CPIC Update

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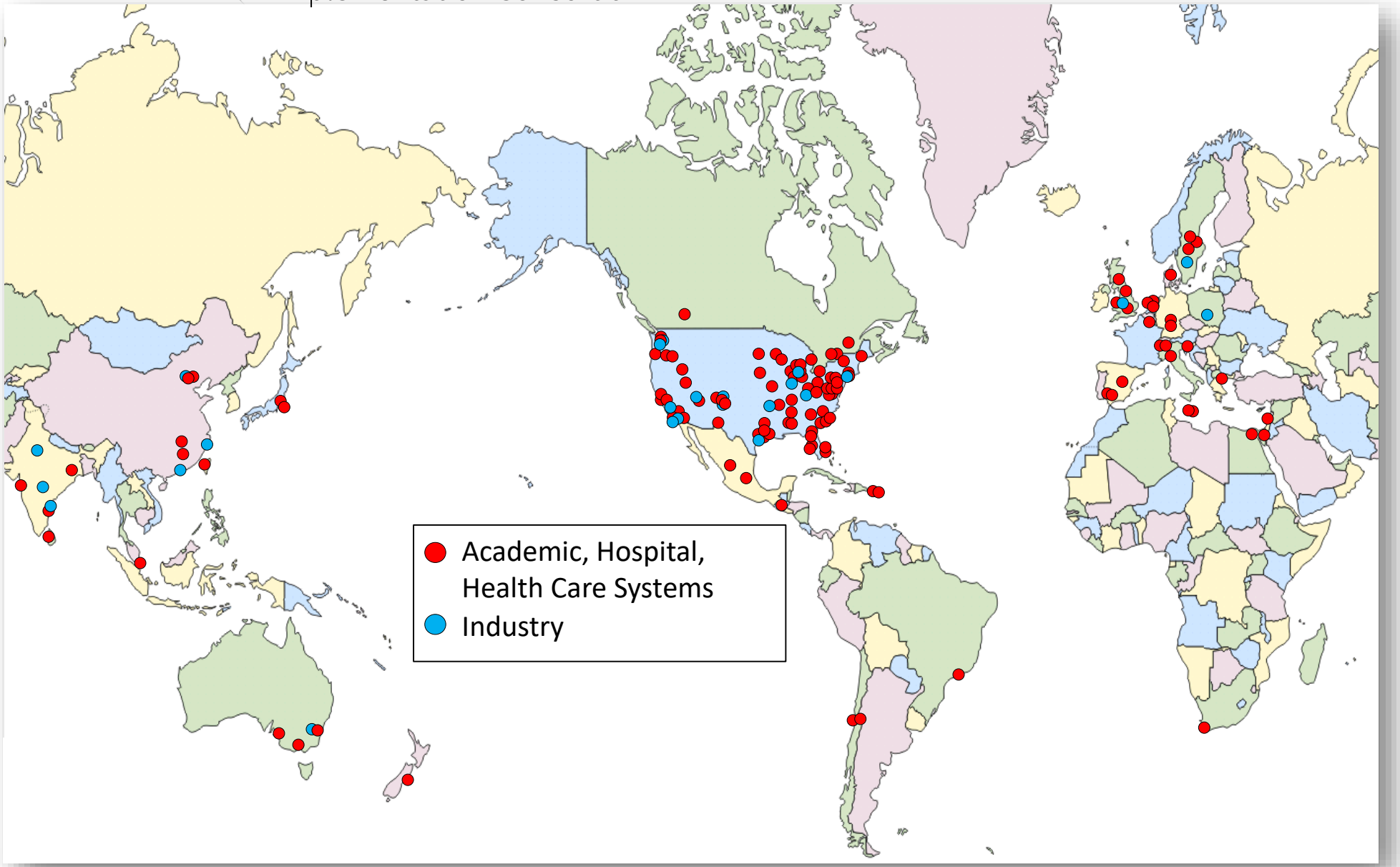
CPIC™
Clinical Pharmacogenetics Implementation Consortium

- As of October 2019:
  - >385 Members
    - Clinicians and scientists
    - 292 institutions
    - 35 countries
  - 14 Observers (NIH, FDA, professional societies)
  - CPIC Informatics
    - >35 members from 25 organizations

CPIC™
Clinical Pharmacogenetics Implementation Consortium

>385 members



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2011

- *TPMT* – thiopurines
- *CYP2C19*– clopidogrel
- *CYP2C9, VKORC*1 – warfarin

2012

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

2013

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

https://cpicpgx.org/guidelines/

2014

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

2015

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

2016

- *CYP2C19* – voriconazole
- *CYP2D6* – ondansetron
- *CYP2C9, VKORC*1 – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs--UPDATE

2017

- *CYP2D6* – tamoxifen
- *HLA-B* – carbamazepine—UPDATE
- *DPYD* -- 5FU / capecitabine—UPDATE

2018

- *RYR1/CACNA1S*– inhaled anesthetics
- *TPMT/NUDT15* – thiopurines—UPDATE

2019 (in progress included)

- *CYP2B6*—efavirenz-published
- *CYP2D6*—atomoxetine-published
- *CYP2C19*/PPI
- *CYP2C9*/HLA-phenytoin—UPDATE
- *CYP2C9*/NSAIDS
- CYP2D6/codeine-UPDATE (to include other opioids)
- *CYP2C19*/clopidogrel-UPDATE
- *mtRNR1*/aminoglycosides

23 guidelines; 20 genes and 46 drugs

- *TPMT, NUDT15*
  - MP, TG, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs, tamoxifen, SSRIs, ondansetron, tropisetron, atomoxetine
- *CYP2C19*
  - TCAs, clopidogrel, voriconazole, SSRIs, PPIs (in progress)
- *VKORC1*
  - Warfarin
- *CYP2C9*
  - Warfarin, phenytoin, NSAIDs (in progress)
- *CYP4F2*
  - Warfarin
- *HLA-B*

  --Allopurinol, CBZ, Oxcarbazepine, abacavir, phenytoin
- *HLA-A*
  - CBZ

https://cpicpgx.org/guidelines/

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- *CFTR*

  -- Ivacaftor
- *DPYD*
  - 5FU, capecitabine, tegafur
- *G6PD*
  - Rasburicase
- *UGT1A1*
  - Atazanavir
- *SLCO1B1*
  - Simvastatin
- *IFNL3 (IL28B)*
  - Interferon
- *CYP3A5*
  - Tacrolimus
- *CYP2B6*
  - Efavirenz
- *RYR1, CACNA1S*
  - Inhaled anesthetics
- *mRNR1* (in progress)
  - aminoglycosides

https://cpicpgx.org/prioritization-of-cpic-guidelines/

Prioritization of CPIC Guidelines

Prioritizing the order of writing guidelines for CPIC genes/drugs is based on the following criteria:

- Is there prescribing actionability?
- What is the severity of the clinical consequences (adverse effects, lack of response) if genetics are not used to inform prescribing?
- Is the gene already subject to other CPIC guidelines?
- Is there an available genetic test for that gene?
- How commonly used are the affected drugs?
- How common are the high-risk genetic variants?
- Is there mention of genetic testing in drug labelling?
- Are there pharmacogenetically-based prescribing recommendations from professional organizations or others?

CPIC guidelines published, in progress, or planned

Gene – Drug	Current CPIC level*	Status
TPMT, NUDT15 – thiopurines	A	Published
CYP2C19 – clopidogrel	A	Published; **update in progress**
CYP2C9,VKORC1, CYP4F2 – warfarin	A	Published
CYP2D6 – codeine	A	Published; **update in progress**

https://cpicpgx.org/guidelines/

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

Guidelines

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

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

Links to guideline pages

prioritizing CPIC guidelines

Search:

GUIDELINES	DRUGS	GENES
Guideline for CFTR Genotype and Ivacaftor Therapy	ivacaftor	CFTR
Guideline for CYP2C19 Genotype and Clopidogrel Therapy	clopidogrel	CYP2C19
Guideline for CYP2C19 Genotype and Voriconazole Therapy	voriconazole	CYP2C19

CPIC® Guideline for Voriconazole and CYP2C19

Most Recent Guideline Publication

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

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

Tables provided in the main manuscript of the guideline

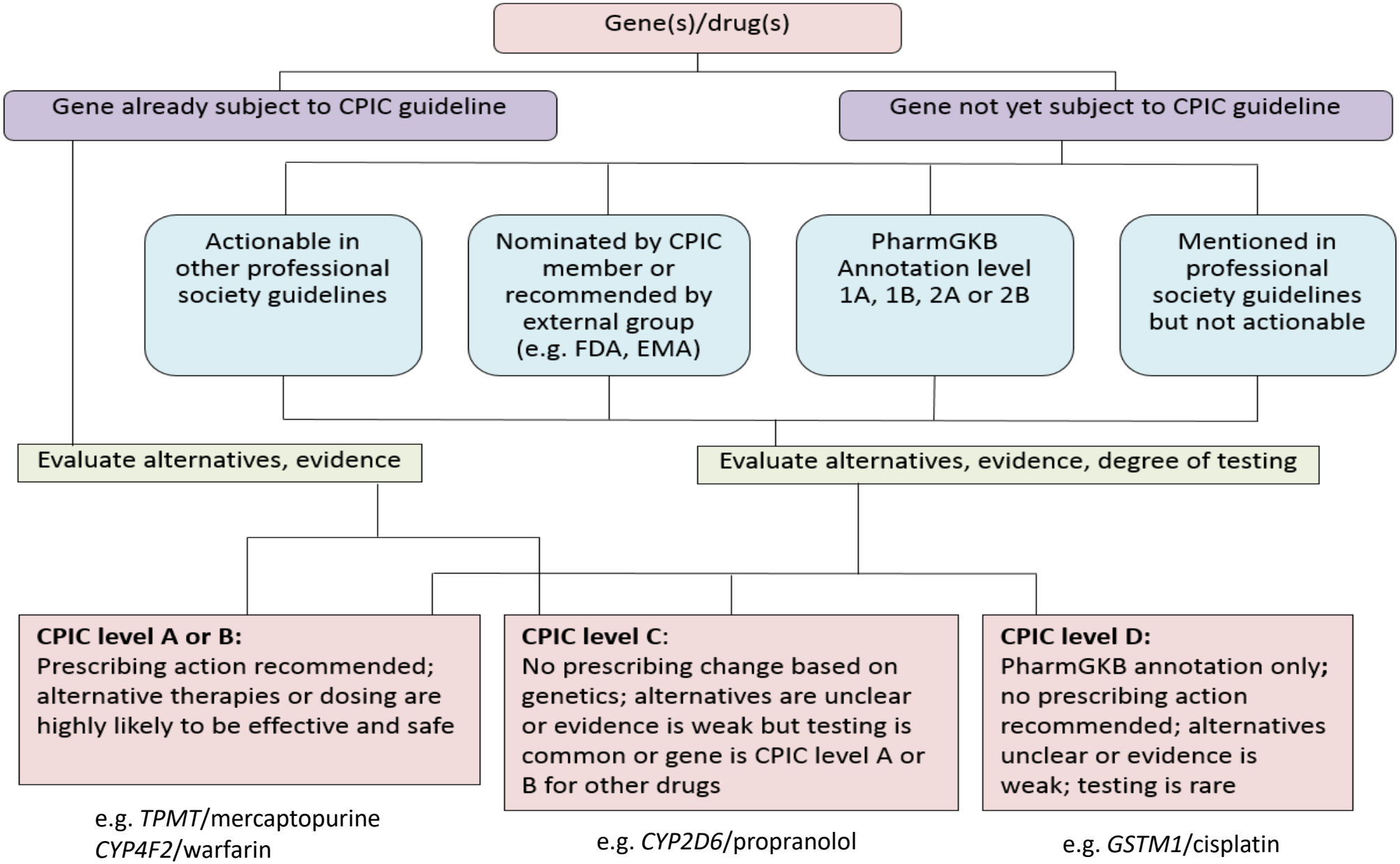
Table 1. Assignment of likely CYP2C29 phenotype based on genotypes
Table 2. Dosing recommendations for voriconazole based on CYP2C19 phenotype for adult patients
Table 3. Dosing recommendations for voriconazole based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

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

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

Levels of Evidence Linking Genotype to Phenotype
CYP2C19 Allele Definition Table
CYP2C19 Allele Functionality Table

CPIC assigns actionability levels to gene/drug pairs



/genes-drugs/

Genes-Drugs

> 52,000 hits/year

https://cpicpgx.org/genes-drugs/

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

The levels (A, B, C, and D) assigned are subject to change; only those gene/drug pairs that have been the subject of guidelines have had sufficient in-depth review of evidence to provide definitive CPIC level assignments.

Note that only CPIC level A and B gene/drug pairs have sufficient evidence for at least one prescribing action to be recommended. CPIC level C and D gene/drug pairs are not considered to have adequate evidence or actionability to have prescribing recommendations.

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

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

Download Table (CSV)

Search:

# (N=359)	GENE (UNIQUE = 127)	DRUG (UNIQUE = 226)	GUIDELINE	CPIC LEVEL	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)

Resources

Overview Presentation

This presentation describes CPIC, the underlying assumptions of CPIC guidelines, the guideline development process and how the guidelines can be implemented in a clinical setting. Overview Presentation

A brief overview of CPIC can be found here.

Implementation

View a list of current implementers

CPIC users and media mentions

Term Standardization for Clinical Pharmacogenetic Test Results

Learn about CPIC's Term Standardization Project

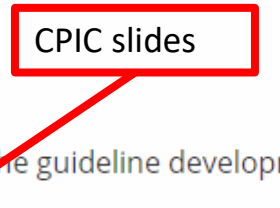
Genotype to Phenotype Standardization Project

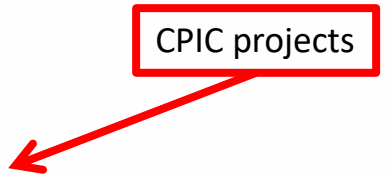
Learn about the *CYP2D6* Genotype to Phenotype Project

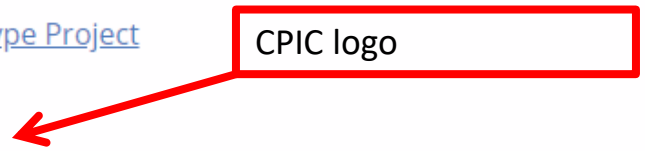
CPIC Logo Graphics

Logo image files that you can use for referring to CPIC. The images are in PNG and SVG format.

- logo without full name
  - 200px width PNG
  - 400px width PNG







Implementation

https://cpicpgx.org/implementation/

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

Institution	Website and/or Contact (if available)
BJC Healthcare	
Boston Children's Hospital	Shannon Manzi; shannon.manzi@childrens.harvard.edu
Children's Minnesota	
Cincinnati Children's Hospital Medical Center	CCHMC Genetic Pharmacology Service
Clearview Cancer Institute	Emily K Pauli; emily.pauli@ccihsv.com
Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology	Matthias Schwab; matthias.schwab@ikp-stuttgart.de
Erasmus MC	Ron van Schaik; r.vanschaik@erasmusmc.nl
Geisinger Health System	Geisinger Health System Genomic Medicine Institute
Icahn School of Medicine at Mount Sinai	Stuart Scott lab Aniwaa Owusu Obeng; aniwaa.owusu-obeng@mssm.edu

Endorsements

CPIC guidelines and projects have been endorsed by several professional societies.

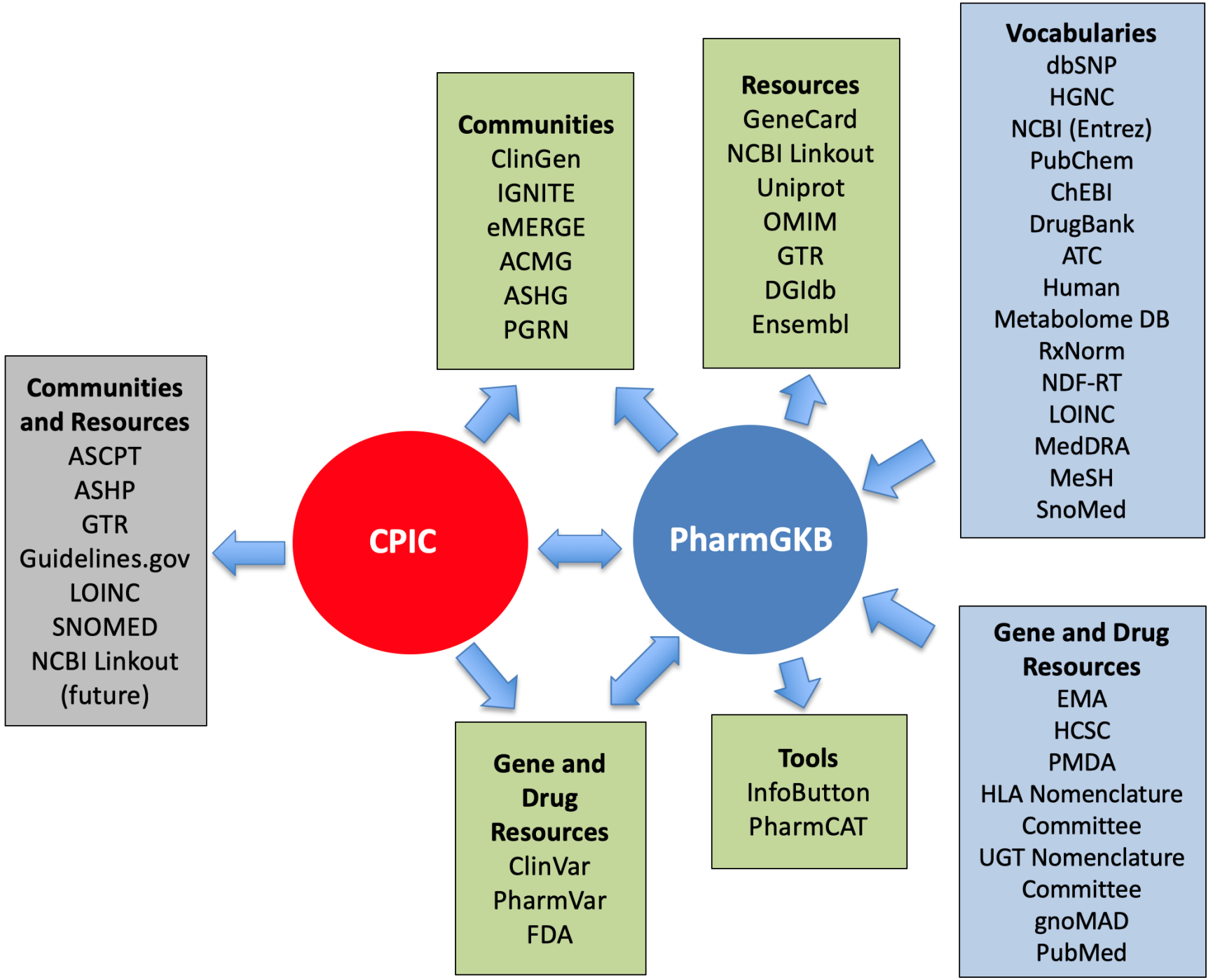
The Association for Molecular Pathology (AMP) has endorsed CPIC's Term Standardization for Clinical Pharmacogenetics Test Results Project.

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) Board of Directors has endorsed CPIC guidelines.

The American Society of Health-System Pharmacists (ASHP) has endorsed multiple CPIC guidelines.

https://cpicpgx.org/endorsements/

“external” interactions



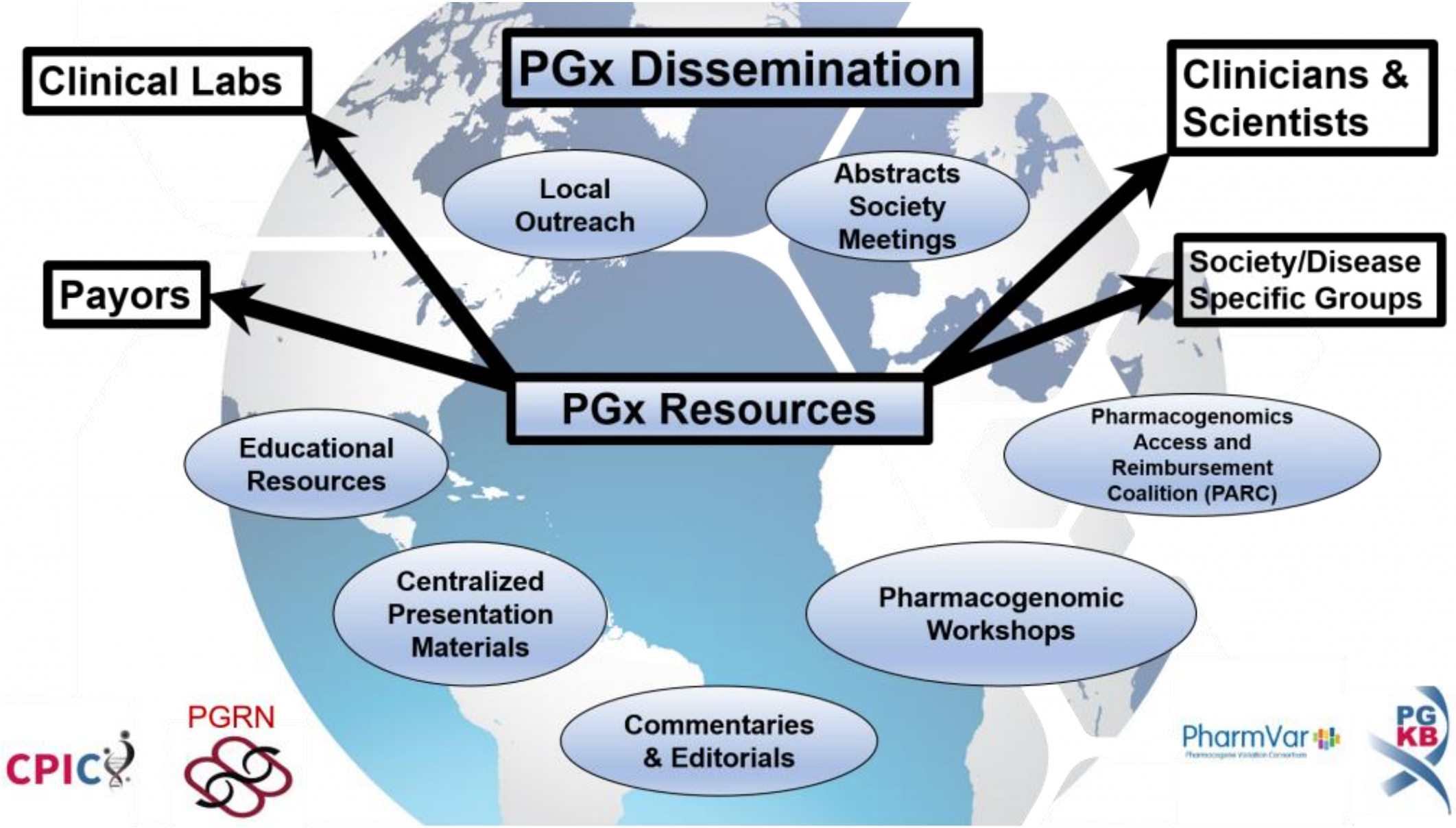

PGx Dissemination
Clinical Labs
Clinicians & Scientists
Local Outreach
Abstracts Society Meetings
Payors
Society/Disease Specific Groups
PGx Resources
Educational Resources
Pharmacogenomics Access and Reimbursement Coalition (PARC)
Centralized Presentation Materials
Pharmacogenomic Workshops
Commentaries & Editorials
CPIC
PGRN
PharmVar
PG KB

Table 1 Assignment of likely CYP2D6 phenotypes based on genotypes

Phenotype[a]		Genotype	Examples of *CYP2D6* diplotypes[b]
Metabolizer	Activity score		
CYP2D6 ultrarapid metabolizer	> 2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[c]
CYP2D6 normal metabolizer	1.5 and 2.0	An individual carrying two normal function alleles or one normal function and one decreased function allele	**1/*1, *1/*2, *1/*9, *1/*41, *2/*2,*
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[d]	1.0	An individual carrying two decreased function alleles or one normal function and one no function allele. *An activity score (AS) of 1.0 is associated with decreased tamoxifen metabolism to endoxifen compared to those with an AS of 1.5 or 2.*	**1/*4, *1/*5, *41/*41*
CYP2D6 intermediate metabolizer	0.5	An individual carrying one decreased function and one no function allele	**4/*10,*4/*41, *5/*9*
CYP2D6 poor metabolizer	0	An individual carrying only no functional alleles	**3/*4,*4/*4, *5/*5, *5/*6*

Clin Pharmacol Ther. 2018 May;103(5):770-777.

Table 2 Dosing recommendations for tamoxifen based on *CYP2D6* phenotype

Phenotype		Implications	Therapeutic recommendation[b]	Classification of recommendation[a]
Metabolizer status	Activity score			
CYP2D6 ultrarapid metabolizer	>2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 normal metabolizer	1.5 to 2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (no *10 allele present)[b]	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype.[43] If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day).[45] Avoid CYP2D6 strong to weak inhibitors.	Optional[b]
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (*10 allele present)[b]	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype.[43] If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day).[45] Avoid CYP2D6 strong to weak inhibitors.	Moderate[b]
CYP2D6 intermediate metabolizer	0.5	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype.[43] If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day).[45] Avoid CYP2D6 strong to weak inhibitors.	Moderate
CYP2D6 poor metabolizer	0	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	Recommend alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype[43] and based on knowledge that *CYP2D6* poor metabolizers switched from tamoxifen to anastrozole do not have an increased risk of recurrence.[38] Note, higher dose tamoxifen (40 mg/day) increases but does not normalize endoxifen concentrations and can be considered if there are contraindications to aromatase inhibitor therapy.[45,56]	Strong

Clin Pharmacol Ther. 2018 May;103(5):770-777.

CYP2D6 Genotype to Phenotype Standardization Project

Since pharmacogenetic clinical recommendations are based on phenotype, the assignment of phenotype based on genotype is an important aspect to clinical implementation and reporting of different inferred phenotypes across laboratories and guidelines has created considerable confusion and inconsistencies in recommendations. To maximize the utility of pharmacogenetic test results, it is desirable to standardize the phenotype prediction from genotype data. The purpose of this project was to determine consensus among CYP2D6 experts as to the definitions used to assign CYP2D6 phenotype based on genotype.

- Final Consensus CYP2D6 genotype to phenotype table_final_Mar2019

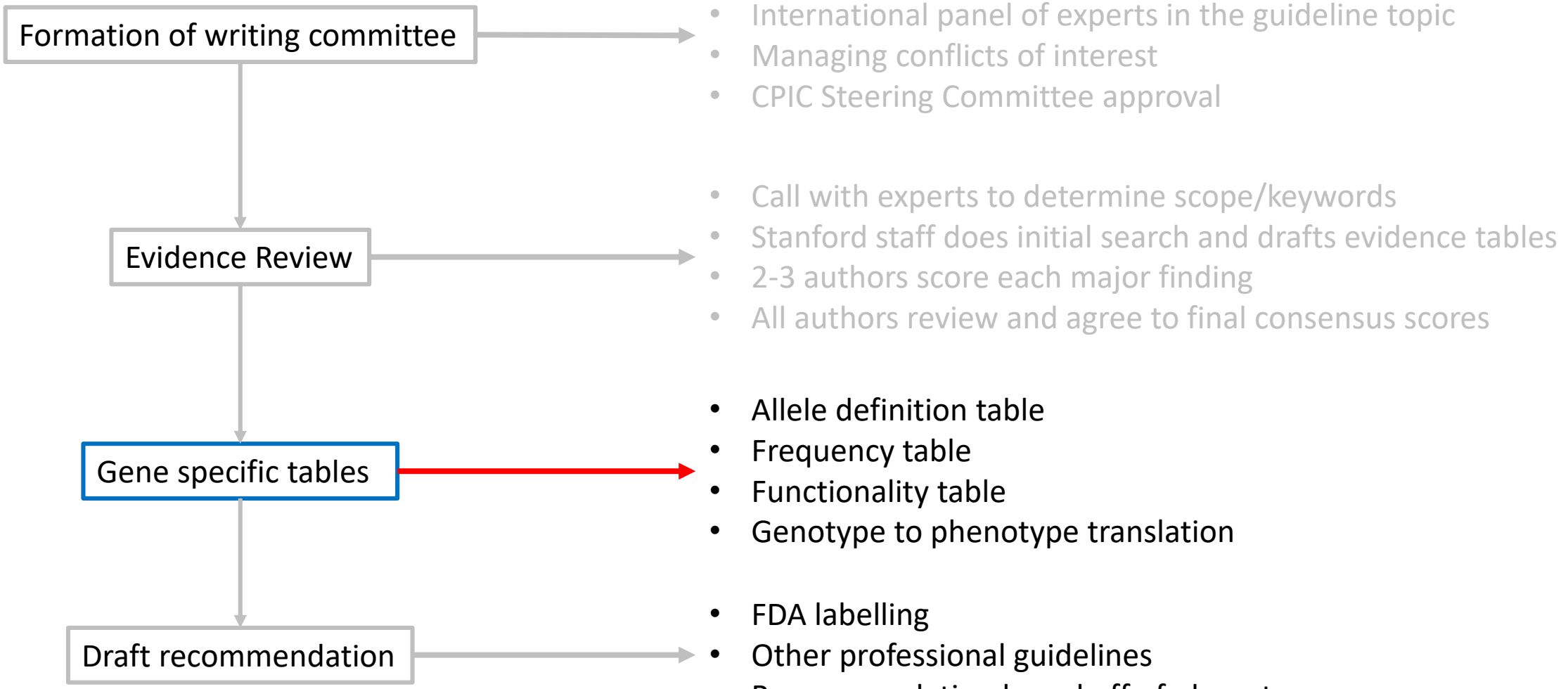
Project details and survey results:

- Project background and methods
- Evidence review summary
- Survey 1 results
- Survey 2 results
- Survey 3 results
- Survey 4 results
- Survey 5 results
- Survey 6 results
- Survey 7 results
- Survey 8 results

https://cpicpgx.org/resources/cyp2d6-genotype-to-phenotype-standardization-project/

Inferred CYP2D6 Phenotype	Previous CPIC Definition (AS)	Previous DPWG Definition (AS)	Consensus Definition (AS)	Consensus Contiguous Definition (AS)	Examples of CYP2D6 diplotypes for consensus translation method
Ultrarapid Metabolizer	>2	>2.5	>2.25	>2.25	*1/*1xN, *1/*2xN, *2[1]/*2xN, *1x2/*9
Normal Metabolizer	1-2	1.5-2.5	1.25 1.5 2.0 2.25	$1.25 \leq x \leq 2.25$	*1/*1, *1/*2, *1/*9, *1/*41, *1/*10, *2x2/*10
Intermediate Metabolizer	0.5	0.5-1	0.25 0.5 0.75 1	$0 < x < 1.25$	*4/*10, *4/*41, *1/*5, *10/*10, *41/*41
Poor Metabolizer	0	0	0	0	*3/*4, *4/*4, *5/*5, *5/*6

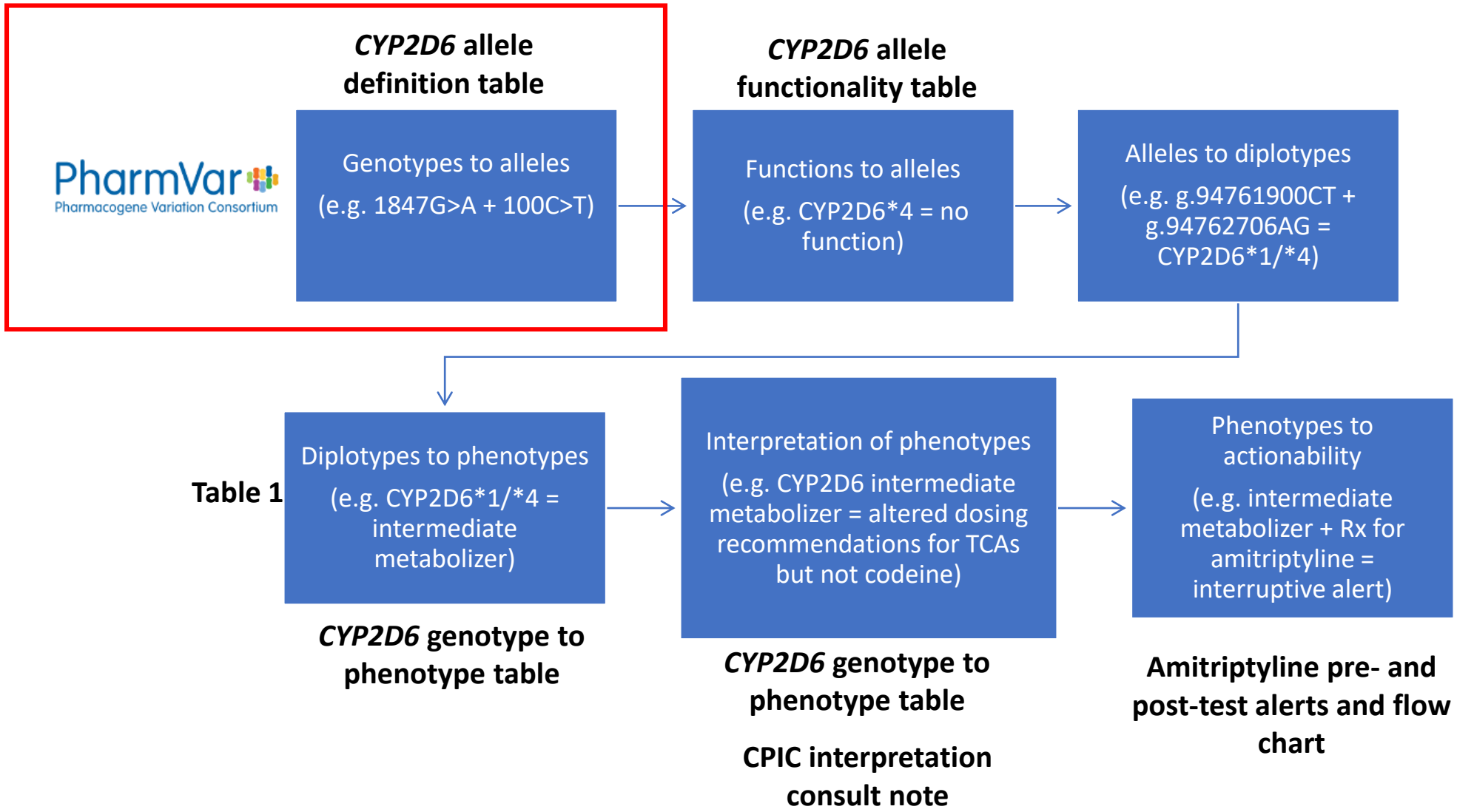
CPIC guideline development process



Supporting Tables and Materials

- Allele definition table
- Allele functionality table
- Allele frequency table
- Diplotype/phenotype table
  - Example EHR interpretation consult note text
  - Implementation workflow
- Pre and post test alerts
  - Flow chart
- Files mapping gene and drug names to other nomenclatures/IDs

CPIC tables allow translation of genetic test results to actionability



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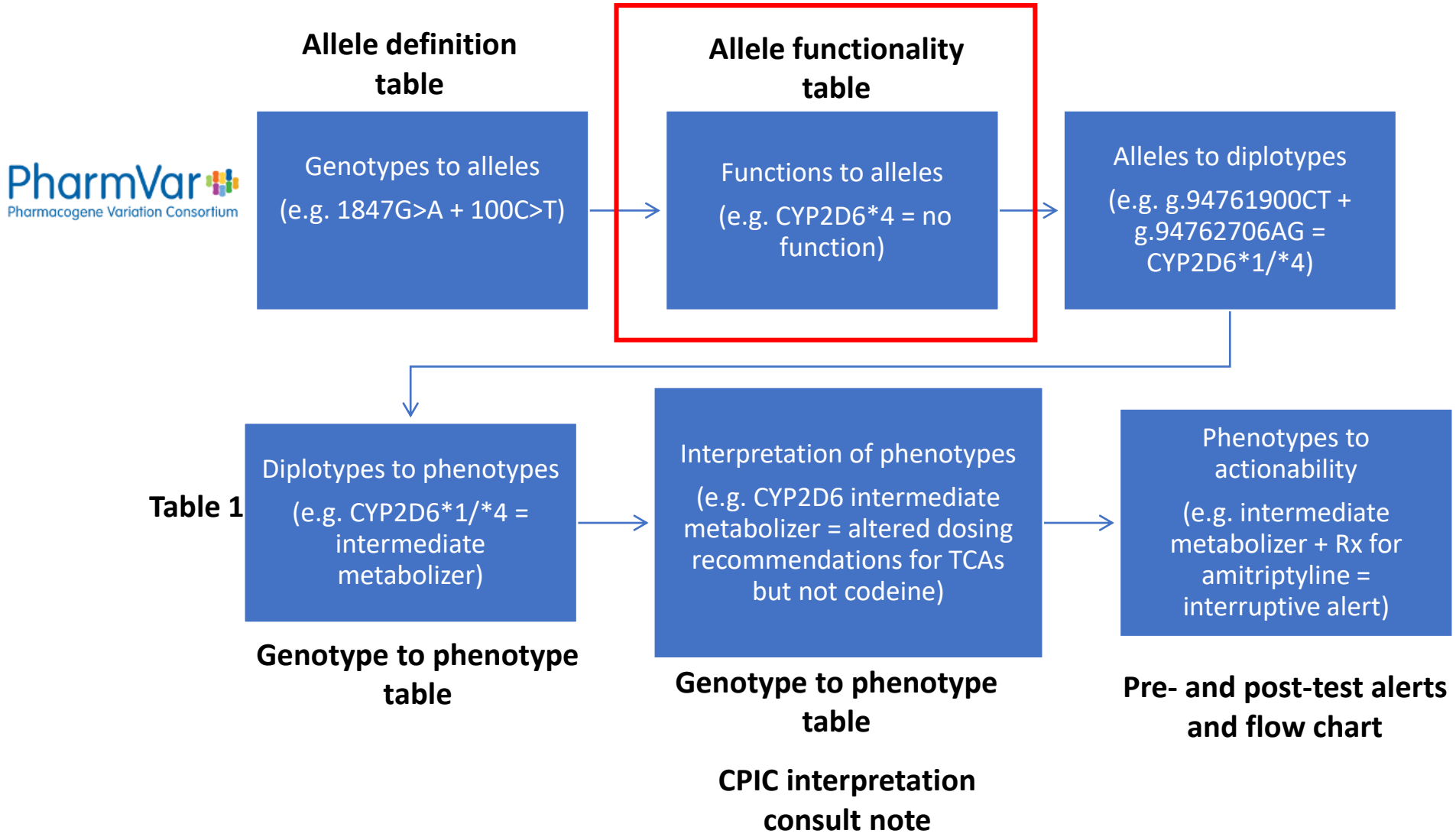


Assignment of phenotype based on allele function

Table 1 Assignment of likely CYP2D6 phenotypes based on diplotypes

Likely phenotype	Activity score	Genotypes[a]	Examples of *CYP2D6* diplotypes
CYP2D6 Ultrarapid Metabolizer (~1–2% of patients)[b]	>2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[c]
CYP2D6 Normal Metabolizer (~77–92% of patients)	2.0–1.0[d]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0–2.0	**1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41*
CYP2D6 Intermediate Metabolizer (~2–11% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*10,*4/*41, *5/*9*
CYP2D6 Poor Metabolizer (~5–10% of patients)	0	An individual carrying only no functional alleles	**3/*4,*4/*4, *5/*5, *5/*6*

Clin Pharmacol Ther. 2017 Aug;102(2):213-218.

CPIC Allele Clinical Function

- Will be used to generate lists of clinically actionable variants
  - If that variant were present in the right gene dosage (e.g. usually as part of a diplotype with another similarly actionable variant), prescribing decisions would be altered from the normal baseline prescribing actions.

- Clinical function assignment will be given if the evidence is strong enough to inform prescribing actionability

- The threshold for what evidence is enough to inform actionability may differ for different genes.

Allele Clinical Function to the allele vs categorizing as “uncertain”

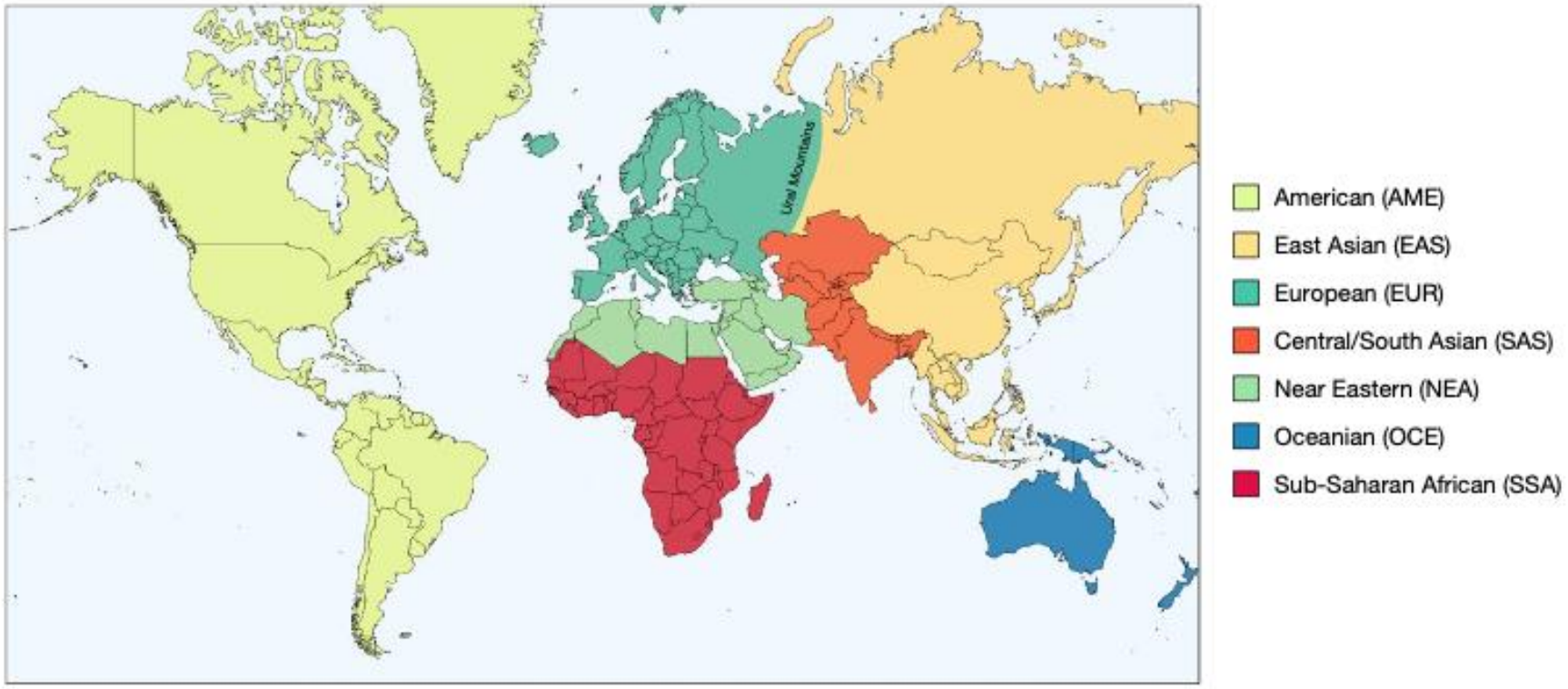
Supportive Evidence needed to assign function vs uncertain	DEFINITIVE	The role of this variant in this particular drug phenotype has been repeatedly demonstrated, and has been upheld over time (in general, at least 3 years). No convincing evidence has emerged that contradicts the role of the variant in the specified drug phenotype.
	STRONG	The role of this variant in the drug phenotype has been independently demonstrated in at least two separate clinical studies providing strong supporting evidence for this variant’s role in drug phenotype and there is compelling variant-level evidence from different types of supporting experimental data. In addition, no convincing evidence has emerged that contradicts the role of the variant in the noted drug phenotype.
	MODERATE	There is moderate evidence to support a causal role for this variant in this drug phenotype, including both of the following types of evidence: • At least 2 patient cases evidence for drug phenotype causality • Some experimental data supporting the variant-drug phenotype association And no convincing evidence has emerged that contradicts the role of the variant in the noted drug phenotype.
	LIMITED	There is limited evidence to support a causal role for this variant in this drug phenotype, such as: • Fewer than 2 patient cases • experimental or computational data supporting the variant-drug phenotype association And no convincing evidence has emerged that contradicts the role of the variant in the noted drug phenotype.
Inadequate EVIDENCE = uncertain function		* Fewer than 2 patient cases with no convincing experimental data, or * fewer than 2 patient cases and extremely limited or conflicting experimental data. This designation should be used when the evidence is not strong enough to support a clinical functional status that can inform prescribing actionability. The threshold for what evidence is enough to inform actionability may differ for different genes.

GENE: CYP2C9							
Allele/cDNA/rsID	**Activity Score (Optional)**	**Allele Functional Status (Optional)**	**Allele Clinical Functional Status (Required)*- initial assessment**	**Allele Clinical Function Substrate Specificity (Optional)**	**PMID (Required)**	**Strength of Evidence (Optional)**	**Findings (Optional)**
*1		Normal function	**Normal function**		23752738		23752758: N/A
*2		Decreased Function	**Decreased function**	S-warfarin, warfarin, tolbutamide, phenytoin, phenprocoumon, fluribiprofen, perazine, sulphamethoxazole, fluoxetine, phenprocoumon, tenoxicam, clopidogrel, carvediol, propofol, mestranol, meloxicam, avatrombopag, siponimod, piroxicam, metamizole	23752738; 10413320; 8004131; 12496751; 21110013; 11668218; 9698079; 22547083; 25144335; 25775139; 27298492; 12520632; 12698304; 9698079; 9686881; 15824753; 17895500; 24322786; 27199745; 12621390; 9522436; 21148049; 12621390; 9522436; 21148049; 12426520; 19298642; 8873200; 24077631; 22547083; 25075423; 12520632; 11875364; 9522436; 27163851; 11908757; 11434505; 16815679; 21068649; 22561479; 22641027; 28820457; 23287317; 10510154; 11026737; 19298642; 24663076; 14726986; 16236141; 25884291; 15128047; 15742978; 15229460; 18992346; 17900275;		23752738: S-warfarin (in v tolbutamide (in vitro) 1041 phenytoin (in vitro); 80041 (in vivo); 12496751: S-wa 21110013: phenprocoum 11668218: phenytoin (in v fluribiprofen (in vitro) Lowe for oxidation of S-flurbipro (minor differences betwee 22547083: fluribiprofen (i *2 have similar Km values reduced Vmax compared clearance is substantially than *1; 25144335: fluribip 61.36% relative clearance *1; 25775139: fluribiprofe measured metabolic ratio and the *1/*2 genotype wa

Allele Frequency File Updates

- Populations binned into different supersets based on guideline
  - E.g. Egyptians: African, Middle Eastern, Caucasian

- Biogeographical population groups from
  - Standardized biogeographic grouping system for annotating populations in pharmacogenetic research. (2018) *Clinical Pharmacology and Therapeutics*, epub.



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

Open

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

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Table 2 Final consensus terms for allele functional status and phenotype

Term/gene category	Final term[a]	Functional definition	Genetic definition	Example diplotypes/alleles
Allele functional status: all genes	Increased function	Function greater than normal function	N/A	*CYP2C19*17*
	Normal function	Fully functional/wild-type	N/A	*CYP2C19*1*
	Decreased function	Function less than normal function	N/A	*CYP2C19*9*
	No function	Nonfunctional	N/A	*CYP2C19*2*
	Unknown function	No literature describing function or the allele is novel	N/A	*CYP2C19*29*
	Uncertain function	Literature supporting function is conflicting or weak	N/A	*CYP2C19*12*
Phenotype: drug-metabolizing enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)	Ultrarapid metabolizer	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles, or more than 2 normal function alleles	*CYP2C19*17/*17* *CYP2D6*1/*1XN*
	Rapid metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
	Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
	Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
	Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*
Phenotype: transporters (SLCO1B1)	Increased function	Increased transporter function compared to normal function.	One or more increased function alleles	*SLCO1B1*1/*14*
	Normal function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
	Decreased function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
	Poor function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles	*SLCO1B1*5/*5*
Phenotype: high-risk genotype status (*HLA-B*)	Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
	Negative	High-risk allele not detected	No copies of high-risk allele	

[a]All terms should begin with the gene name (e.g., CYP2D6 Poor metabolizer, TPMT Normal metabolizer, SLCO1B1 decreased function).

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Standardization not completed for all known pharmacogenes or consensus not reached

Additional standardization opportunities exist beyond the genes presented here. For example, *VKORC1* is the one CPIC level A gene (https://cpicpgx.org/genes-drugs) on which we did not reach a consensus. This gene is tested primarily in the context of predicting starting doses of the common anticoagulant warfarin, which is also dependent on *CYP2C9*. Therefore, many laboratories report a drug-centered phenotype such as "greatly increased sensitivity to warfarin" (see the CPIC guideline for warfarin[21]), which complicated standardization of *VKORC1* terms following the formats used for other genes. In addition, *VKORC1* genotype and inferred phenotypes for warfarin dosing are also reported by some laboratories and the CAP proficiency testing surveys according to the *CYP2C9* and *VKORC1* policy statement published by the ACMG in 2008,[22] which further could have added to the difficulty in standardizing *VKORC1*.

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RYR1 Allele Functionality Table

GENE: RYR1	8/16/2018					
	rsID[a]	Nucleotide change[b]	Protein change[c]	Allele Functional Status[d]	Finding	
	rs193922878	c.14512C>G	p.L4838V	Increased function	increased caffeine-induced calcium release in CHO cells	11928716
					accelatered CICR	11928716, 167
					associated with MH (supplemental material)	16917943
					positive IVCT; increased sensitivity to caffeine and chloro	19191329
	rs118192168				associated with MH (supplemental material)	16917943
					d to the left i	28403410
					n the homozy	16372898
						15731587, 214
						16163667, 193
	rs63749869	c.14582G>A	p.R4861H	Uncertain function[e]	4-chloro-m-cresol resulted in almost no increase in the [C	11741831
					mutation detected was concordant with CCD status only;	14985404
					positive IVCT in CCD patient	12565913, 170
					positive CHCT	23558838
	rs118192170	c.14693T>C	p.I4898T	Decreased function	I4898T led to a simultaneous increase in intracellular calc	10097181
					homozygous expression of I4897T in dyspedic myotubes r	11274444
					not elevated resting calcium; no spontaneous calcium osc	11524458
					incorporation of the I4897T mutation into leaky release ch	12642598
					no high-affinity 3H-ryanodine binding was detected; Ca2-	15175001
					myotubes from the CCD pa-tients harboring the I4898T an	15299003
					positive IVCT in CCD patient	17081152
					RYR1 mutant linked to CCD, I4898T, did not show any resp	20461000
					in 4-6-mo-old heterozygous Ryr1(I4895T/+) knock-in mice	21149547
					Inhibition of voltage-gated Ca(2+) release due to reductio	21825032
					decreases voltage-gated calcium release and resting cyto	28337975

Term Standardization II

Non-standardized genes with CPIC guidelines

Gene	Drug	CPIC Level	Efficacy, adverse reaction, both?	Description
RYR1/CACNA1S	halogenated anesthetics, succinylcholine	A	Adverse reaction only	Variants in Ca channels cause adverse drug reaction
CFTR	ivacaftor	A	Efficacy only	Loss of function variants predict drug efficacy (drug targets specific Cl channel variants)
G6PD	rasburicase	A	Adverse reaction only	Variants cause adverse drug reaction through loss of drug detoxification pathway
IFNL3	peginterferon alfa-2a	A	Efficacy only	Genotype predicts drug efficacy
VKORC1	warfarin	A	Both efficacy and adverse reaction	Variants cause altered efficacy and adverse reaction risk due to dose sensitivity

Database & Application Programming Interface (API) Development

- Goals:
  - Create a database to house CPIC information including recommendations, all supplemental table information (allele mappings, frequencies, function, diplotypes, etc.) and publications
  - Create an API to query the database for internal CPIC use (eg. populate CPIC website, automatic table generation) and for external users wanting CPIC data

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PharmGKB

CPIC™ Clinical Pharmacogenetics Implementation Consortium

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