Initiate therapy with recommended starting dose.
Classification of Recommendation	Strong

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors [PMID:25974703] *Clinical pharmacology and therapeutics*. 2015.

Guideline annotation last modified: 2015.05.08

simvastatin

The FDA recommends against 80mg daily simvastatin dosage. In patients with the C allele at SLCO1B1 rs4149056, there are modest increases in myopathy risk even at lower simvastatin doses (40mg daily); if optimal efficacy is not achieved with a lower dose, alternate agents should be considered.

The official guideline can be found on the CPIC website.

SLCO1B1: *1B/*21, *21/*29
rs4149056T/rs4149056T

SLCO1B1 star allele nomenclature represents various SNPs alone or in combination. The SLCO1B1 genotype (star nomenclature) will be displayed if determinable with the provided VCF based on the SLCO1B1 star allele definition published by CPIC and recommendations are provided based on the genotype.

In case no genotype can be determined, recommendations are based on the rs4149056 genotype alone as per guideline. The minor C allele at rs4149056 is contained in SLCO1B1*5 (rs4149056 alone) as well as the *15 and *17 alleles, and is associated with lower plasma clearance of simvastatin. The magnitude of this effect is similar for *5, *15, and *17 alleles. A number of SLCO1B1 alleles (*2, *3, *6, *9, *10, *23, *31) are classified by CPIC as 'possible decreased function' alleles. These alleles are not accounted for in the recommendation based on the rs4149056 genotype. Carriage of additional variants is possible.

Type	Annotation
Allele Functionality	SLCO1B1:Normal Function/Unknown or Uncertain Function SLCO1B1:Unknown or Uncertain Function/Unknown or Uncertain Function
Phenotype	Indeterminate
Recommendations	This guideline does not contain recommendations for this allele combination.
Classification of Recommendation	N/A

In all cases, the potential for drug-drug interaction should be evaluated prior to initiating a prescription. FDA recommends against 80mg of simvastatin (unless already tolerated for 12 months).

For more information see the annotation on PharmGKB.

Citations:

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update [PMID:24918167] *Clinical pharmacology and therapeutics*. 2014.
- The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for SLCO1B1 and Simvastatin-Induced Myopathy [PMID:22617227] *Clinical pharmacology and therapeutics*. 2012.

Guideline annotation last modified: 2014.06.30

tacrolimus

The CPIC dosing guideline for tacrolimus recommends increasing the starting dose by 1.5 to 2 times the recommended starting dose in patients who are CYP3A5 intermediate or extensive metabolizers, though total starting dose should not exceed 0.3 mg/kg/day. Therapeutic drug monitoring should also be used to guide dose adjustments.

The official guideline can be found on the CPIC website.

CYP3A5: *1/*3

Type	Annotation
Allele Functionality	CYP3A5:No Function/Normal Function
Phenotype	Intermediate Metabolizer
Implications	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.
Recommendations	Increase starting dose 1.5 to 2 times recommended starting dose. Total starting dose should not exceed 0.3mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments. *Further dose adjustments or selection of alternative therapy may be necessary because of other clinical factors (e.g., medication interactions, or hepatic function).*
Classification of Recommendation	Strong

For more information see the annotation on PharmGKB.

Citations:

- Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing [PMID:25801146] *Clinical pharmacology and therapeutics*. 2015.

Guideline annotation last modified: 2015.08.11

trimipramine

Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including trimipramine. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

The official guideline can be found on the CPIC website.

CYP2D6: not called
CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function CYP2D6:Unknown/Unknown
Phenotype	CYP2C19 Normal Metabolizer
Implications	Normal metabolism of tertiary amines
Recommendations	Initiate therapy with recommended starting dose. *Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of amitriptyline for treatment of conditions such as depression.*
Classification of Recommendation	Strong

Classification of recommendation might differ based on the availabilty of CYP2D6 or CYP2C19 genotypes only or a combination of CYP2D6 and CYP2C19 genotypes; see full guideline at cpicpgx.org.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update [PMID:27997040] *Clinical pharmacology and therapeutics*. 2016.
- Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants [PMID:23486447] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.12.14

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voriconazole

The CPIC dosing guideline for voriconazole recommends selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers. In pediatric patients, an alternative agent should be used in patients who are ultrarapid metabolizers or poor metabolizers. In pediatric rapid metabolizers, therapy should be initiated at recommended standard case dosing, then therapeutic dosing monitoring should be used to titrate dose to therapeutic trough concentrations.

The official guideline can be found on the CPIC website.

CYP2C19: *1/*1

Type	Annotation
Allele Functionality	CYP2C19:Normal Function/Normal Function
Phenotype	Normal Metabolizer
Implications	Normal voriconazole metabolism
Recommendations	For pediatric or adult patients: initiate therapy with recommended standard of care dosing. *Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, TDM, and comorbidities.*
Classification of Recommendation	Strong

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC®) Guideline for CYP2C19 and Voriconazole Therapy [PMID:27981572] *Clinical pharmacology and therapeutics*. 2016.

Guideline annotation last modified: 2016.12.02

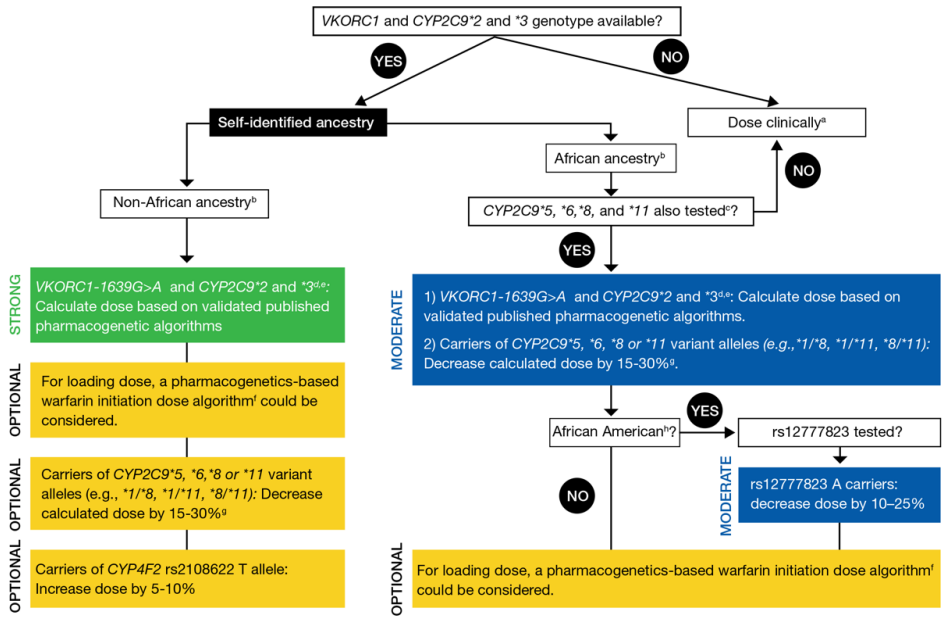
warfarin

The updated guideline for pharmacogenetics-guided warfarin dosing is published by the *Clinical Pharmacogenetics Implementation Consortium*. The recommendations for dosing are for adult and pediatric patients that are specific to continental ancestry, and are based on genotypes from *CYP2C9*, *VKORC1*, *CYP4F2*, and rs12777823.

The official guideline can be found on the CPIC website.

VKORC1: not called
CYP2C9: *1/*1
CYP4F2: not called
rs12777823: missing

Please follow the flow chart in figure 2 of the CPIC warfarin guideline to determine the appropriate dosing recommendation.



The CPIC warfarin guideline only considers a single SNV in VKORC1 (rs9923231), which is found in the highest frequency in Caucasians and extremely low frequency in those of African descent. While other functional variants in VKORC1 have been observed in much higher frequencies in some populations, there are currently no CPIC recommendations for how to use these other variants in warfarin dosing. An alternate name for rs9923231 is -1639G>A (note that VKORC1 is on the negative chromosomal strand, so displayed alleles are complemented).

For more information see the annotation on PharmGKB.

Citations:

- Clinical pharmacogenetics implementation consortium (cpic) guideline for pharmacogenetics-guided warfarin dosing: 2017 update [PMID:28198005] *Clinical pharmacology and therapeutics*. 2017.
- Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing [PMID:21900891] *Clinical pharmacology and therapeutics*. 2011.

Guideline annotation last modified: 2017.02.08

atazanavir

The CPIC dosing guideline recommends considering advising individuals who carry two decreased function *UGT1A1* alleles about a substantial likelihood of developing jaundice, which may cause non-adherence. The dosing guideline recommends that alternative agents be considered if the risk of non-adherence due to jaundice is high. The risk of discontinuation is low and very low for individuals carrying one, or no decreased function *UGT1A1* alleles, respectively.

The official guideline can be found on the CPIC website.

UGT1A1: not called

Unphased data: all variant alleles found are listed based on the vcf input and the UGT1A1 definition table. Phased data: the subject's phased UGT1A1 genotype is listed. The CPIC recommendations are provided based on an exception logic. UGT1A1*28 and *80 are assumed in cis for unphased data, see http://pharmcat.org/ and the UGT1A1 gene section for details on *80.

No genotypes matched for UGT1A1 so annotations cannot be shown.

> *These recommendations are for the use of atazanavir (boosted with either ritonavir or cobicistat) by UGT1A1 phenotype. All studies correlating UGT1A1 genotypes with atazanavir adverse events have involved ritonavir boosting. However, concentration-time profiles are equivalent when boosted with either cobicistat or ritonavir, and bilirubin-related adverse events including discontinuation of atazanavir occur in a similar percentage of patients prescribed atazanavir with cobicistat or ritonavir. Associations between UGT1A1 genotype, bilirubin elevations, and atazanavir discontinuation therefore almost certainly translate to atazanavir/cobicistat.*

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing [PMID:26417955] *Clinical pharmacology and therapeutics*. 2015.

Guideline annotation last modified: 2015.09.18

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azathioprine

Consider an alternate agent or extreme dose reduction of azathioprine for patients with low or deficient TPMT activity. Start at 30-70% of target dose for patients with intermediate enzyme activity.

The official guideline can be found on the CPIC website.

TPMT: not called

No genotypes matched for TPMT so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update [PMID:23422873] *Clinical pharmacology and therapeutics*. 2013.
- Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing [PMID:21270794] *Clinical pharmacology and therapeutics*. 2011.

Guideline annotation last modified: 2016.05.11

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capecitabine

The CPIC Dosing Guideline for 5-fluorouracil and capecitabine recommends an alternative drug for patients who are DPYD poor metabolizers with an activity score of 0. In those who are poor metabolizers with an activity score of 0.5, an alternative drug is also recommended, but if this is not considered a suitable therapeutic option, 5-fluorouracil or capecitabine should be administered at a strongly reduced dose with early therapeutic drug monitoring. Patients who are intermediate metabolizers with an activity score of 1 or 1.5 should receive a dose reduction of 50% and 25%-50%, respectively.

The official guideline can be found on the CPIC website.

DPYD: not called

The 2017 CPIC DPYD guideline update includes normal function variants with strong, moderate or in vitro data only evidence. These variants are not included in the PharmCAT DPYD gene definition table. The CPIC DPYD functionality table includes further no and decreased function variants with 'In vitro data only and/or limited clinical/ex vivo data' evidence. According to the guideline, to date, there are no studies linking the variants listed in the "in vitro data only and/or limited clinical/ex vivo data" category as decreased or no function variants directly to toxicity related to fluoropyrimidines and therefore, these variants are not specifically included in the CPIC recommendations. These variants are not included in the PharmCAT DPYD gene definition table. Refer to the DPYD gene section for a list of these variants.

No genotypes matched for DPYD so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update [PMID:29152729] *Clinical pharmacology and therapeutics*. 2017.
- Clinical Pharmacogenetics Implementation Consortium Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing [PMID:23988873] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2017.11.13

codeine

Alternate analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers. A label recommended age- or weight-specific codeine dose is warranted for CYP2D6 extensive and intermediate metabolizers.

The official guideline can be found on the CPIC website.

CYP2D6: not called

No genotypes matched for CYP2D6 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 2D6 (CYP2D6) genotype and codeine therapy: 2014 Update [PMID:24458010] *Clinical pharmacology and therapeutics*. 2014.
- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype [PMID:22205192] *Clinical pharmacology and therapeutics*. 2011.

Guideline annotation last modified: 2017.05.02

desipramine

Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline/nortriptyline and CYP2C19, CYP2D6 to other tricyclics including desipramine. The CPIC Dosing Guideline update for nortriptyline recommends a 25% dose reduction for CYP2D6 intermediate metabolizers. For CYP2D6 ultrarapid or poor metabolizers, an alternative drug should be considered. If nortriptyline is warranted, consider a 50% dose reduction in CYP2D6 poor metabolizers.

The official guideline can be found on the CPIC website.

CYP2D6: not called

No genotypes matched for CYP2D6 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update [PMID:27997040] *Clinical pharmacology and therapeutics*. 2016.
- Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants [PMID:23486447] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.12.14

fluorouracil

The CPIC Dosing Guideline for 5-fluorouracil and capecitabine recommends an alternative drug for patients who are DPYD poor metabolizers with an activity score of 0. In those who are poor metabolizers with an activity score of 0.5, an alternative drug is also recommended, but if this is not considered a suitable therapeutic option, 5-fluorouracil or capecitabine should be administered at a strongly reduced dose with early therapeutic drug monitoring. Patients who are intermediate metabolizers with an activity score of 1 or 1.5 should receive a dose reduction of 50% and 25%-50%, respectively.

The official guideline can be found on the CPIC website.

DPYD: not called

The 2017 CPIC DPYD guideline update includes normal function variants with strong, moderate or in vitro data only evidence. These variants are not included in the PharmCAT DPYD gene definition table. The CPIC DPYD functionality table includes further no and decreased function variants with 'In vitro data only and/or limited clinical/ex vivo data' evidence. According to the guideline, to date, there are no studies linking the variants listed in the “in vitro data only and/or limited clinical/ex vivo data” category as decreased or no function variants directly to toxicity related to fluoropyrimidines and therefore, these variants are not specifically included in the CPIC recommendations. These variants are not included in the PharmCAT DPYD gene definition table. Refer to the DPYD gene section for a list of these variants.

No genotypes matched for DPYD so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update [PMID:29152729] *Clinical pharmacology and therapeutics*. 2017.
- Clinical Pharmacogenetics Implementation Consortium Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing [PMID:23988873] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2017.11.28

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fluvoxamine

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor fluvoxamine recommends to consider a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6 for CYP2D6 poor metabolizers.

The official guideline can be found on the CPIC website.

CYP2D6: not called

No genotypes matched for CYP2D6 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors [PMID:25974703] *Clinical pharmacology and therapeutics*. 2015.

Guideline annotation last modified: 2015.05.08

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ivacaftor

Ivacaftor treatment is recommended only in cystic fibrosis (CF) patients that are either homozygous or heterozygous for certain *CFTR* variants. See full guideline for disclaimers, further details and supporting evidence.

The official guideline can be found on the CPIC website.

CFTR: not called

No genotypes matched for CFTR so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Ivacaftor Therapy in the Context of CFTR Genotype [PMID:24598717] *Clinical pharmacology and therapeutics*. 2014.

Guideline annotation last modified: 2017.06.02

mercaptopurine

Start with reduced doses of mercaptopurine for patients with one nonfunctional TPMT allele, or drastically reduced doses for patients with malignancy and two nonfunctional alleles; adjust dose based on degree of myelosuppression and disease-specific guidelines. Consider alternative nonthiopurine immunosuppressant therapy for patients with nonmalignant conditions and two nonfunctional alleles.

The official guideline can be found on the CPIC website.

TPMT: not called

No genotypes matched for TPMT so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update [PMID:23422873] *Clinical pharmacology and therapeutics*. 2013.
- Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing [PMID:21270794] *Clinical pharmacology and therapeutics*. 2011.

Guideline annotation last modified: 2016.05.11

nortriptyline

The CPIC Dosing Guideline update for nortriptyline recommends a 25% dose reduction for CYP2D6 intermediate metabolizers. For CYP2D6 ultrarapid or poor metabolizers, an alternative drug should be considered. If nortriptyline is warranted, consider a 50% dose reduction in CYP2D6 poor metabolizers.

The official guideline can be found on the CPIC website.

CYP2D6: not called

No genotypes matched for CYP2D6 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update [PMID:27997040] *Clinical pharmacology and therapeutics*. 2016.
- Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants [PMID:23486447] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.12.14

ondansetron

The CPIC dosing guideline for ondansetron recommends selecting an alternate drug for CYP2D6 ultrarapid metabolizers. It is recommended that the alternate drug not be predominantly metabolized by CYP2D6 (eg. granisetron).

The official guideline can be found on the CPIC website.

CYP2D6: not called

No genotypes matched for CYP2D6 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 Genotype and Use of Ondansetron and Tropisetron [PMID:28002639] *Clinical pharmacology and therapeutics*. 2016.

Guideline annotation last modified: 2016.12.23

paroxetine

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor paroxetine recommends an alternative drug not predominantly metabolized by CYP2D6 for CYP2D6 ultrarapid metabolizers and for CYP2D6 poor metabolizers. For CYP2D6 poor metabolizers, if paroxetine use is warranted, consider a 50% reduction of recommended starting dose and titrate to response.

The official guideline can be found on the CPIC website.

CYP2D6: not called

No genotypes matched for CYP2D6 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors [PMID:25974703] *Clinical pharmacology and therapeutics*. 2015.

Guideline annotation last modified: 2015.05.08

peginterferon alfa-2a, peginterferon alfa-2b, ribavirin

IFNL3 (IL28B) variation (rs12979860) is the strongest baseline predictor of response to PEG-interferon-alpha-containing regimens in HCV genotype 1 patients. Patients with the favorable response genotype (rs12979860 CC) have increased likelihood of response (higher SVR rate) to PEG-interferon-alpha-containing regimens as compared to patients with unfavorable response genotype (rs12979860 CT or TT). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

The official guideline can be found on the CPIC website.

IFNL3: not called

No genotypes matched for IFNL3 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for IFNL3 (IL28B) genotype and peginterferon alpha based regimens [PMID:24096968] *Clinical pharmacology and therapeutics*. 2013.

Guideline annotation last modified: 2016.02.25

thioguanine

Start with reduced doses of thioguanine for patients with one nonfunctional TPMT allele, or drastically reduced doses for patients with malignancy and two nonfunctional alleles; adjust dose based on degree of myelosuppression and disease-specific guidelines. Consider alternative nonthiopurine immunosuppressant therapy for patients with nonmalignant conditions and two nonfunctional alleles.

The official guideline can be found on the CPIC website.

TPMT: not called

No genotypes matched for TPMT so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update [PMID:23422873] *Clinical pharmacology and therapeutics*. 2013.
- Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing [PMID:21270794] *Clinical pharmacology and therapeutics*. 2011.

Guideline annotation last modified: 2016.05.11

tropisetron

The CPIC dosing guideline for tropisetron recommends selecting an alternate drug for CYP2D6 ultrarapid metabolizers. It is recommended that the alternate drug not be predominantly metabolized by CYP2D6 (eg. granisetron).

The official guideline can be found on the CPIC website.

CYP2D6: not called

No genotypes matched for CYP2D6 so annotations cannot be shown.

For more information see the annotation on PharmGKB.

Citations:

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 Genotype and Use of Ondansetron and Tropisetron [PMID:28002639] *Clinical pharmacology and therapeutics*. 2016.

Guideline annotation last modified: 2016.12.23

Allele Matching Details

1. CFTR allele match data
2. CYP2C19 allele match data
3. CYP2C9 allele match data
4. CYP2D6 allele match data
5. CYP3A5 allele match data
6. CYP4F2 allele match data
7. DPYD allele match data
8. IFNL3 allele match data
9. SLCO1B1 allele match data
10. TPMT allele match data
11. UGT1A1 allele match data
12. VKORC1 allele match data

CFTR allele match data

Genotype matched

- not called

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 53 missing positions of the total 53 positions: 621+1G->T, 711+1G->T, 1717-1G->A, 1898+1G->A, 2184delA, 2789+5G->A, 3120+1G->A, 3659delC, 3849+10kbC- >T, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, F508del(CTT), F1052V, F1074L, G85E, G178R, G542X, G551D, G551S, G1069R, G1244E, G1349D, I507, K1060T, L206W, N1303K, P67L, R74W, R117C, R117H, R334W, R347H, R347P, R352Q, R553X, R560T, R1070Q, R1070W, R1162X, Reference, S549N, S549R(A>C), S549R(T>G), S945L, S977F, S1251N, S1255P, W1282X

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
117642528	rs11971167	*missing*	G	D1270N
117611649	rs202179988	*missing*	C	R1070W
117627581	rs121908747	*missing*	C	3659delC
117534363	rs397508759	*missing*	G	E193K
117611640	rs121909020	*missing*	G	A1067T
117587811	rs74597325	*missing*	C	R553X
117590409	rs397508288	*missing*	A	D579G
117587800	rs121908755	*missing*	G	S549N

117559592	rs113993960	*missing*	CTT	F508del(CTT)
117627537	rs74767530	*missing*	C	R1162X
117540285	rs121908753	*missing*	G	R352Q
117530975	rs78655421	*missing*	G	R117H
117559590	rs121908745	*missing*	ATC	I507
117611595	rs150212784	*missing*	T	F1052V
117509089	rs115545701	*missing*	C	R74W
117587799	rs121908757	*missing*	A	S549R(A>C)
117611646	rs200321110	*missing*	G	G1069R
117642483	rs121909041	*missing*	T	S1255P
117587805	rs121909013	*missing*	G	G551S
117509035	rs397508256	*missing*	G	E56K
117606754	rs75096551	*missing*	G	3120+1G->A
117509123	rs75961395	*missing*	G	G85E
117530974	rs77834169	*missing*	C	R117C
117587738	rs76713772	*missing*	G	1717-1G->A
117639961	rs75039782	*missing*	C	3849+10kbC- >T
117611663	rs186045772	*missing*	T	F1074L
117592219	rs121908746	*missing*	A	2184delA
117614699	rs75541969	*missing*	G	D1152H
117530953	rs113993958	*missing*	G	D110H
117587806	rs75527207	*missing*	G	G551D
117534318	rs80282562	*missing*	G	G178R
117642566	rs77010898	*missing*	G	W1282X
117531115	rs78756941	*missing*	G	621+1G->T
117534366	rs77188391	*missing*	G	711+1G->T
117509069	rs368505753	*missing*	C	P67L
117587801	rs121909005	*missing*	T	S549R(T>G)
117535285	rs121908752	*missing*	T	L206W
117590440	rs121908748	*missing*	G	1898+1G->A
117540230	rs121909011	*missing*	C	R334W
117611620	rs397508513	*missing*	A	K1060T
117602868	rs80224560	*missing*	G	2789+5G->A
117530955	rs397508537	*missing*	C	D110E
117611650	rs78769542	*missing*	G	R1070Q
117587778	rs113993959	*missing*	G	G542X

117642472	rs74503330	*missing*	G	S1251N
117548795	rs74551128	*missing*	C	A455E
117606695	rs141033578	*missing*	C	S977F
117540270	rs77932196	*missing*	G	R347H R347P
117652877	rs80034486	*missing*	C	N1303K
117587833	rs80055610	*missing*	G	R560T
117642451	rs267606723	*missing*	G	G1244E
117664770	rs193922525	*missing*	G	G1349D
117603708	rs397508442	*missing*	C	S945L

CYP2C19 allele match data

Genotype matched

- *1/*1

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 16 missing positions of the total 34 positions: *5, *7, *14, *17, *18, *19, *23, *25, *26, *27, *29, *31, *32, *35

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

CYP2C19*17, a common variant found in some populations and an increased function allele, is defined by a variant (rs12248560) in the CYP2C19 promoter region. Due to missing information on rs12248560 in the VCF file, the presence of this allele cannot be ruled out, and further testing may be warranted.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
94762706	rs28399504	A|A	A	*4A *4B
94762712	rs367543002	C|C	C	*34
94762715	rs367543003	T|T	T	*34
94762760	rs17882687	A|A	A	*15 *28
94775106	rs145328984	C|C	C	*30
94775416	rs41291556	T|T	T	*8
94775453	rs72552267	G|G	G	*6
94775489	rs17884712	G|G	G	*9
94775507	rs58973490	G|G	G	*11
94780574	rs140278421	G|G	G	*22
94780579	rs370803989	G|G	G	*33
94780653	rs4986893	G|G	G	*3
94781858	rs6413438	C|C	C	*10
94781859	rs4244285	G|G	G	*2
94842879	rs118203757	G|G	G	*24
94849995	rs17879685	C|C	C	*13
94852765	rs192154563	C|C	C	*16
94852914	rs55640102	A|A	A	*12
94761900	rs12248560	*missing*	C	*4B *17
94781944		*missing*	G	*26
94852785	rs118203759	*missing*	C	*25
94762856		*missing*	A	*19
94761665	rs7902257	*missing*	G	*27
94762788		*missing*	A	*29
94852738	rs56337013	*missing*	C	*5
94775367	rs12769205	*missing*	A	*2 *35
94781999	rs72558186	*missing*	T	*7
94775160	rs118203756	*missing*	G	*23
94842861	rs138142612	*missing*	G	*18
94762755	rs55752064	*missing*	T	*14
94849964	rs377184510	*missing*	A	*24
94775185		*missing*	A	*32
94775121		*missing*	C	*31
94842995	rs113934938	*missing*	G	*28

CYP2C9 allele match data

Genotype matched

- *1/*1

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 29 missing positions of the total 53 positions: *4, *7, *10, *15, *16, *17, *19, *20, *22, *23, *25, *28, *30, *32, *33, *38, *40, *42, *46, *48, *49, *50, *51, *52, *54, *55, *56, *57

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
94938683	rs114071557	A|A	A	*36
94938771	rs142240658	C|C	C	*21
94938828	rs564813580	A|A	A	*37
94941958	rs72558187	T|T	T	*13
94941982	rs762239445	G|G	G	*39
94942216		A|A	A	*41
94942230	rs767576260	C|C	C	*43
94942234	rs72558189	G|G	G	*14 *35
94942249	rs200965026	C|C	C	*26 *44
94942254	rs199523631	C|C	C	*45
94942290	rs1799853	C|C	C	*2 *35
94942309	rs7900194	G|G	G	*8 *27
94947785	rs774550549	C|C	C	*47
94949217	rs2256871	A|A	A	*9
94949282	rs9332131	A|A	A	*6
94972119	rs182132442	C|C	C	*29
94972233		C|C	C	*53
94981201	rs57505750	T|T	T	*31
94981224	rs28371685	C|C	C	*11
94981225	rs367826293	G|G	G	*34
94981281	rs749060448	G|G	G	*24
94981296	rs1057910	A|A	A	*3 *18
94981301	rs28371686	C|C	C	*5
94989020	rs9332239	C|C	C	*12
94942018		*missing*	T	*40
94949129		*missing*	A	*49
94947907		*missing*	A	*57

94941976		*missing*	G	*38
94972179	rs72558192	*missing*	A	*16
94942255	rs200183364	*missing*	G	*33
94988984	rs781583846	*missing*	G	*30
94942231	rs12414460	*missing*	G	*42
94981297	rs56165452	*missing*	T	*4
94941897	rs371055887	*missing*	G	*20
94941915		*missing*	G	*23
94972134		*missing*	A	*51
94947782	rs72558190	*missing*	C	*15
94942305	rs754487195	*missing*	G	*46
94981302		*missing*	C	*55
94986042	rs764211126	*missing*	A	*56
94938803		*missing*	A	*22
94949144		*missing*	C	*50
94938737	rs67807361	*missing*	C	*7
94981365		*missing*	C	*17
94947917		*missing*	T	*48
94986073	rs72558193	*missing*	A	*18
94942213		*missing*	AGAAATGGAA	*25
94947938		*missing*	A	*28
94981250	rs750820937	*missing*	C	*54
94989023		*missing*	G	*32
94949280	rs9332130	*missing*	A	*10
94972180		*missing*	C	*52
94988917	rs769942899	*missing*	G	*19

Other Positions of Interest

Position	RSID	Call
94645745	rs12777823	*missing*

CYP2D6 allele match data

Genotype matched

- not called

Phasing status

Unphased

No variant data available.

CYP3A5 allele match data

Genotype matched

- *1/*3

Phasing status

Unphased

Alleles Not Considered

The following alleles are not considered due to 1 missing positions of the total 8 positions: *9

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

CYP3A5 is known to have one or more functional variants in intronic regions. Since intronic variants are important for CYP3A5 genotype assignment, further testing may be warranted for exome data.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
99652613	rs28365083	G|G	G	*2
99652770	rs41303343	del|del	del	*7
99665212	rs10264272	C|C	C	*6
99665237	rs56411402	T|T	T	*4
99666950	rs55965422	A|A	A	*5
99672916	rs776746	**C/T**	T	*3
99676198	rs55817950	G|G	G	*8
99660516	rs28383479	*missing*	C	*3 *9

CYP4F2 allele match data

Genotype matched

- not called

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 2 missing positions of the total 2 positions: *1, *2, *3

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
15897578	rs3093105	*missing*	A	*2
15879621	rs2108622	*missing*	C	*3

DPYD allele match data

Genotype matched

- not called

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 10 missing positions of the total 10 positions: Reference, c.295_298delTCAT, c.557A>G, c.703C>T, c.1129-5923C>G, c.1156G>T, c.1679T>G, c.1898delC, c.1905+1G>A, c.2846A>T, c.2983G>T

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
97699474	rs115232898	*missing*	T	c.557A>G
97573943	rs78060119	*missing*	C	c.1156G>T
97079071	rs1801268	*missing*	C	c.2983G>T
97082391	rs67376798	*missing*	T	c.2846A>T
97450066	rs72549303	*missing*	G	c.1898delC
97691776	rs1801266	*missing*	G	c.703C>T
97579893	rs75017182	*missing*	G	c.1129-5923C>G
97515787	rs55886062	*missing*	A	c.1679T>G
97740415	rs72549309	*missing*	AGTA	c.295_298delTCAT
97450058	rs3918290	*missing*	C	c.1905+1G>A

Other Positions of Interest

Position	RSID	Call
97078987	rs114096998	*missing*
97078993	rs148799944	*missing*
97079005	rs140114515	*missing*
97079076	rs139459586	*missing*
97079077	rs202144771	*missing*
97079121	rs72547601	*missing*
97079133	rs72547602	*missing*
97079139	rs145529148	*missing*
97082365	rs141044036	*missing*
97098598	rs1801267	*missing*
97098599	rs147545709	*missing*
97098616	rs55674432	*missing*
97098632	rs201035051	*missing*
97193109	rs60139309	*missing*
97193209	rs200687447	*missing*
97234958	rs199634007	*missing*
97234991	rs56005131	*missing*
97235033	rs12137711	*missing*
97305279	rs112766203	*missing*
97305363	rs60511679	*missing*

97305364	rs1801160	*missing*
97305372	rs146529561	*missing*
97306195	rs145548112	*missing*
97373598	rs137999090	*missing*
97373629	rs138545885	*missing*
97382461	rs55971861	*missing*
97450059	rs3918289	*missing*
97450068	rs17376848	*missing*
97450168	rs147601618	*missing*
97450187	rs145773863	*missing*
97450189	rs138616379	*missing*
97450190	rs59086055	*missing*
97515686	rs2811178	*missing*
97515687	rs2786783	*missing*
97515784	rs201615754	*missing*
97515839	rs1801159	*missing*
97515851	rs142619737	*missing*
97515865	rs1801158	*missing*
97515889	rs190951787	*missing*
97515923	rs148994843	*missing*
97549565	rs138391898	*missing*
97549600	rs111858276	*missing*
97549609	rs72549304	*missing*
97549681	rs199549923	*missing*
97549713	rs57918000	*missing*
97549726	rs144395748	*missing*
97549735	rs72975710	*missing*
97549850	rs61789183	*missing*
97573785	rs186169810	*missing*
97573805	rs142512579	*missing*
97573821	rs764666241	*missing*
97573839	rs200064537	*missing*
97573881	rs61622928	*missing*
97573918	rs143815742	*missing*
97573919	rs140602333	*missing*
97573985	rs56293913	*missing*

97573998	rs368600943	*missing*
97593238	rs72549305	*missing*
97593289	rs143154602	*missing*
97593322	rs183385770	*missing*
97593343	rs72549306	*missing*
97593379	rs201018345	*missing*
97594925	rs2811202	*missing*
97595083	rs145112791	*missing*
97595088	rs150437414	*missing*
97595149	rs146356975	*missing*
97679004	rs138924556	*missing*
97679054	rs112550271	*missing*
97679170	rs45589337	*missing*
97679300	rs3790387	*missing*
97691806	rs74774246	*missing*
97699212	rs6668296	*missing*
97699399	rs72549307	*missing*
97699430	rs72549308	*missing*
97699506	rs6670886	*missing*
97699533	rs139834141	*missing*
97699535	rs2297595	*missing*
97721542	rs200562975	*missing*
97721650	rs141462178	*missing*
97740400	rs150385342	*missing*
97740602	rs41309171	*missing*
97828265	rs115632870	*missing*
97883329	rs1801265	*missing*
97883352	rs80081766	*missing*
97883353	rs72549310	*missing*
97883368	rs150036960	*missing*

IFNL3 allele match data

Genotype matched

- not called

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 1 missing positions of the total 1 positions: rs12979860C, rs12979860T

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
39248147	rs12979860	*missing*	C	rs12979860T

SLCO1B1 allele match data

Genotype matched

- *1B/*21
- *21/*29
- rs4149056T/rs4149056T

Phasing status

Unphased

Alleles Not Considered

The following alleles are not considered due to 14 missing positions of the total 29 positions: *2, *3, *6, *7, *8, *10, *11, *12, *13, *23, *36

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
21176804	rs2306283	**G|G**	A	*1B *14 *15 *17 *18 *20 *21 *24 *25 *27 *28 *29 *30 *31 *32 *33 *35
21176827	rs11045818	G|G	G	*18
21176868	rs2306282	A|A	A	*16
21176879	rs11045819	C|C	C	*4 *14 *18 *25 *32
21178615	rs4149056	T|T	T	*5 *15 *17
21178665	rs4149057	T|T	T	*18 *19
21178691	rs2291075	**C/T**	C	*20 *21
21178957	rs79135870	A|A	A	*30
21196951	rs11045852	A|A	A	*24 *25 *28 *32 *33
21196976	rs11045853	G|G	G	*25 *28 *33
21202555	rs59113707	C|C	C	*27
21202664	rs142965323	G|G	G	*26
21205999	rs59502379	G|G	G	*9 *31
21239042	rs34671512	A|A	A	*19 *20 *22 *35
21239145	rs200995543	C|C	C	*34
21205921	rs72559748	*missing*	A	*8
21174595	rs56061388	*missing*	T	*3 *13
21172734	rs139257324	*missing*	C	*33
21178672	rs72559746	*missing*	T	*18
21239077	rs56199088	*missing*	A	*10 *12
21239113	rs55737008	*missing*	A	*11 *13
21202553		*missing*	T	*36
21202649	rs56387224	*missing*	A	*7
21176883	rs72559745	*missing*	A	*3 *13
21239158	rs140790673	*missing*	C	*29
21130388	rs4149015	*missing*	G	*17 *21
21172776	rs373327528	*missing*	G	*23
21172782	rs56101265	*missing*	T	*2 *12
21200595	rs55901008	*missing*	T	*6

TPMT allele match data

Genotype matched

- not called

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 16 missing positions of the total 30 positions: *5, *7, *10, *11, *13, *14, *17, *19, *20, *21, *25, *26, *27, *28, *29, *31

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
18130687	rs1142345	T|T	T	*3A *3C
18130762	rs56161402	C|C	C	*8
18130781	rs1800584	C|C	C	*4
18133845	rs75543815	T|T	T	*6
18133847	rs6921269	C|C	C	*24
18133884	rs74423290	G|G	G	*23
18133890	rs9333570	**CTACAAAGAACACAAGAAG|CTACAAAGAACACAAGAAG**	C	*15
18138969	rs144041067	C|C	C	*16 *22
18138997	rs1800460	C|C	C	*3A *3B
18139710	rs200220210	G|G	G	*12
18143606	rs151149760	T|T	T	*9
18143724	rs1800462	C|C	C	*2
18147845		C|C	C	*18
18149022		C|C	C	*30
18147851	rs200591577	*missing*	G	*21
18143597		*missing*	T	*19
18130725	rs72552736	*missing*	A	*7
18149127	rs9333569	*missing*	T	*14
18130694	rs150900439	*missing*	T	*20
18130772	rs377085266	*missing*	A	*25
18132147	rs79901429	*missing*	A	*31
18143643		*missing*	A	*27
18149045	rs72552742	*missing*	T	*13
18139027	rs72552737	*missing*	C	*10
18143613		*missing*	C	*28
18139689	rs72552738	*missing*	C	*11
18149004		*missing*	G	*17
18149126	rs267607275	*missing*	A	*29
18132136	rs72556347	*missing*	A	*26
18147910	rs72552740	*missing*	A	*5

Other Positions of Interest

Position	RSID	Call
18138983	rs2842934	A/G

UGT1A1 allele match data

Genotype matched

- not called

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 5 missing positions of the total 5 positions: *1, *6, *27, *28, *36, *37, *60, *80+*28, *80+*37

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
233759924	rs887829	*missing*	C	*80+*28 *80+*37
233760233		*missing*	CAT	*28 *36 *37 *80+*28 *80+*37
233760498	rs4148323	*missing*	G	*6
233757013	rs4124874	*missing*	T	*60
233760973	rs35350960	*missing*	C	*27

VKORC1 allele match data

Genotype matched

- not called

Phasing status

Phased

Alleles Not Considered

The following alleles are not considered due to 1 missing positions of the total 1 positions: -1639A, -1639G

Carriage of these alleles might result in a different metabolizer phenotype and different guideline recommendations.

Calls at Positions

Position	RSID	Call	Reference	Related Alleles
31096368	rs9923231	*missing*	C	-1639A

Disclaimers and Other Information

Liability: PhamCAT assumes no responsibility for any injury to person or damage to persons or property arising out of, or related to any use of PharmCAT, or for any errors or omissions. The user recognizes that PharmCAT is a research tool and that they are using PharmCAT at their own risk.

A. Allele and Genotype Determination

i. PharmCAT uses gene allele definitions from CPIC, with exceptions as noted in Gene Definition Exceptions document. For allele definitions and the positions used in PharmCAT, see the gene definition tables.

ii. PharmCAT results are dependent on the supplied vcf calls for the queried positions (for technical information about PharmCAT input formatting and requirements, please go to pharmcat.org). PharmCAT does not assume any reference calls for positions missing from the submitted vcf; all missing queried positions are not considered in the allele determination process. See the gene definition tables for more information about what positions are queried in the vcf. Missing positions might alter the assigned genotype, subsequent phenotype prediction and CPIC recommendation. If the supplied vcf is missing positions, those positions will be noted in Section 3: Allele Calls for each gene of this report. For the most reliable allele

determination, reference calls as well as variant calls in the vcf for every queried position must be provided by the user.

iii. For cytochrome P450 genes, TPMT, DPYD, and SLCO1B1, the *1 (or reference in case of DPYD) allele is defined by the absence of variation specified in the gene definition tables. This allele cannot be identified by variants; rather, *1 is assigned by default when no variation for the queried positions is reported in the submitted vcf. It is always possible un-interrogated variation can occur which could potentially affect allele function, but because it is undetected, the assignment would be defaulted to a *1 allele and normal function.

iv. For all genes, variation reported in the vcf but NOT included in the gene definition table will not be considered during allele assignment. There is a possibility that any such variation results in a reduced or no activity allele which could lead to inaccurate phenotype and CPIC recommendation, similar to the situation in point iii, above.

v. PharmCAT matches variants to genotypes using unphased data (unless phased data is provided in the vcf and noted as such, see pharmcat.org for details). The assumption is that defined alleles exist in trans configuration, i.e. on opposite chromosomes, with exceptions noted in Section 3: Allele Calls under “Gene-specific warnings.” However, in cases where an allele is defined by a combination of two or more variants, where each variant alone also defines an allele, the match is based on the longer allele (except for UGT1A1). For example, CYP2C19*4A is defined one SNP, *17 is defined by another SNP, and *4B is defined by the combination of those two SNPs. In the case of unphased data that is heterozygous for both SNPs, the *1/*4B genotype is returned though the possibility of *4A/*17 cannot be ruled out.

vi. Nucleotide base calls are displayed on the positive chromosomal strand regardless of the gene strand; further information is provided under Gene-specific warnings in Section 3: Allele Calls.

B. CPIC Allele Function, Phenotype and Recommendation

i. Allele functionality and phenotype terms are based on the CPIC Term Standardization Project [PMID: 27441996]. Please see this reference for details but note the following changes from original CPIC guidelines based on this project:
   a. This terminology replaces the term ‘extensive’ metabolizer with ‘normal’ metabolizer for drug metabolizing enzymes such as CYPs, DPYD, TPMT, UGT1A1. Guidelines published prior to this recommendation used the term ‘extensive’ metabolizer whereas the PharmCAT report uses ‘normal’.
   b. The terminology introduces the use of the term ‘rapid’ metabolizer for CYP2C19*1/*17 to distinguish between *1/*17 and *17/*17 (‘ultrarapid’ metabolizer). CYP2C19 *1/*17 was grouped as ‘ultrarapid’ metabolizer in prior guidelines. PharmCAT uses the ‘rapid’ metabolizer group.
   c. PharmCAT uses allele functions from gene information tables, including alleles with ‘possible’ or ‘likely’ added to the function term.

ii. PharmCAT uses metabolizer phenotypes from gene information tables. ‘Likely’ or ‘possible’ metabolizer phenotypes are originally based on supplemental materials for respective guidelines and are listed in the gene “Diplotype-Phenotype Table.”

iii. PharmCAT uses recommendation wording as provided in the CPIC guideline. CPIC typically provides the same recommendations for ‘likely’ or ‘possible’ metabolizer phenotypes in supplemental and gene information tables as those without the ‘likely’ or ‘possible’ labels, but do not provide a strength of therapeutic recommendation.

C. CYP2D6 Allele Determination and Metabolizer Status

i. CYP2D6 genotypes are based on Astrolabe calls. For specific disclaimers and limitations, see the Astrolabe documentation and specifications made available with the product.

ii. Metabolizer Status: CPIC classifies genotypes with a gene activity score of 1.0 as normal metabolizers; however, other guidelines or reference laboratories may classify the same genotypes as intermediate metabolizers.

D. Prescribing Change Designations

i. The drugs in Section 1: Genotype summary table are colored to indicate whether CPIC recommends a prescribing change based on the given genotype; highlighting is not based on CPIC classification of recommendation.
   a. ✖ Red indicates a prescribing change is recommended for the given genotype. That is, the recommendation is different than ‘use label recommendation’ or ‘use recommended starting dose’, except for ivacaftor.
   b. ⚠ Orange indicates possible prescribing changes depending on additional information, e.g. pediatrics vs. adult, or the specific number of CYP2D6 normal alleles present (copy number).
   c. ● Green indicates that there is no CPIC recommended prescribing change for the given genotype, except for ivacaftor.
   d. ■ Blue indicates the specific guideline must be consulted because a CPIC recommended action cannot be provided based solely on genotype (eg. warfarin and ribavirin/peginterferon).

ii. When multiple genotypes are possible for a gene, the drug is highlighted according to the highest level of prescribing change.

E. PharmCAT Exceptions to the CPIC Guideline Gene List

i. HLA-B and G6PD are currently not included in PharmCAT. Therefore, no CPIC guideline recommendations are included for these genes.

ii. Further genes will be incorporated into PharmCAT as the tool is developed.

F. PharmCAT Updates

i. PharmCAT monitors publication of new CPIC guidelines and guideline updates. New publication content will be included into PharmCAT within one month of CPIC publication.

ii. Updates to the gene definition tables may occur, the latest version can be found alongside the software releases.

iii. Updates to PharmCAT may occur, for the latest version go to the PharmCAT release page.

G. CPIC Guideline Disclaimers and Caveats

i. A version of the following quoted disclaimer is part of each CPIC guideline and applies to the CPIC recommendations as used in PharmCAT. For the full description of potential benefits and risks, additional considerations (general and specific to gene-drug pairs), limitations, information about respective gene nomenclature systems, potential drug-drug interactions and clinical factors to consider, please see individual CPIC guidelines (cpicpgx.org).
   a. “CPIC guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care

provider to determine the best course of treatment for a patient. Adherence to any guidelines is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of CPIC's guidelines, or for any errors or omissions." (PMID: 27997040)

b. "Caveats: appropriate use and/or potential misuse of genetic tests. The application of genotype-based dosing is most appropriate when initiating therapy with a tricyclic. Obtaining a pharmacogenetic test after months of drug therapy may be less helpful in some instances, as the drug dose may have already been adjusted based on plasma concentrations, response, or side effects. Similar to all diagnostic tests, genetic tests are one of several pieces of clinical information that should be considered before initiating drug therapy." (PMID: 27997040)

ii. CPIC guidelines reflect the alleles/genotypes known and considered by the guideline authors for inclusion by the time of publication, however they may be updated online at cpicpgx.org in between publications. Additional alleles and/or more extensive allele definitions might exist by the representative gene nomenclatures for various genes.

iii. CPIC is a registered service mark of the U.S. Department of Health & Human Services (HHS).

H. PharmGKB Disclaimers and Caveats

i. PharmGKB is a registered service mark of the U.S. Department of Health & Human Services (HHS).