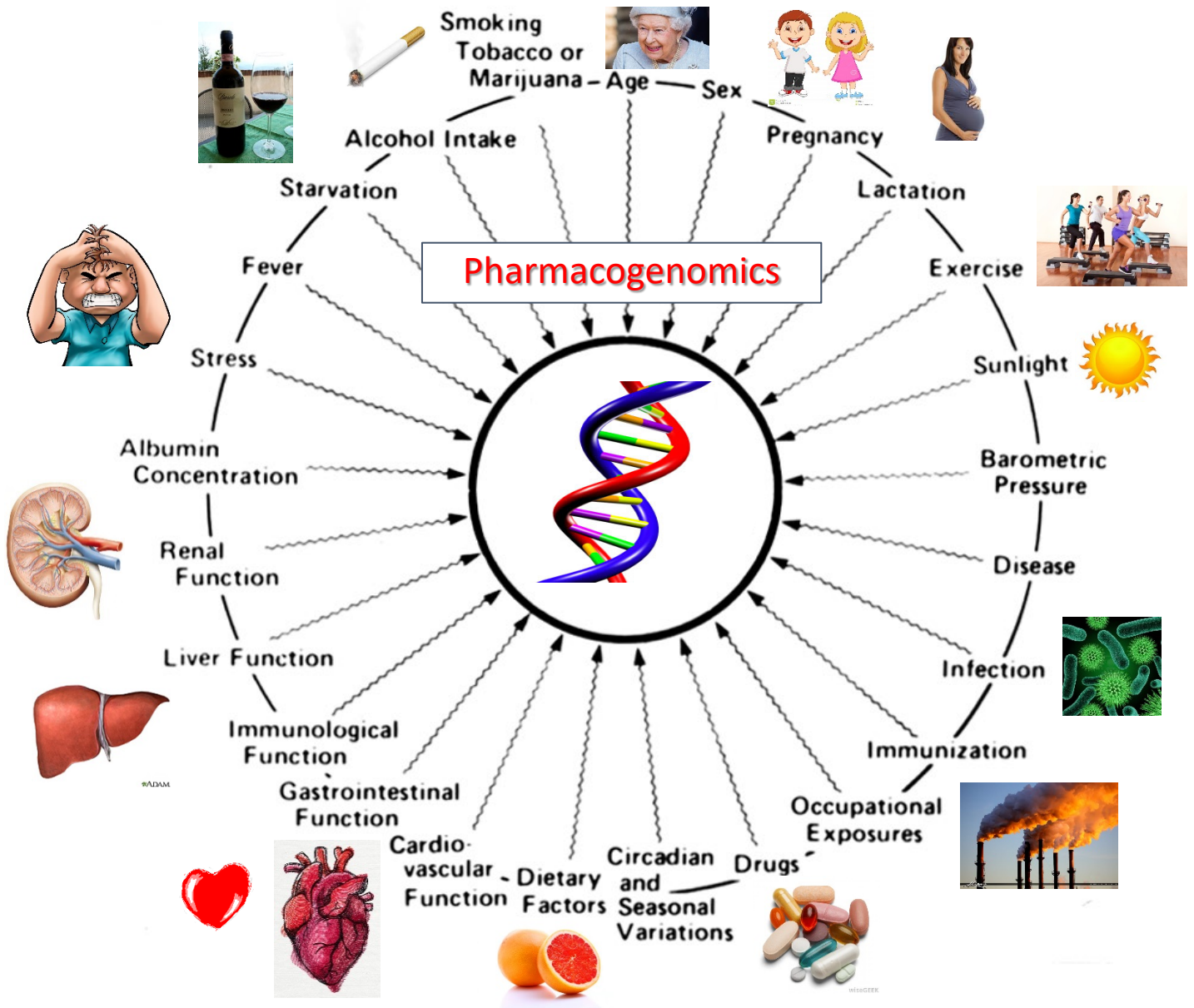
Many factors cause interindividual variability in drug effects; genetics is just one factor

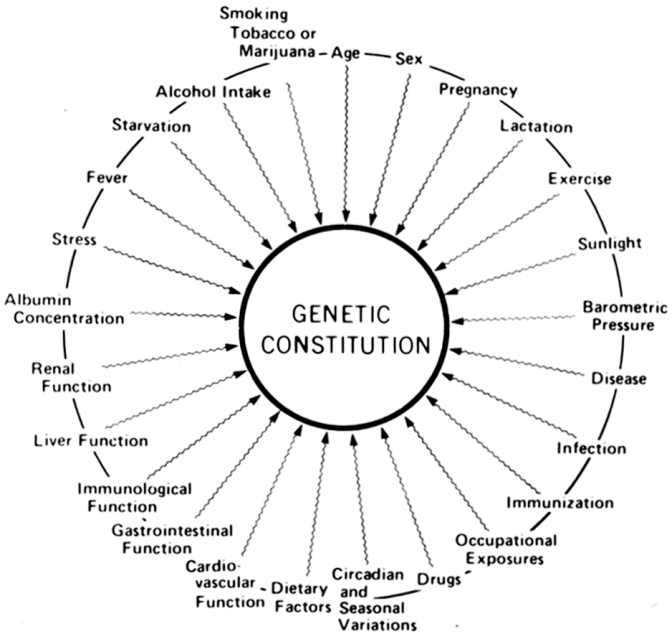


Evans; Vesell for the original, *Pharm. Ther.* 1989

Many resources are used to guide prescribing based on interindividual factors

- Micromedex
- Up-to-date
- Pubmed
- Lexicomp
- AHFS
- Medline plus

- Facts and Comparisons
- USP dictionary
- Approved Drug labels (e.g. FDA)
- Professional association guidelines
- CPIC guidelines (for Pgx)



CPIC has multiple levels and grading systems, not all equivalent to “evidence” level.

- Gene/drug pair prescribing actionability (A, B, C, D)
- Guideline prescribing recommendations (strong, moderate, optional, or none)
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- Allele clinical functional assignments to alleles are also graded for strength of evidence (high, moderate, weak)

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CPIC's goal is to write guidelines for all CPIC actionability level A and B gene/drug pairs

- For all drugs/genes encompassed by the guideline, provide prescribing recommendations (including dosage and alternatives) for all phenotype/drug possibilities
- Experts consider other existing guidelines, and regulatory agency comments (e.g. FDA, EMA) in deciding on prescribing recommendations and in evaluating evidence
- Provide a strength for each prescribing recommendation
- All grading of evidence (findings for gene/drug pair, alternative, and alleles) informs the expert authors' prescribing recommendations

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Table 2 Efavirenz dosing recommendations based on CYP2B6 phenotype in children ≥40 kg and adult patients

CYP2B6 phenotype[a]	Implications for efavirenz pharmacologic measures	Therapeutic recommendations	Classification of recommendations[b]
CYP2B6 ultrarapid metabolizer	Slightly lower dose-adjusted trough concentrations of efavirenz compared with normal metabolizers	Initiate efavirenz with standard dosing (600 mg/day)	Strong
CYP2B6 rapid metabolizer	Slightly lower dose-adjusted trough concentrations of efavirenz compared with normal metabolizers	Initiate efavirenz with standard dosing (600 mg/day)	Strong
CYP2B6 normal metabolizer	Normal efavirenz metabolism	Initiate efavirenz with standard dosing (600 mg/day)	Strong[c]
CYP2B6 intermediate metabolizer	Higher dose-adjusted trough concentrations of efavirenz compared with normal metabolizers; increased risk of CNS adverse events	Consider initiating efavirenz with decreased dose of 400 mg/day[c,d]	Moderate
CYP2B6 poor metabolizer	Higher dose-adjusted trough concentrations of efavirenz compared with normal metabolizers; significantly increased risk of CNS adverse events and treatment discontinuation	Consider initiating efavirenz with decreased dose of 400 or 200 mg/day[c,d]	Moderate

CNS, central nervous system; CYP, cytochrome P450

Table 2 Dosing recommendations for omeprazole, lansoprazole, pantoprazole, and dexlansoprazole based on CYP2C19 phenotype

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation	Classification of recommendation[b] – omeprazole, lansoprazole, and pantoprazole	Classification of recommendation[b] – dexlansoprazole
CYP2C19 ultrarapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy	Optional	Optional
CYP2C19 rapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *Helicobacter pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.	Moderate	Optional
CYP2C19 normal metabolizer	Normal PPI metabolism; may be at increased risk of therapeutic failure compared with CYP2C19 IMs and PMs	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *H. pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy	Moderate	Optional
CYP2C19 likely intermediate metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional[c]	Optional[c]
CYP2C19 intermediate metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional	Optional
CYP2C19 likely poor metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Moderate[c]	Optional[c]
CYP2C19 poor metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Moderate	Optional

Table 2 Dosing recommendations for ondansetron and tropisetron based on *CYP2D6* genotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]	Consideration for alternative 5-HT_3 receptor antagonists antiemetics[b]
CYP2D6 Ultrarapid Metabolizer	Increased metabolism to less active compounds when compared to NMs and is associated with decreased response to ondansetron and tropisetron (i.e., vomiting)	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron).[c]	Moderate	Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide use of these drugs.
CYP2D6 Normal Metabolizer	NM	Initiate therapy with recommended starting dose.[c]	Strong	
CYP2D6 Intermediate Metabolizer	Very limited data available for CYP2D6 IMs	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	
CYP2D6 Poor Metabolizer	Very limited data available for CYP2D6 PMs	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	

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It's not CPIC level of evidence, it's CPIC actionability level

It's not identical to PharmGKB level of evidence or to PGX on FDA label

Genes-Drugs

CPIC assigns actionability levels to gene/drug pairs

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Download this table (CSV) Last modified: Jan 13, 2021

# (N=440)	GENE (UNIQUE = 118)	DRUG (UNIQUE = 267)	GUIDELINE	CPIC LEVEL	CPIC LEVEL STATUS	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)
1	HLA-B	abacavir	Guideline	A	Final	1A	Testing required	• 24561393 • 22378157
2	HLA-B	allopurinol	Guideline	A	Final	1A		• 23232549 • 26094938
3	CYP2D6	amitriptyline	Guideline	A	Final	1A	Actionable PGx	• 23486447 • 27997040
4	CYP2C19	amitriptyline	Guideline	A	Final	1A		• 23486447 • 27997040
5	UGT1A1	atazanavir	Guideline	A	Final	1A		• 26417955
6	CYP2D6	atomoxetine	Guideline	A	Final	1A	Actionable PGx	• 30801677
7	TPMT	azathioprine	Guideline	A	Final	1A	Testing recommended	• 21270794 • 23422873 • 30447069
8	NUDT15	azathioprine	Guideline	A	Final	1A	Testing	• 21270794

PHARMGKB

Search PharmGKB

Drug Label Information and Legend

Information about PharmGKB's annotations of drug labels:

Drug Label Sources

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

- Information is gathered from the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels" and from FDA-approved labels brought to our attention. Drugs listed on the Table to our knowledge are tagged with the Biomarker icon. A drug label that has been removed from the Table will not have the Biomarker icon but will continue to have an annotation on PharmGKB stating the label has been removed from the FDA's Table. We acquire label PDF files from Drugs@FDA.
- Please note that drugs may be removed from or added to the FDA's Table. We have set up automated alerts to detect when FDA has made changes to the Table and we update PharmGKB accordingly. There is often a lag between an FDA Table update and the update on PharmGKB.

PGx Level

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

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

Actionable PGx The label may contain information about changes in efficacy, dosage, metabolism or toxicity due to gene/protein/chromosomal variants or phenotypes (e.g. "poor metabolizers"). Or the label may mention contraindication of the drug in a particular subset of patients with particular variants/genotypes/phenotypes. However, the label does not require or recommend gene, protein or chromosomal testing.

Informative PGx

1. The label contains information stating that particular gene/protein/chromosomal variants or metabolizer phenotypes do not affect a drug's efficacy, dosage, metabolism or toxicity. Or, the label states that particular variants or phenotypes affect a drug's efficacy, dosage, metabolism or toxicity, but this effect is not "clinically" significant.

OR

2. The label appears or appeared on the FDA Biomarker List but does not currently meet the requirements to be assigned as "Testing required", "Testing recommended" or "Actionable PGx". PharmGKB annotates every label that appears on the FDA Biomarker list, regardless of whether we would otherwise annotate the label.

There are two main tables of pgx on FDA sites

- Table of pharmacogenomic biomarkers in drug labelling (CDER)
- Table of pharmacogenetic associations (CDRH)

Table of Pharmacogenomic Biomarkers in Drug Labeling

8/18/2020
431 entries

Includes somatic/ cancer genes

"The table below lists therapeutic products from Drugs@FDA with pharmacogenomic information found in the drug labeling. The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information. Pharmacogenomic information can appear in different sections of the labeling depending on the actions."

https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Table of Pharmacogenomic Biomarkers in Drug Labeling

https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

8/18/2020
431 entries

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Pharmacogenomic Biomarkers in Drug Labeling

Search:

Export Excel

Drug	Therapeutic Area*	Biomarker†	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions
Abemaciclib (1)	Oncology	ESR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies
Abemaciclib (2)	Oncology	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Ado-Trastuzumab Emtansine	Oncology	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alectinib	Oncology	ALK	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alglucosidase Alfa	Inborn Errors of Metabolism	GAA	Warnings and Precautions
Alpelisib (1)	Oncology	ERBB2 (HER2)	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alpelisib (2)	Oncology	ESR (Hormone Receptor)	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies

Table of Pharmacogenetic Associations

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

Up to date 2/25/20

Pharmacogenetic associations for which the data support therapeutic management recommendations

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Amifampridine	NAT2	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	NAT2	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
			May affect systemic concentrations and adverse reaction risk. Consider lower

Pharmacogenetic associations for which the data indicate a potential impact on safety or response

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Allopurinol	HLA-B	*58:01 allele positive	Results in higher adverse reaction risk (severe sk
Carbamazepine	HLA-A	*31:01 allele positive	Results in higher adverse reaction risk (severe sk and benefit of carbamazepine use in patients pos Genotyping is not a substitute for clinical vigilanc
Carvedilol	CYP2D6	poor metabolizers	Results in higher systemic concentrations and hig (dizziness).
Cevimeline	CYP2D6	poor metabolizers	May result in higher adverse reaction risk. Use wi

Pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only.

The impact of these genetic variants or genetic variant inferred phenotypes on the safety or response of the corresponding drug has not been established.

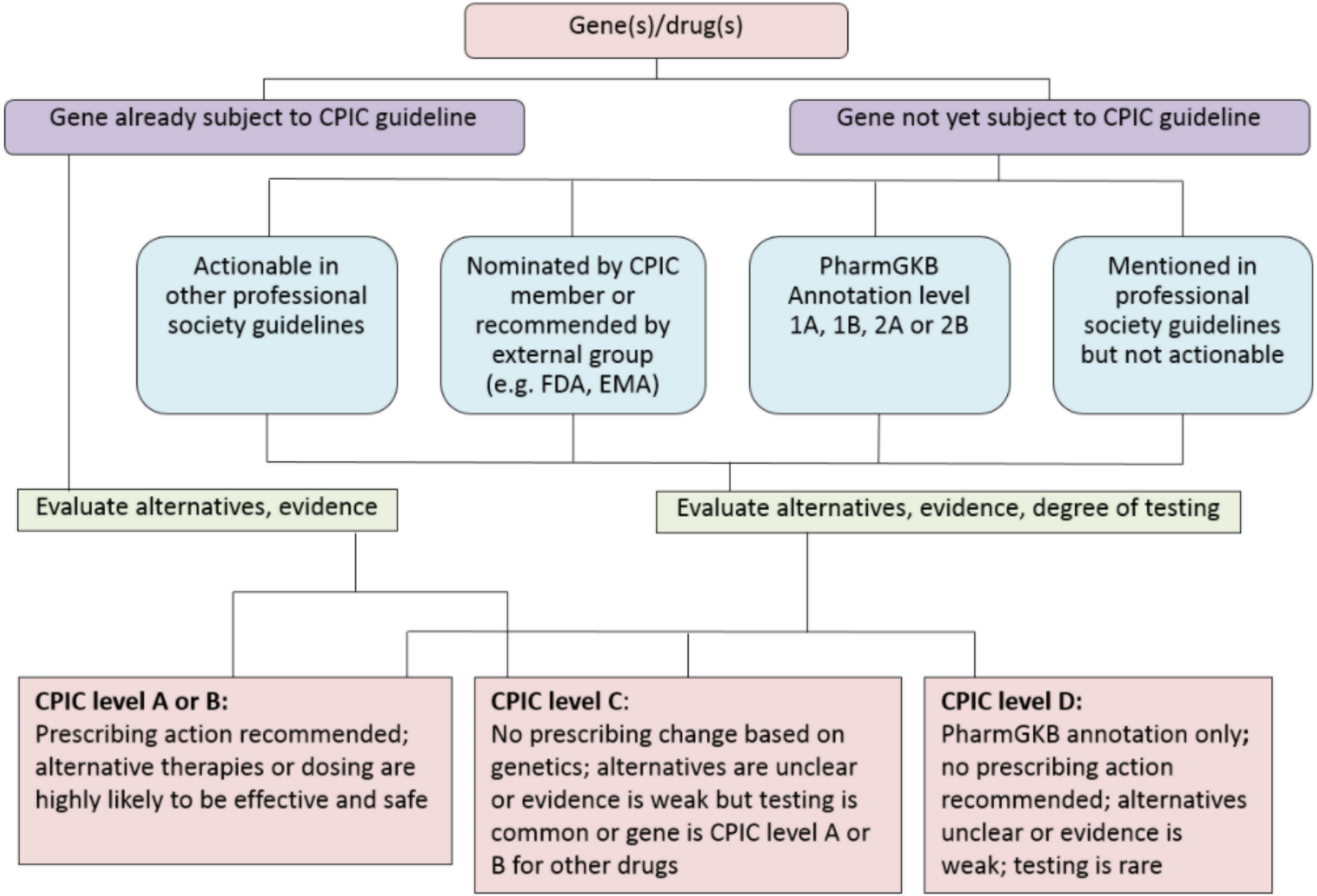
Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Amitriptyline	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Amoxapine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Avatrombopag	CYP2C9	intermediate or poor metabolizers	Results in higher systemic concentrations.
Carisoprodol	CYP2C19	poor metabolizers	Results in higher systemic concentrations. Use with caution.

Table of Pharmacogenetic Associations

“The table below lists pharmacogenetic associations that FDA has evaluated and believes there is sufficient scientific evidence to suggest that subgroups of patients with certain genetic variants, or genetic variant-inferred phenotypes (i.e., affected subgroup in the table below), are likely to have altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events. The fact that FDA has included a particular gene-drug interaction in the table does not necessarily mean FDA advocates using a pharmacogenetic test before prescribing the corresponding medication, unless the test is a companion diagnostic. Tests that are essential for the safe and effective use of a therapeutic product, including those that identify patients for which the drug is contraindicated, are companion diagnostics. This table is not intended to affect current regulatory requirements or policies, including FDA's policy regarding companion diagnostics.2 Nor is the table intended to make an assessment on the safe and effective use of, or regulatory requirements for, tests that detect variants in the referenced genes, or to provide comprehensive information on the described gene-drug interactions.

This version of the table is limited to pharmacogenetic associations that are related to drug metabolizing enzyme gene variants, drug transporter gene variants, and gene variants that have been related to a predisposition for certain adverse events. FDA recognizes that various other pharmacogenetic associations exist that are not listed here, and this table will be updated periodically with additional pharmacogenetic associations supported by sufficient scientific evidence.”

Considerations for Assignment of CPIC Level for Genes/Drugs



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Genes-Drugs

CPIC assignments are provisional until evaluated by a guideline writing group

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70	VKORC1	warfarin	Guideline	A	Final	1A	Actionable PGx	• 21900891 • 28198005
71	CYP4F2	warfarin	Guideline	A	Final	1A		• 21900891 • 28198005
72	CYP2C9	warfarin	Guideline	A	Final	1A	Actionable PGx	• 21900891 • 28198005
73	MT-RNR1	amikacin		A/B	Provisional	1B		
74	G6PD	aspirin		A/B	Provisional	4		
75	POLG	divalproex sodium		A/B	Provisional		Testing required	
76	CYP2D6	eliglustat		A/B	Provisional		Testing required	
77	MT-RNR1	gentamicin		A/B	Provisional	1B		
78	NAT2	hydralazine		A/B	Provisional	2A		
79	MT-RNR1	kanamycin		A/B	Provisional	1B		
80	CYP2D6	oliceridine		A/B	Provisional		Actionable PGx	
81	CYP2D6	pimozide		A/B	Provisional	4	Testing required	

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.
A/B	Preliminary review indicates it is likely that the definitive CPIC level will be either A or B	Full evidence review needed to assess level of evidence, but prescribing actionability is likely.	Full review by expert guideline group to assign strength of recommendation
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.
B/C	Preliminary review indicates it is likely that the definitive CPIC level will be either B or C.	Prescribing actionability based on genetics is not clear without further evidence review.	Full review by expert guideline group to assess strength of recommendation.
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 or (c) few published studies or mostly weak evidence and clinical actions are unclear. 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.
C/D	Preliminary review indicates it is likely that the definitive CPIC level will be either C or D.	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. Criteria for “widely tested” includes: 1) CAP proficiency testing is available; or 2) Gene is in disease specific panels (e.g., pain, psychiatric, cancer, etc); or 3) evidence exist for implementation of gene into clinical practice (CPIC member feedback, publications, etc).	Evidence levels can vary	No prescribing actions are recommended.

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Actionable (CPIC level A and B) drugs (n=114)

abacavir	clomipramine	glimepiride*	moxifloxacin	primaquine	tamoxifen
acenocoumarol	clopidogrel*	glipizide*	mycophenolate	probenecid	tenoxicam
allopurinol*	codeine*	halothane	nalidixic acid	quinine	tetrabenazine
amikacin	dapsone	hydralazine	nitrofurantoin	rasburicase	thioguanine
amitriptyline	desflurane	hydrocodone*	norfloxacin	risperidone	tobramycin
aripiprazole	desipramine	ibuprofen*	nortriptyline	rosuvastatin*	tramadol*
aspirin	dexlansoprazole	imipramine	oliceridine	sertraline*	trimipramine
atazanavir	dimercaprol	irinotecan	omeprazole*	sevoflurane	tropisetron
atomoxetine	divalproex Na	isoflurane	ondansetron	simvastatin*	valproic acid
azathioprine	doxepin	ivacaftor	oxcarbazepine	siponimod	velaglucerase alf
belinostat	efavirenz	kanamycin	pantoprazole*	sodium nitrite	venlafaxine*
brivaracetam	eliglustat	lansoprazole*	paroxetine*	streptomycin	voriconazole
capecitabine	enflurane	lornoxicam	peginterferon alf	succinylcholine	vortioxetine
carbamazepine	escitalopram*	mafenide	pegloticase	sulfacetamide	warfarin
carglumic acid	fluorouracil	meloxicam*	phenazopyridine	sulfadiazine	
celecoxib*	flurbiprofen	mercaptopurine	phenprocoumon	sulfamethoxazole*	
chloramphenicol	fluvoxamine	mesalazine	phenytoin	sulfasalazine	
chlorpropamide	fosphenytoin	methadone	pimozide	sulfisoxazole	
ciprofloxacin*	gentamicin	methoxyflurane	piroxicam	tacrolimus	
citalopram*	glibenclamide	methylene blue	pitolisant	tafenoquine	

*Top 100 drugs, Jan 2021

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Strength of recommendations

From CPIC SOP

Member Resources

- Manage your CPIC profile (including your password)
- Conference call minutes
- CPIC guideline drafts (for member review)
- CPIC SOP
- Draft allele function SOP
- CPIC authorship guidelines and conflict of interest standards
- CPIC Informatics Working Group
- CPIC Dissemination Working Group
- CPIC Scientific Advisory Board

from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf). Therapeutic recommendations are graded as:

Strong recommendation for the statement**:** "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."

Moderate recommendation for the statement: "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

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Score the evidence

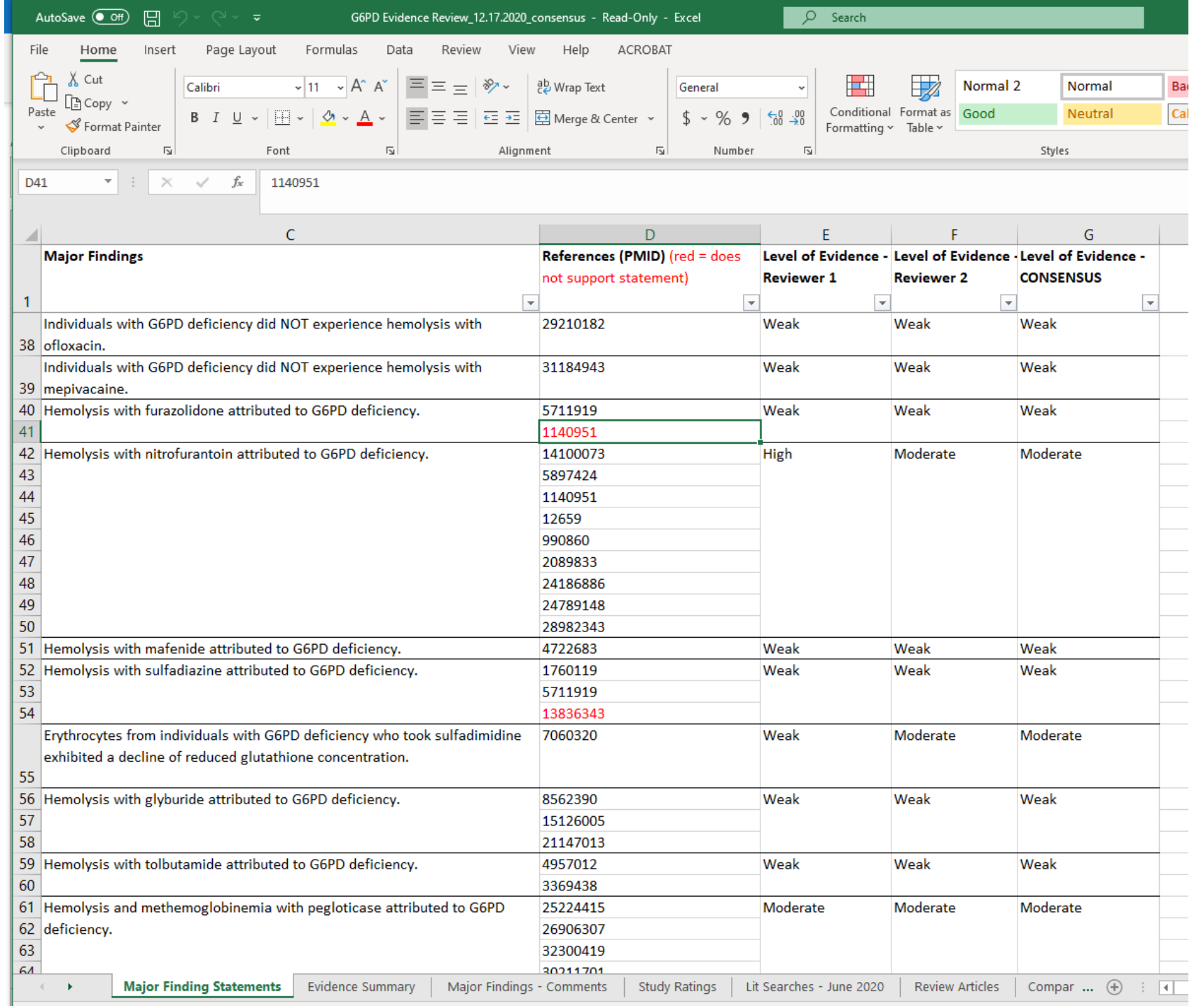
Initially, three or more authors will independently evaluate the literature. These authors will be responsible for presenting studies and recommending a level of evidence for each major finding to all guideline authors on a series of conference calls. All authors will be responsible for reviewing the evidence prior to a conference call and all authors will discuss and decide on the final score during these conference calls. Interim evidence tables will be circulated to the entire author group after each call; any disagreements with assignment of evidence will need to be sent in writing by 10 days after each summation. Re-addressing review of previous evidence summations on future calls will not take place unless circumstances are extraordinary, so all authors are required to review and declare their disagreements in real time.

Publications supporting a major finding should be grouped together and scored based on all the evidence that supports that major finding using the following criteria:

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

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

Worksheet for evidence review for current guideline: evidence linking hemolysis with drug us in G6PD deficiency



G6PD Evidence Review_12.17.2020_consensus - Read-Only - Excel

D41: 1140951

	C	D	E	F	G
1	**Major Findings**	**References (PMID)** (red = does not support statement)	**Level of Evidence - Reviewer 1**	**Level of Evidence - Reviewer 2**	**Level of Evidence - CONSENSUS**
38	Individuals with G6PD deficiency did NOT experience hemolysis with ofloxacin.	29210182	Weak	Weak	Weak
39	Individuals with G6PD deficiency did NOT experience hemolysis with mepivacaine.	31184943	Weak	Weak	Weak
40	Hemolysis with furazolidone attributed to G6PD deficiency.	5711919	Weak	Weak	Weak
41		1140951			
42	Hemolysis with nitrofurantoin attributed to G6PD deficiency.	14100073	High	Moderate	Moderate
43		5897424			
44		1140951			
45		12659			
46		990860			
47		2089833			
48		24186886			
49		24789148			
50		28982343			
51	Hemolysis with mafenide attributed to G6PD deficiency.	4722683	Weak	Weak	Weak
52	Hemolysis with sulfadiazine attributed to G6PD deficiency.	1760119	Weak	Weak	Weak
53		5711919			
54		13836343			
55	Erythrocytes from individuals with G6PD deficiency who took sulfadimidine exhibited a decline of reduced glutathione concentration.	7060320	Weak	Moderate	Moderate
56	Hemolysis with glyburide attributed to G6PD deficiency.	8562390	Weak	Weak	Weak
57		15126005			
58		21147013			
59	Hemolysis with tolbutamide attributed to G6PD deficiency.	4957012	Weak	Weak	Weak
60		3369438			
61	Hemolysis and methemoglobinemia with pegloticase attributed to G6PD	25224415	Moderate	Moderate	Moderate
62	deficiency.	26906307			
63		32300419			
64		30211701			

Major Finding Statements | Evidence Summary | Major Findings - Comments | Study Ratings | Lit Searches - June 2020 | Review Articles | Compar ...

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From CPIC Allele Function SOP

Member Resources

- Manage your CPIC profile (including your password)
- Conference call minutes
- CPIC guideline drafts (for member review)
- CPIC SOP
- Draft allele function SOP
- CPIC authorship guidelines and conflict of interest standards
- CPIC Informatics Working Group
- CPIC Dissemination Working Group
- CPIC Scientific Advisory Board

OVERVIEW OF PHARMACOGENETIC VARIANT CURATION for

Assigning CPIC Allele Clinical Function

and

Translating Diplotypes to Phenotypes

Standard Operating Procedure

Clinical Pharmacogenetics Implementation Consortium (CPIC)

July 2020

Version 1.0

Scoring the Evidence Process Overview

- Two authors will independently
  - summarize the evidence
  - assign strength of evidence
  - assign allele clinical function
  - assign activity value for genes using activity scores
- Independent evaluations are compiled into a working draft of the Allele functionality table
- Table is disseminated to all other authors for review

Allele/cDNA/rsID	Activity Value (Optional)	Allele Biochemical Functional Status (Optional)	Allele Clinical Functional Status (Required)	Allele Clinical Function Substrate Specificity (Optional)	PMID (Required)	Strength of Evidence (Required)	Summary of Findings (Required)
*1	1	Normal Function	Normal Function				
*2	0.5	Decreased function	Decreased function		29283396; 20150829; 15637526; 12742136; 10413320; 27179628; 25775139; 19082874;	Definitive	CYP2C9*2 is assigned decreased function based on definitive evidence in homozygous and heterozygous patients and in vitro experimental data. CYP2C9*2 has been studied for more than 20 years and its association with impaired function compared to wildtype is well-established (29283396, 20150829, 15637526). The phenotype for patients homozygous for the CYP2C9*2 variant was updated from poor metabolizer to intermediate metabolizer after reevaluation of prior and new evidence demonstrating CYP2C9*2 has more enzyme activity than CYP2C9*3, which results in in a similar phenotype for

Strength of evidence to assign clinical function

- Modified process from that used by ClinGen for their gene-disease validity evaluation
- Classified as to the type of the evidence supporting the assignment

DEFINITIVE	The causal role of this allele in this particular drug phenotype has been repeatedly demonstrated, and has been upheld over time (in general, at least 3 years). No convincing, adequately powered evidence has emerged that contradicts the role of the allele in the specified drug phenotype.

Supportive Evidence needed to assign function vs uncertain	**DEFINITIVE**	The causal role of this allele in this particular drug phenotype has been repeatedly demonstrated, and has been upheld over time (in general, at least 3 years). No convincing, adequately powered evidence has emerged that contradicts the role of the allele in the specified drug phenotype.
	STRONG	The causal role of this allele in the drug phenotype has been independently demonstrated in at least two separate clinical studies providing **strong** supporting evidence for this allele's role in drug phenotype; there is compelling allele-level evidence from different types of supporting experimental data. In addition, no convincing evidence has emerged that contradicts the role of the allele in the noted drug phenotype.
	MODERATE	There is **moderate** evidence to support a causal role for this allele in this drug phenotype, including at least two of the following types of evidence: • At least 2 patient cases demonstrated drug phenotype causality • *in vitro* experimental data (e.g. engineered variant and effect measures support the variant-drug phenotype association) • At least one clinical study providing evidence for the allele's role in drug phenotype AND no convincing evidence has emerged that contradicts the role of the allele in the noted drug phenotype.
	LIMITED	There is limited evidence to support a causal role for this allele in this drug phenotype, including at least two independent studies based on the following types of evidence: • A case report • *in vitro* data (e.g. experimental or correlative data) support the variant-drug phenotype association • Computational activity predictions overall support *in vivo* and/or *in vitro* data (5) AND no convincing evidence has emerged that contradicts the role of the allele in the noted drug phenotype. Function assignment based on limited data should only be made for genes whose resulting drug phenotype dictates changes to prescribing that are much more likely to result in improved clinical outcomes than not changing prescribing based on genetic test results, including consideration of life-threatening consequences if not considered.
Inadequate EVIDENCE = uncertain function		Fewer than 2 patient cases with no convincing *in vitro* experimental data, with extremely limited or conflicting *in vitro* data. This designation should be used when the evidence is not sufficiently strong to support a clinical functional status that can inform prescribing actionability. The threshold for what evidence is sufficient to inform actionability may differ among genes.
No EVIDENCE = unknown function		There is no literature describing function

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Strength of evidence to assign clinical function

- Modifications to this general framework
  - Threshold for what evidence is enough to inform actionability may differ for different genes/drugs
    - E.g. bolus chemotherapy drug that could cause death (*DPYD*/5FU) vs chronic oral drug for which some titration is possible in clinic (*CYP2C9*/warfarin)
  - Gene-specific modifications by experts will be documented and publicly available
  - Allele clinical function assignment may be modified based on clinical expertise
    - Summary of Findings column will document the rationale for modification and the assigned function prior to modification

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Evidence based on allele function characterization, findings for the gene/drug association, and findings for the alternative therapy are weighed by the experts to create the prescribing recommendations in "Table 2"; all actionable gene/drug pairs are assigned actionability levels of A or B

Table 2 Dosing recommendations for omeprazole, lansoprazole, pantoprazole, and dexlansoprazole based on CYP2C19 phenotype

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation	Classification of recommendation[b] – omeprazole, lansoprazole, and pantoprazole	Classification of recommendation[b] – dexlansoprazole
CYP2C19 ultrarapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy	Optional	Optional
CYP2C19 rapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *Helicobacter pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.	Moderate	Optional
CYP2C19 normal metabolizer	Normal PPI metabolism; may be at increased risk of therapeutic failure compared with CYP2C19 IMs and PMs	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *H. pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy	Moderate	Optional
CYP2C19 likely intermediate metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional[c]	Optional[c]
CYP2C19 intermediate metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional	Optional
CYP2C19 likely poor metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Moderate[c]	Optional[c]
CYP2C19 poor metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Moderate	Optional

It's not CPIC level of evidence, it's CPIC actionability level

Genes-Drugs

CPIC assigns actionability levels to gene/drug pairs

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# (N=440)	GENE (UNIQUE = 118)	DRUG (UNIQUE = 267)	GUIDELINE	CPIC LEVEL	CPIC LEVEL STATUS	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)
1	HLA-B	abacavir	Guideline	A	Final	1A	Testing required	• 24561393 • 22378157
2	HLA-B	allopurinol	Guideline	A	Final	1A		• 23232549 • 26094938
3	CYP2D6	amitriptyline	Guideline	A	Final	1A	Actionable PGx	• 23486447 • 27997040
4	CYP2C19	amitriptyline	Guideline	A	Final	1A		• 23486447 • 27997040
5	UGT1A1	atazanavir	Guideline	A	Final	1A		• 26417955
6	CYP2D6	atomoxetine	Guideline	A	Final	1A	Actionable PGx	• 30801677
7	TPMT	azathioprine	Guideline	A	Final	1A	Testing recommended	• 21270794 • 23422873 • 30447069
8	NUDT15	azathioprine	Guideline	A	Final	1A	Testing	• 21270794

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Clinical Pharmacogenetics Implementation Consortium

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