CLINICAL PRACTICE GUIDELINE STANDARD OPERATING PROCEDURE

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CPIC
Clinical Pharmacogenetics Implementation Consortium

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FOREWORD

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international consortium of volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests to optimize drug therapy to improve patient care. CPIC staff and volunteers create, curate, and post freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines.

The development and updating of CPIC guidelines follow a rigorous process to review and grade relevant scientific literature with the assistance of content experts (e.g., clinicians, researchers, etc.). CPIC closely follows Institute of Medicine (IOM) (now the National Academy of Medicine) and ECRI Guidelines Trust practices for guideline development (1) .

This guidance document, *Clinical Practice Guideline Standard Operating Procedure,* provides a standard tool that should be used in the development and updating of CPIC guidelines.

Questions regarding this document or other CPIC related documents should be directed to contact@cpicpgx.org.

INTRODUCTION

Overview

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is dedicated to providing evidence-based guidelines for the application of pharmacogenetic testing in clinical practice. CPIC's purpose is to facilitate the integration of pharmacogenetic information into patient care to optimize drug therapy, minimize adverse drug reactions, and improve therapeutic outcomes. By offering standardized, actionable recommendations, CPIC aims to support healthcare providers in making informed decisions about drug prescriptions based on genetic factors, ultimately enhancing personalized medicine practices and promoting the safe and effective use of medications across diverse patient populations.

CPIC guidelines assume the test results are in hand and may have been generated preemptively. CPIC guidelines do not discuss the merits of doing the test, nor cost effectiveness. Prescribing recommendations are guided based on the principle that genotypes are known: what gene/drug relations are so clear that clinicians should be provided with prescribing advice when test results are in hand?

Each guideline includes a table containing prescribing recommendations (generally "Table 2" of the guideline) and is the heart of the CPIC guideline. Standardized formats for all tables and standardized terms for diplotypes, phenotypes, drugs, and genes should be used whenever possible to facilitate machine-readable compatibility of content.

The guidelines will be updated as needed to accommodate important new evidence as it emerges (see "Guideline Updates" for further details). Users of guidelines are encouraged to access content from the website; all have the wording "Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for" and are periodically updated at www.cpicpgx.org/guidelines/.

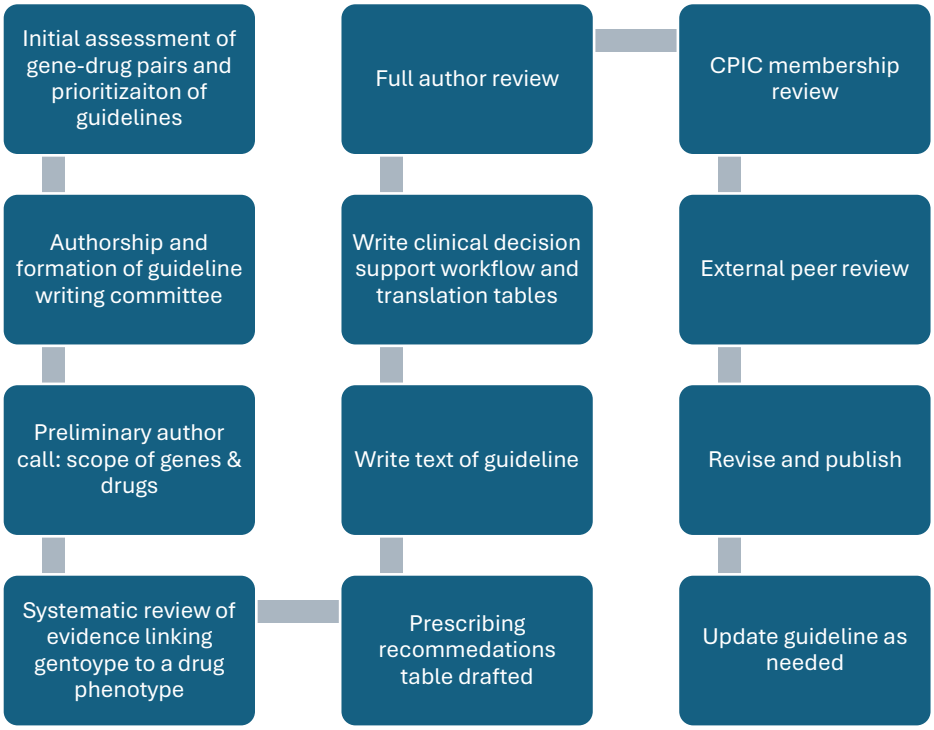
Finished documents are posted and updated on the CPIC website (https://cpicpgx.org) and the PharmGKB website (https://www.pharmgkb.org).

Purpose

Clinical Practice Guideline Standard Operating Procedure guidance document highlights procedures for creating, updating and publishing evidence-based guidelines developed by CPIC staff and volunteer experts. The SOP details important aspects of the guideline and follows standards set by IOM and ECRI Guidelines Trust for guideline development. The purpose of this SOP is to ensure guideline developers follow standardized formats and terminology when developing or updating CPIC guidelines.

CPIC GUIDELINE DEVELOPMENT PROCESS

Figure 1. Overview of CPIC Guideline Development Process



Initial Assessment of Gene-Drug Pairs and Prioritization of Guidelines

CPIC and the CPIC Steering Committee use a systematic process for tentative prioritization of genes/drugs. CPIC classifies genes/drugs into actionability levels A, A/B, B, B/C, C, C/D and D. Only CPIC level A and level B gene/drug pairs are considered to have prescribing actionability and are the highest priority to be the subject of guidelines (see https://cpicpgx.org/prioritization/#flowchart).

Genes-Drugs in Published Guidelines

The levels A, B, C, and D are assigned after sufficient in-depth review of the evidence has been completed to provide definitive CPIC actionability level assignments. The level definitions for CPIC genes/drugs are as follows:

- CPIC level A gene/drug pairs include at least one strong or moderate actionable prescribing recommendation.
- CPIC level B gene/drug pairs are written for genes/drugs with an optional prescribing recommendation.
- CPIC level C gene/drug pairs apply to drugs that are linked to CPIC level A or B genes, but for which prescribing changes cannot be recommended, as well as to genes that are highly touted to be actionable but for which there is little literature to support an actionable prescribing recommendation.
- CPIC level D genes/drugs do not result in CPIC guidelines due to lack of actionability/evidence but may be encompassed in the PharmGKB clinical annotations process.

Provisional Genes-Drugs

Provisional genes-drugs may be assigned CPIC level A, A/B, B, B/C, C, C/D and D. These levels are considered tentative and subject to change until an in-depth review of evidence is completed. CPIC gene-drug level assignments A, B, C and D have the same definition as above. CPIC levels A/B and B/C are used to denote that the actionability level is not clear without having an expert panel review the evidence to assess the actionability of the gene/drug pair and C/D is used when no prescribing actions are recommended.

Additionally, the Genes-Drugs list posted at https://cpicpgx.org/genes-drugs/ includes:

1. Genes/drugs with PharmGKB Level of Evidence 2B and higher
2. Genes/drugs for which regulatory bodies (e.g. FDA, EMA) include pharmacogenetic information in the approved drug labeling related to germline variants
3. Other genes/drugs nominated by CPIC members

Guideline Prioritization

Guidelines are prioritized based on the following criteria:

- Likelihood of prescribing actionability
- Severity of the clinical consequences (adverse effects, lack of response) if genetics are not used to inform prescribing
- Whether the gene is already subject to other CPIC guidelines
- Availability of a commercial genetic test
- Frequency of use of the affected drugs
- Frequency of the high-risk genetic variants
- Genetic testing mentioned in drug labelling
- Availability of pharmacogenetically-based prescribing recommendations from professional organizations or others

Additional details about CPIC prioritization along with CPIC guideline status can be found at https://cpicpgx.org/prioritization-of-cpic-guidelines/.

Nominations for changes to the CPIC level assignments and for creating or updating guidelines are discussed on regular, monthly CPIC conference calls and are approved by both CPIC members and the CPIC Steering Committee. The CPIC leadership, with input from CPIC members, Stanford PGx Group, and guideline authors, are responsible for updating and maintaining this list as needed.

Authorship and Formation of Guideline Writing Committee

Once a topic has been approved by CPIC members and the CPIC Steering Committee, a senior author is identified through self-nomination or by request of the CPIC Steering Committee. The CPIC Steering Committee must approve authorship plans for each new gene/drug CPIC Guideline and at each update.

The CPIC Director will submit an authorship plan to the CPIC Steering Committee. The authorship plan includes:

- Suggested senior author
- List of potential authors, including affiliations and interest/expertise regarding this guideline topic (1-2 sentences or list areas of research or clinical expertise)
- Signed conflicts of interest disclosure (see below)
- Signed CPIC Publication Memorandum of Understanding (MOU)

Senior Author

Senior authors must be approved by the CPIC Steering Committee and should not have any conflicts of interest (COIs). It is preferred that senior authors be self-identified and be leaders in the content area addressed by the guideline. If no senior author self-identifies, the CPIC Steering Committee will identify a suitable author to take lead responsibility for completing the guideline. The senior author is responsible for completing the CPIC guideline based on a mutually agreed upon schedule, and according to CPIC templates for the main and supplementary manuscripts. The senior author may elect to delegate this responsibility to the CPIC staff for the guideline.

Generally, a senior author should not lead more than one guideline writing group at a time, although the CPIC Steering Committee can designate exceptions, if appropriate.

Writing Committee

The writing committee should be multidisciplinary, comprising a variety of scientists and clinicians, ideally between 10-20 authors. Senior authors can designate a less experienced trainee as a member of the writing committee, with the understanding that they are mentoring the trainee and supervising their participation. Other exceptions regarding content expertise of the authors should be approved by the senior author and by the CPIC Steering Committee. Authors can be added later in the process with the approval of the senior author and the CPIC Steering Committee.

Desirable characteristics for authorship include:

- International representation
- Evidence of prior publications relevant to the gene, drug, and/or disease state
- Expertise in clinical pharmacogenetics or specific topic area of guideline that will lend credibility to prescribing recommendations
- Adequate representation of senior individuals

Inclusion is limited to those with an identified authorship role. CPIC guidelines will include at least one team member from Stanford and one from St. Jude (i.e. CPIC staff).

Authorship for Guideline Updates

CPIC guidelines are regularly updated to reflect feedback, evolving best practices, and any relevant updates (see "Guideline Updates" for further details). Authors will be contacted at the time of any proposed update on an already published guideline. Authorship for formal updates to published guidelines will be treated with the same considerations as for new guidelines. The senior author of the original guideline will be contacted about plans for the update, and the CPIC director will work to identify a senior author for the update (who may or may not be the senior author for the original guideline) and to develop a new authorship plan. The CPIC Steering Committee must approve authorship plans for new guidelines. Authors on the original guideline will not necessarily be invited to participate in the update. Additionally, the senior author is encouraged to consider whether there are additional authors they might wish to include as part of the update, particularly in response to new evidence or new practices that have emerged or taken on new prominence since the original guideline.

Changes to the approved authorship plan will need senior author approval and then CPIC Steering Committee approval.

Writing Committee Responsibilities

Once the author group has been finalized and approved by the Steering Committee, the writing committee will start the guideline process. The goal for the first guideline conference call is to review the CPIC Clinical Practice Guideline SOP, committee

responsibilities and decide how to define scope. After reviewing the CPIC Clinical Practice Guideline SOP, the group will discuss the likelihood that there will be some recommendations (for at least one phenotype and for at least one drug), and review whether the scope of genes and drugs to include is clear, or whether defining the scope will itself require evidence review. This may also then necessitate changes to the author group (which must be approved by the Steering Committee if changed).

If a review of evidence is needed to determine the scope of genes and drugs, the authors will establish inclusion criteria and keywords for the literature search and initial evidence review. They will also assign authors to the "early rule-out" phase and proceed with the preliminary evidence review. Once the scope of genes and drugs to be included in the CPIC guideline evidence review is clear, authors will provide criteria and keywords for literature search for the definitive evidence review.

Responsibilities of the writing committee include, but are not limited to:

a. Actively participate in conference calls and assignments
b. Meet deadlines
c. Review and score evidence
d. Comply with CPIC guideline templates
e. Write and submit the guideline for publication, according to standardized format agreed upon by CPIC and the journal, and for final approval of all accompanying tables
    a. Tables must comply with CPIC formatting requirements, so that they may be uploaded into the CPIC database

All authors must meet the criteria for authorship and adhere to the standards of *Clinical Pharmacology and Therapeutics*, and as outlined by ICMJE's Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

The CPIC Director should review all guidelines for compliance with templates and SOP and should be a co-author if their contributions meet standards for the applicable journal (e.g., *Clinical Pharmacology and Therapeutics*).

Management of Conflicts of Interest

CPIC is guided by the IMO Standards for Developing Trustworthy Clinical Practice Guidelines and ECRI Guidelines Trust to minimize conflicts of interest (COIs) of its authors and staff (see Figure 2).

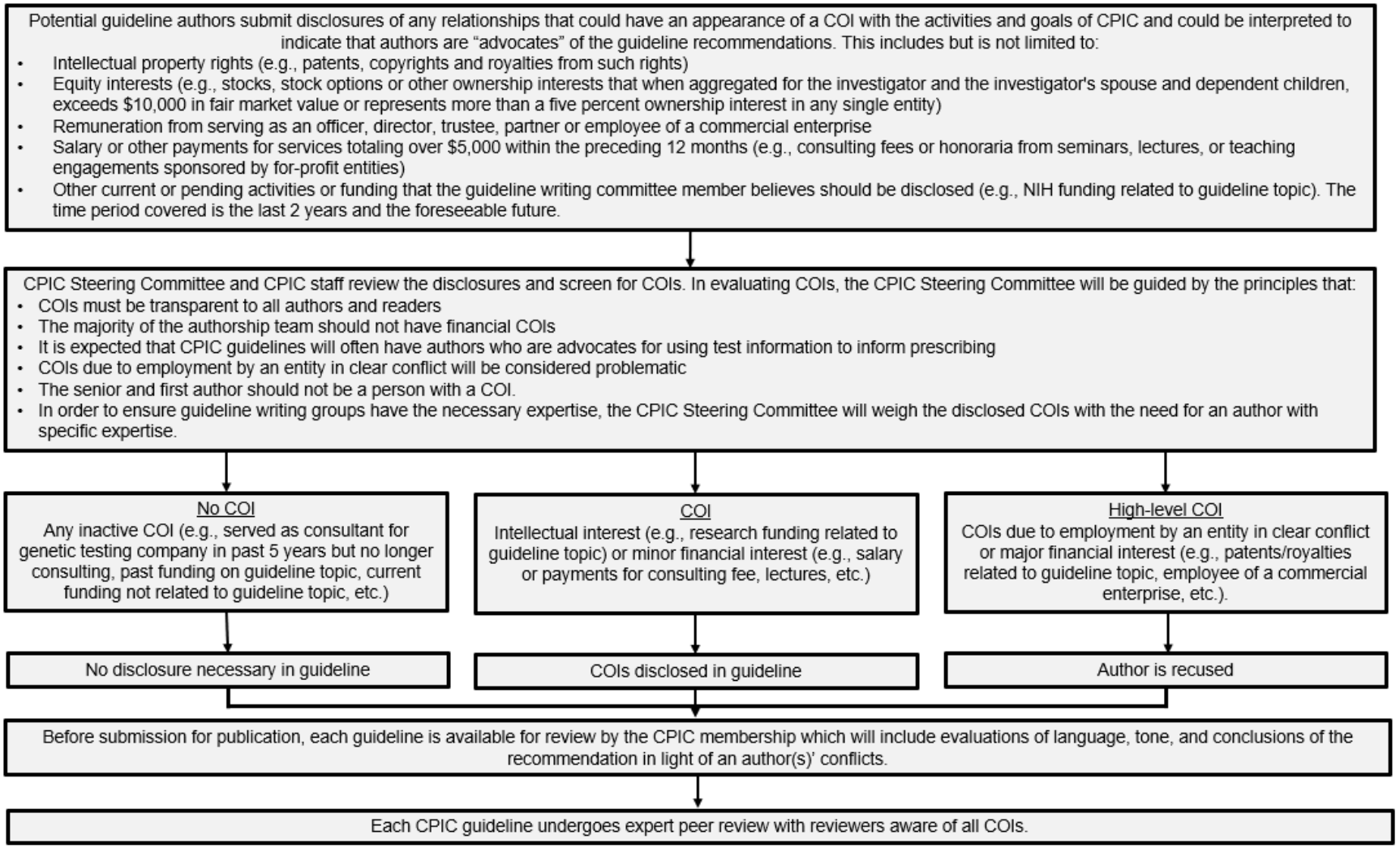
All potential authors must complete and sign the CPIC COI disclosure form. All authors should declare all current interests and activities potentially resulting in a COI by written disclosure to the CPIC Steering Committee and writing committee before the approval of the authorship plan. Potential authors must include all possible conflicts, including NIH funding, that could be interpreted to indicate that authors are "advocates" of the enclosed recommendations, as well as any sources of revenue from patents, stock ownership, etc. They must include spouses/family members in declarations. All COIs that could be interpreted to indicate that authors are "advocates" of the enclosed recommendations will be reported in guideline manuscript. Each author with an established or possible COI should explain how their relationship(s) could (or does not) influence the guideline development process or specific recommendations. Authors are responsible for reporting any new COIs that arise during the guideline development process to CPIC leadership. Any new COIs will be managed using the same procedures that were applied prior to the start of the guideline.

In evaluating COIs, the CPIC Steering Committee will be guided by the principles that:

a. COIs must be transparent to all authors and readers
b. Majority of the authorship team should not have financial COIs
c. It is expected that CPIC guidelines will often have authors who are advocates for using test information to inform prescribing
d. COIs due to employment by an entity in clear conflict will be considered problematic
e. The senior and first author should not be a person with a COI

In order to ensure guideline writing groups have the necessary expertise, the CPIC Steering Committee will weigh the disclosed COIs with the need for an author with specific expertise. Before submission for publication, each guideline will be reviewed by CPIC members without any conflicts to evaluate the language, tone, and conclusions of the recommendation in light of the author(s)' conflicts. CPIC members are not considered part of the authorship team, and CPIC members are not routinely evaluated for COIs. In addition, each CPIC guideline undergoes expert peer review, with all COIs documented for peer reviewers to evaluate.

Figure 2. COI Management



Preliminary Collation of Other Clinical Guidelines

CPIC staff will collate for preliminary review any existing relevant guidelines. These will include those from the Royal Dutch Pharmacists association – Pharmacogenetics Working Group (2), professional societies, legacy guidelines on NIH, and drug labelling recommendations from FDA and other major regulatory bodies.

Systematic Review of Evidence Linking Genotype to a Drug-Related Phenotype

Criteria for Compiling Evidence

- Search PubMed and/or OVID MEDLINE using the following format for the gene and drug(s) of interest
    - Keywords: (gene name) OR (gene symbol) AND (drug name)
- Evidence must be from published data only (no unpublished data should be included)
- Time period searched comprehensively must be specified
- Keywords and inclusion/exclusion criteria will be discussed and/or determined by authors on the first author call
    - Inclusion criteria
        - Includes genotype to phenotype associations, enzyme activity to phenotype associations, and any types of evidence the authors have determined are relevant to support or refute the recommendations (including alternative therapy)
            - It is permissible to individualize the types of evidence reviewed depending on the genes and drugs involved, but the criteria used to perform the literature search must be specified and must be accurately summarized in the Methods section for evidence review when writing up the findings
    - Exclusion criteria:
        - Unpublished data
        - Non-English manuscripts

- Review articles
    - High-quality reviews are permissible for "canonical" findings backed up by many years of evidence, but this approach must be summarized in the Methods section for evidence review
- Additional criteria based on guideline

Documenting Criteria for Compiling the Evidence

a. Number of papers and keywords for each PubMed or OVID MEDLINE search should be recorded in the guideline manuscript
b. Following application of predetermined inclusion and exclusion criteria, the number of papers included in the Prescribing Evidence Table should also be noted in the guideline manuscript
c. PRISMA diagram will be added to the supplement detailing inclusion/exclusion criteria
    a. The following links can be utilized to create the PRISMA diagram
        i. https://www.prisma-statement.org/prisma-2020-flow-diagram
        ii. https://www.eshackathon.org/software/PRISMA2020.html
d. Citations will go into the Prescribing Evidence Table in the supplement and underlies the key prescribing recommendations

Authors will cross-check for papers listed on PharmGKB for the drug of interest, where there may be annotations on the relevant literature. This may also aid in capturing all the identifiers (dbSNP rs number, additional common names, etc.) that are used for assessing relevant genomic variants.

Summarizing the Evidence

A working document to summarize the evidence for and against prescribing actionability will be made, requiring review by the expert authors. The summary of evidence working document should be an excel file that lists a relevant major finding (or finding from a single paper) on each row, and how the literature supports or refutes that finding, with an eye toward impact on prescribing recommendations. The key aspects of the papers as

determined by the author group should be noted (e.g., which variants measured, study size, study type, statistical significance, and key findings). The CPIC staff will create a working document that can be used to discuss the evidence with the author group. For access to the evidence table working document, please contact CPIC at contact@cpicpgx.org.

Evidence types included to summarize the evidence:

- Randomized trials with PGx-based dosing vs. conventional dosing*
- Clinical trials demonstrating drug effects linked to functional pharmacogenetic loci or enzyme activity
- Preclinical studies demonstrating drug effects linked to functional pharmacogenetic loci or enzyme activity
- Data relating to drug or drug metabolite pharmacokinetics or pharmacodynamics
- Case studies associating rare variants and drug effects (e.g. *G6PD* and rasburicase and *DPYD* and 5FU)
- In vitro or in vivo evidence that drug A is handled identically to drug B, with strong pharmacogenetic evidence linking the variation to drug B
- Evidence relating to the safety or efficacy of the alternative therapy (altered dosages or alternative drugs) to be included in prescribing recommendations

**Note: randomized, controlled trials comparing outcomes with genotype-guided dosing vs conventional dosing will be rare*

Scoring Individual Studies

The quality elements for individual studies can be assigned as to their compliance with the following criteria: yes, no, partially, unclear, or not relevant (adapted from ASCO guidelines development process (3)):

- Confounders and use of concomitant medications with possible drug interactions are reported and potential impact on the major findings are analyzed and reported

- Phenotype assignments (when comparing phenotype groups) are based on CPIC phenotype assignment or similar
- Reported data are based on steady-state kinetics where appropriate
- Sample size adequate to assess difference between genotype/phenotype groups, especially for negative findings
    - Negative findings from underpowered studies should be graded "weak"
- Adequate phenotyping or genotyping methods:
    - States all genetic variants screened
    - Alleles tested are adequate to determine "wild-type" genotype
    - Adequate phenotyping or genotyping method used
    - Appropriate attainment of samples
    - Describes how * alleles defined, if applicable
    - Clearly states which genotypes were found in the study
- Race and/or ancestry is discussed and appropriately considered
- Outcome definition clearly defined and measured
- Appropriate statistics performed

Rating how studies supports the major finding statement, including preclinical *in vitro* or *in vivo* (adapted from ASCO guideline development process (3)):

1. Determine if the study supports the major finding statement or does not support it
2. Qualify the statement (if needed) based on the quality elements listed above:
    - **Some study quality flaws**: Enough of the items in step 1 are rated "partially," "unclear," or "no" to introduce some uncertainty about the validity of the conclusions
    - **Major study quality flaws**: Enough of the items in step 1 are rated "partially," "unclear," or "no" to introduce serious uncertainty about the validity of the conclusions
    - **No qualification on statement is needed if** few items in step 1 are rated as "partially," "unclear," or "no"

3. There are six possible ratings:
    - Supports the statement
    - Supports the statement but with some quality flaws
    - Supports the statement but with major quality flaws
    - Does not support the statement
    - Does not support the statement but with some quality flaws
    - Does not support the statement but with major quality flaws

Scoring the Major Findings

Initially, a minimum of two authors or staff will independently evaluate the literature that supports or refutes a finding. These authors will be responsible for presenting studies and providing a level of evidence (high, moderate, or weak) for each major finding to all guideline authors and consensus will be reached for each major finding on a series of conference calls.

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 (3,4):

- **High:** Evidence includes consistent results from well-designed, well-conducted studies. “High confidence that the available evidence reflects the true magnitude and direction of the net effect and further research is very unlikely to change the magnitude or direction of this net effect.”
- **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. “Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.”
- **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. “Further research may change the magnitude and/or direction of the net effect.”

As shown in Figure 3, all authors will be responsible for reviewing the summary 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 the assignment of evidence must be sent in writing within 10 days after each summation. CPIC staff are responsible for seeking additional independent review for any serious discordances: for example, if the same evidence is graded "High" by one and graded "Weak" by the other reviewer. Multiple iterations of evidence review among the authors may be necessary in order to achieve consensus, with at least 70% of authors agreeing on the final consensus score for a finding.

In the rare instance of a finding for which consensus cannot be reached on the strength of the evidence despite multiple rounds of review will be marked as "consensus on strength of finding not reached," and will not be considered as a finding that can influence the authors' prescribing recommendations.

Figure 3. Initial Evidence Review Process

The findings are summarized in an Evidence Table that is available in the supplement (see Figure 4). The expert authors' interpretation of this evidence is used for their deliberations in developing the Table of Prescribing Recommendations.

Figure 4. Example Evidence Table

Supplemental Table S5. Evidence linking genotype with phenotype			
Type of experimental model (in vitro, in vivo preclinical, or clinical)	**Major findings**	**References**	**Level of evidence***
In vitro	MP's catabolism to methylmercaptopurine absent in human erythrocytes, lymphocytes, liver, and kidneys from *TPMT* homozygous deficient individuals	**(28, 113-115)**	High
In vitro	TG's catabolism to methylthioguanine	**(116)**	High
In vitro	Mechanisms of functional inactivation for *TPMT* *2, *3A, *3B, *3C, *4 demonstrated by expression of specific variant alleles	**(31, 117, 118)**	High
In vitro	Heterologous expression of *TPMT* catabolizes mercaptopurine to methylmercaptopurine, thioguanine to methylthioguanine, and TIMP to methylTIMP	**(119, 120)**	High

Prescribing Recommendations Table

The primary goal of a CPIC guideline is to provide prescribing recommendations based on genotypic variability. The recommendations are briefly described and summarized in a table (usually Table 2) in the manuscript. Figures can be used if algorithms are needed. At least one complete gene/drug pair should be included in the published manuscript; when multiple drugs or multiple genes are included, prescribing recommendation tables may be included in the supplementary material. The authors should consider listing dosages (per kg or per m^2) for those guidelines that focus on genetic-directed changes in dosing; genetics may not play a role in dosing if "normal" dosages are too high or too low for genetics to have an influence. Language should be used that would not prohibit using the test results in a poorly studied population (e.g. pediatrics, geriatrics, racial minorities) unless there is a specific reason to exclude that population. For example, "at the time of this writing there are no/sparse data available on this gene's effects on this drug's response in pediatric patient populations, although there is no reason to suspect that gene's

polymorphisms will affect this drug's metabolism differently in children compared to adults" is preferred to "there are no recommendations in pediatrics." If the authors recommend that prescribing actions only be limited to certain racial or ethnic populations, they must summarize the evidence that supports population-specific prescribing. The assumption is that allele frequencies vary among populations, but the prescribing recommendations driven by genotype apply to all populations unless there are explicit data otherwise. If there are any gender-specific considerations linked to the pharmacogenetic prescribing recommendations, they should be included (e.g., G6PD).

For every drug and every gene included in a CPIC guideline, recommendations must be provided for each phenotype group and for each drug. To assign strength to a prescribing recommendation, CPIC uses a transparent four category system for rating recommendations that was adopted with slight modification from the rating scale for evidence-based recommendations on the use of antiretroviral agents (5). Therapeutic recommendations are assigned to one of 4 grades:

1. **Strong** recommendation for the statement (CPIC Level A)**:** "The evidence is high quality, and the desirable effects clearly outweigh the undesirable effects."
2. **Moderate** recommendation for the statement (CPIC Level A): "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
3. **Optional** recommendation for the statement (CPIC Level B): 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.
4. **No recommendation** (CPIC Level C): There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

CPIC recommendations should always include an assessment of their likely usefulness in pediatric patients as described above.

The phenotype, diplotype, drug, and gene terms in the recommendation table should use standardized terminology that facilitates machine-readability and that can be repurposed for other guidelines when possible. CPIC has standardized phenotype and allele function terms for some genes, and additional standardizations are ongoing. Expert authors should also designate prescribing recommendations for those with uncertain or "possible" diplotypes.

Example of the Prescribing Recommendations Table can be found in each CPIC guideline (see Figure 5):

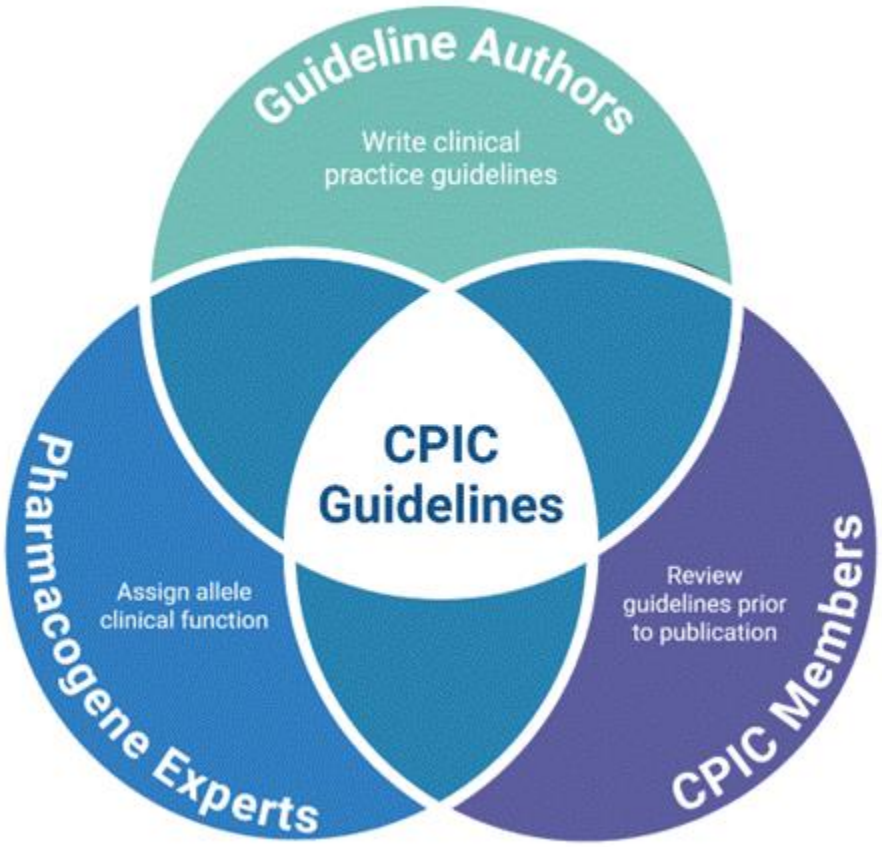
Figure 5. Example Prescribing Recommendations Table

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[e]
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.
[a]The online *CYP2B6* Frequency Table provides phenotype frequencies for major race/ethnic groups, and the online *CYP2B6* Diplotype-Phenotype Table provides a complete list of possible diplotypes and phenotype assignments. [b]Rating scheme described in the Supplementary Material online. [c]If therapeutic drug monitoring is available and a decreased efavirenz dose is prescribed, consider obtaining steady-state plasma efavirenz concentrations to ensure concentrations are in the suggested therapeutic range (~ 1–4 μg/mL). [d]To prescribe efavirenz at a decreased dose of 400 mg/day or 200 mg/day in a multidrug regimen may require prescribing more than one pill once daily. If so, the provider should weigh the potential benefit of reduced dose against the potential detrimental impact of increased pill number. [e]The ENCORE study showed that in treatment-naive patients randomized to initiate efavirenz-based regimens (combined with tenofovir and emtricitabine), 400 mg/day was noninferior to 600 mg/day regardless of *CYP2B6* genotype.[32]

Framework for Assigning Pharmacogene Function and Diplotype to Phenotype



Assignment of Allele Function

The CPIC PGx Curation Expert Panel (PCEP) is responsible for determining the clinical function of alleles and converting diplotypes into corresponding phenotypes. The CPIC guideline writing committee has the opportunity to review and provide feedback on the work completed by PCEP. The primary goal of CPIC's PCEP is to assign an allele clinical functional status that leads to an interpretable phenotype assignment. Allele clinical function assignments are used to inform pharmacogene variants' functions across

applicable CPIC guidelines. In this manner, allele clinical function assignments are drug/substrate agnostic. Essentially, these assertions of function are used to determine how diplotypes are translated into pharmacogenetic phenotypes. Furthermore, assignment of allele clinical function and strength of evidence determines which diplotypes drive actionable prescribing decisions. Indeed, allele clinical function assignments are used to create a mapping table which determines how different combinations of alleles give rise to diplotypes with specifically assigned phenotypes. Details of this expert panel can be found by visiting the CPIC Allele Function and Phenotype website along with their SOP - Assigning Allele Function Standard Operating Procedure (SOP). More information regarding gene-specific definitions can be found under "Implementation Resource" section below.

Translating Genotype/Diplotype to Phenotype Table

Based on the work from the PCEP, each CPIC guideline should contain a Table (see Figure 6) indicating the conventions used for assigning phenotype based on diplotype (e.g. one normal plus one no function allele = intermediate metabolizer), containing a few examples. The Stanford Pgx group will prepare a detailed and comprehensive table of Diplotype-to-Phenotype assignments that accompany each CPIC guideline, and authors are responsible for reviewing this content, as it is these phenotypes that will be linked to prescribing recommendations. Phenotype terms should be standardized as shown in Figure 7 (6).

Figure 6. Genotype/Diplotype to Phenotype Table

Table 1. Assignment of likely _____ [gene] phenotypes based on *genotypes*		
Likely Phenotype	**Genotypes**	**Examples of Diplotypes**
Ultrarapid Metabolizer	An individual carrying two increased function alleles *(*17),* or more than 2 normal function alleles	**17/*17*
Rapid Metabolizer	An individual carrying one normal function allele (**1*)	**1/*17*

	and one increased function allele (**17*)	
Normal Metabolizer	An individual carrying two normal function alleles (**1*)	**1/*1*
Intermediate Metabolizer	An individual carrying 1 normal function allele (**1*) plus one no function allele (**2, *3, ___*)	**1/*2, *1/*3,*
Poor Metabolizer	An individual carrying 2 no function alleles (**2, *3, *___, ___*)	**2/*2, *3/*3*
Indeterminate	An individual carrying diplotype combinations containing uncertain function alleles.	**1/*14, *14/*29*

Table 7. Standardized Phenotype Terms

Term/Gene Category	**Final Term***	**Functional Definition**	**Genetic Definition in Relation to Allele Clinical Function**	**Example Diplotypes**
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 ultra-rapid metabolizers	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
	Normal Metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1* *CYP2D6*1/*2*

	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* *CYP2D6*10/*41* *TPMT*1/*2*
	Possible Intermediate Metabolizer#	At least decreased enzyme activity (activity between normal and poor metabolizer) as this individual should be treated with "at least" the same precautions as would apply to an intermediate metabolizer	Combinations of one uncertain/unknown function allele and decreased and/or no function alleles	*TPMT*2/*8* *CYP3A5*1/*2*
	Poor Metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2* *CYP2D6*4/*5* *TPMT*2/*3A*
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*
	Possible Decreased Function#	At least decreased transporter activity (activity	Combinations of one uncertain/unknown	No examples to date

		between normal and poor metabolizer) as this individual should be treated with "at least" the same precautions as would apply to and individual with decreased function	function allele and decreased and/or no function alleles	
	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	

*All terms should begin with the gene name (e.g., CYP2D6 Poor metabolizer, TPMT Normal metabolizer, SLCO1B1 Decreased Function).
#The term "possible" is used to indicate that the patient is likely to have a diplotype/phenotype that is actionable, at least there is some altered function from normal. The presence of an uncertain function allele might modify the phenotype to be even more severe (e.g., the patient is "at least" an intermediate metabolizer but might even be a poor metabolizer) than the presence of the one allele that is known to be no function or decreased function. Thus, clinicians may want to be warned about the high-risk status of the patient, even though the level of risk is not clear because of the presence of an uncertain function allele.

Disclaimer Must be Added to All CPIC Guidelines

Clinical Pharmacogenetics Implementation Consortium (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, as well as 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 variation 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 the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

Conflict of Interest Section Must be Added to All Guidelines

This includes all possible conflicts, including NIH funding, that could be interpreted to indicate that authors are “advocates” of the enclosed recommendations, as well as any sources of revenue from patents, stock ownership, etc. Includes spouse/family member declarations. See additional details about managing COI under “Management of Conflicts of Interest”.

Table Formats

All tables are meant to support each guideline, to provide visual representations of key data, and must follow standardized formats so that they can be used to populate the CPIC database; data can be downloaded from the CPIC database to accommodate formatting needs of users. Data will be version-controlled so that users can document the provenance of downloaded data. Any changes to the tables made after the publication of each CPIC guideline must be approved by guideline authors.

Frequency Tables

Frequency tables are provided for alleles, diplotypes, and phenotypes. Sources for frequencies include published literature searches, specialized variant frequency websites such as that for HLA alleles (www.allelefrequencies.net), Alfred, HapMap, ExAC etc. Detailed methodology for summarizing allele, diplotype, and phenotype frequency by race/ancestry/geographic groups are included with each guideline. Such frequencies are highly dependent upon possible biases in sampling and in the choice of alleles for testing in each biogeographical group. Guidelines follow biogeographical groups as set out in when possible (7).

Implementation Resources

CPIC PGx Gene-Specific Information Tables

CPIC has developed gene specific information tables that contain general resource files for a variety of genes. The files can be found on the CPIC guideline page (e.g., https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/) and are also located at https://www.pharmgkb.org/page/pgxGeneRef. Below is a list of the files for each gene along with the definition of that file:

- Allele Definition Table
    - Information about what variants define star (*) or named alleles
    - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides rsIDs, if available
- Allele Functionality Table
    - Allele function assignments using CPIC standardized terms
    - References for the allele function
- Phenotype Table
    - Mapping allele function combinations to phenotypes
- Diplotype-Phenotype Table
    - Mapping of each diplotype to phenotype
- Example CDS Table
    - Mapping of possible phenotype to EHR priority result notation and consultation text
- Workflow Diagram
    - Possible implementation workflow diagram
- Frequency Table
    - Calculated allele frequency by PharmGKB biogeographical groups based on frequencies reported by references. Further details about the biogeographical grouping system can be found here or publication by Huddart *et a* (7)

- Gene Resource Mappings
    - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

Clinical Decision Support (CDS) Workflow Figures and Translation Tables

A CPIC staff member or author(s) from the guideline writing committee, with expertise in clinical implementation or the specific guideline topic, will collaborate with the CPIC informatics working group to develop CDS workflow diagrams and translation tables. These will link diplotypes for each gene to machine-readable, EHR-compatible diplotype-based phenotypes and provide sample wording for clinical recommendations, including specific drug prescribing actions and guidance for integrating CDS workflows into any EHR system. All tables and figures relevant for a guideline will be linked to the guideline pages on cpicpgx.org. The following CDS workflow resources can be found in each guideline:

- Implementation workflow
- Gene consult
- Pre- and post- test alerts and flowchart

Acknowledgements

Acknowledgements are added for useful advice or contributions not reflected in authorship.

Review Process

After all the tables and evidence have been thoroughly reviewed by the authors and other CPIC staff, the manuscript draft will be reviewed by CPIC leadership (PIs and directors) and all CPIC members. Feedback is systematically gathered and integrated at the discretion of the guideline authors.

The manuscript will be submitted for publication, at which time it will undergo external anonymous peer review. It will be modified until accepted for publication. Any modifications not acceptable to the guideline authors or CPIC staff will be discussed with the CPIC Steering Committee for resolution.

Publishing and Posting

Publishing

The corresponding author's email may include the senior author's academic email address but must include contact@cpicpgx.org. It is CPIC staff's responsibility to notify the senior author of any important correspondence regarding the published guideline at any time during or after publication, and to ensure any errors are corrected (see "Guideline Updates").

Posting

CPIC website:

The CPIC director will create or update the guideline pages on cpicpgx.org.

PubMed Central:

The publishers of the journal with first right of refusal for publication (i.e., Wiley) will make immediate (no embargo period) provision of the manuscript to PubMed Central as part of their regular process for the CPIC guidelines published in in their journal.

It is the responsibility of the CPIC director to notify the NIH of accepted CPIC guidelines: Chris Kelly (chkelly@ncbi.nlm.nih.gov) and Adriana Malheiro (adriana.malheiro@nih.gov).

The CPIC director ensures that CPIC guidelines are indexed as "Practice Guideline" in PubMed.

Genetic Testing Registry (GTR):

For each published guideline, the Stanford PGx Group prepares a short structured descriptive summary ("blurb") for the GTR website, which will be reviewed by CPIC leadership prior to submission to the GTR. The One-Point-of-Contact-with-GTR (OPCG; Stanford co-director) will coordinate the preparation, review, and submission of GTR summaries.

Guideline Updates

CPIC guidelines are regularly updated to reflect feedback, evolving best practices, and any relevant updates. CPIC reviews and revises guidelines at least every 5 to 7 years to ensure they remain current and aligned with the latest developments. Guidelines are updated sooner than every 5 to 7 years if new evidence impacts prescribing recommendations. On an ongoing basis, but at least every 2 years, CPIC will document the date last reviewed on the CPIC site. PharmGKB will review FDA label changes affecting CPIC guideline drugs at least every 6 months (in accordance with the FDA Tables) and notify the CPIC director if changes are found.

Emergent information that should update guidelines will be posted on the CPIC website, after approval of guideline authors, on an as needed basis, without waiting for updated publication.

Minor updates that do not impact the prescribing recommendations, such as those that involve updates to alleles, allele frequency, or changes in the diplotype-to-phenotype tables may be updated online only without a publication update; however, there must be approval of the guideline author group.

CPIC continuously updates guidelines based on feedback received from patients, patient advocates or the general public. Questions or comments about the guidelines can be sent to contact@cpicpgx.org.

Senior authors of the prior guideline versions will be notified of updates as per the Authorship on CPIC guidelines.

Retiring a Guideline

CPIC members or users may nominate guidelines to be retired. Criteria include a change in practice, drug usage, or drug availability that change a guideline to extremely low usage, such that the investment to keep the guideline on a regular review schedule cannot be justified. Such retirements will be announced on the CPIC website and must be approved by CPIC's Steering Committee. Each retired guideline page will have a prominent notation indicating its date of retirement, with a disclaimer that the content has not been reviewed

or updated since that date. The guideline will be marked as follows: "Retired: The evidence for this guideline has not been reviewed since ___. This guideline should be used for historical purposes only."

Additional Guideline Writing Resources

The following two documents should be utilized as templates when preparing the guideline manuscript:

1) Guideline Template (Appendix A)
2) Guideline Supplement Template (Appendix B)

DATABASE AND API

CPIC data are available in structured formats via the database (DB) and the API. This data comes from the clinical practice guidelines sourced from CPIC guideline publications and related sources. Read the cpic-data documentation to get more information about how to use the API and DB. Questions about the DB or API can be submitted via GitHub issues or to the CPIC contact email address.

- DB & API Documentation @ GitHub
- DB Releases @ GitHub (or jump directly to the latest release)
- Submit a DB/API bug or issue @ GitHub

REFERENCES

(1) Caudle, K.E. *et al.* Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab* **15**, 209-17 (2014).

(2) Swen, J.J. *et al.* Pharmacogenetics: from bench to byte. *Clin Pharmacol Ther* **83**, 781-7 (2008).

(3) *American Society of Clinical Oncology (ASCO)*. <https://ascopubs.org/ascopubs/asco-guideline-methodology-manual> (2020).

(4) Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* 2010.

(5) *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV: Introduction*. <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/introduction#:~:text=Basis%20for%20Recommendations,(see%20Table%202%20below)>. Accessed March 28 2025.

(6) Caudle, K.E. *et al.* Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genet Med* **19**, 215-23 (2017).

(7) Huddart, R. *et al.* Standardized Biogeographic Grouping System for Annotating Populations in Pharmacogenetic Research. *Clin Pharmacol Ther* **105**, 1256-62 (2019).

Guideline Manuscript Template (Appendix A)

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for [gene(s)] and [drug/class]

Authors

[1]Affiliations

Corresponding Author:

_____; cpic@pharmgkb.org

Word count (updated 03/25/2025):

Abstract (250 limit):

Text (4,000 limit):

References (50 limit):

Figures/tables (7 limit):

Keywords:

Conflicts of Interest:

Insert authors conflicts. All other authors declared no competing interests for this work.

Funding:

This work was funded by the National Institutes of Health (NIH) for CPIC (R24GM115264 and U24HG010135) and PharmGKB (U24HG010615). Additional grant funding includes *insert other funding, if applicable.*

ABSTRACT

INTRODUCTION

Introduction generally has a brief overview of the guideline with drug/drug class and gene(s) followed by the example wording below.

Example wording from previous guidelines (copy/paste and edit as necessary):

The purpose of this guideline is to provide clinicians with information that facilitates the interpretation of clinical genotype test results to guide *insert drug or drug class* prescribing and to discuss the evidence linking genetics to *insert drug or drug class* exposure and response. Detailed guidelines for the use of *insert drug or drug class*, reflections on the cost-effectiveness of genotyping, or whether to order a genotype test prior to *insert drug or drug class* prescribing are beyond the scope of this document. Clinical Pharmacogenetics Implementation Consortium (CPIC®) guidelines are periodically updated at www.cpicpgx.org/guidelines/.

FOCUSED LITERATURE REVIEW

Example wording from previous guidelines (copy/paste and edit as necessary):

A systematic literature review focused on associations between insert gene(s) genotypes and insert drug/drug class was conducted (details in **Supplemental Material**). The literature search included variations of the drug class name as well as the following specific insert drug(s) (if applicable) names: _____. The evidence is summarized in **Tables SX-SX** *(update with table numbers)*.

GENE(S): *Insert gene(s) for guideline*

Background

Includes brief background about the gene(s) and their function. If available, this section refers to PharmGKB VIP or PharmVar for more details.

Example wording from previous guidelines (copy/paste and edit as necessary):

CYPXXX. *CYPXXX* is a highly polymorphic gene (insert reference), with over insert number haplotypes (or star (*) alleles) defined by the Pharmacogene Variation (PharmVar) Consortium to date (insert PharmVar reference) (see ***CYPXXX*** **Allele Definition Table** online (insert reference(s)). The frequencies of these star alleles differ significantly across ancestrally diverse populations (see ***CYPXXX*** **Allele Frequency Table** online (insert reference(s)). Alleles are categorized into predicted enzyme function groups insert allele enzyme function information. Clinical allele function, as described in the ***CYPXX*** **Allele Functionality Table**, was determined based on reported *in vitro* and/or *in vivo* data when available (insert reference(s)).

Genetic test interpretation

This section provides an overview of systems for allele or variant assignments and interpretation. Links are provided to definitive websites (e.g. PharmVar) for definitions/nomenclature of variants and alleles, and examples of allele nomenclature and definitions are provided in published guideline (genotype to phenotype table), with comprehensive definitions of alleles provided in the supplementary material.

Example wording from previous guidelines (copy/paste and edit as necessary; reference previous guideline if other criteria apply like activity score or rs number):

Clinical laboratories typically interrogate CYPXXX variants with known functional consequences that are of appreciable frequencies in the general population and assign genotype using star (*) allele nomenclature *(insert references)*. Each star (*) allele (or haplotype) represents a specific combination of variants identified by the test for each gene. The **CYPXXX Allele Functionality Tables** provide a list of alleles and their functional status determined based on reported *in vitro* and/or *in vivo* data when available *(insert references)*. Genetic test results are commonly reported as the combination of the inherited maternal and paternal star (*) alleles, which is referred to as a diplotype (e.g., *insert examples*) *(insert references)*. The predicted phenotype (**Table 1**) is influenced by the expected function of each reported allele in the diplotype. The **Supplementary Material S1**

(Genetic Test Interpretation Section) contains additional information regarding CYPXXX genetic test interpretation and phenotype assignment.

Available genetic test options

(Copy and paste into manuscript as is):

See the **Supplemental Material** and the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options.

Incidental findings

Other associations (e.g. disease risk or drugs not captured in the guideline) for the relevant gene(s) may be discussed. These may be disease associations unrelated to medication use, or pharmacogenetic associations seen with other drugs not included in the guideline. Only associations with high penetrance that would likely require clinical disclosure to patients should be discussed.

Reference other guidelines for wording help, as needed.

Other considerations

Issues critical about the gene that do not easily fit into other sections are summarized.

DRUGS: ***Enter Drug Class or Drug(s)***

Background

This includes a brief discussion of the drug, and if available, refer to PharmGKB pathway for more detail. A diagram/figure depicting drug metabolism, transport or mechanism of action may be included in the main text or in the supplement. References are provided to the accompanying Drug Resource Mapping tables (supplement) that provide RxNorm, DrugBank, ATC, and PharmGKB identifiers.

The guideline should focus on genetic impact on the drug, rather than a comprehensive review of the drug's use, drug interactions, and other non-genetic considerations.

An overview of the conclusions based on the evidence linking genotypic with phenotypic variability is provided, with links to the detailed graded evidence review summarized in the supplement. This section should verbally summarize the basis for most of the prescribing recommendations.

Linking genetic variability to variability in drug-related phenotypes

This section should describe any factors that link genetic variability with drug variability. This may include, but not limited to variability in pharmacokinetics, response to therapy, adverse effects, etc.

Therapeutic recommendations

Describe evidence as it relates to genotype with each drug, if applicable. Generally, this is describing at a minimum Table 2 in the manuscript.

Additionally, each guideline should mention pediatrics even if there is not enough data to provide recommendations. The addition of biogeographic groups is optional if there is enough data.

Pediatrics.

Include pediatric recommendations—even if just to acknowledge not enough data are available to make a recommendation. Use language that would not prohibit reimbursement or restrict access of the genetic test in this population (e.g., at the time of this writing there are no/sparse data available on this gene's effects on this drug's response in pediatric patient populations, although there is no reason to suspect that gene's polymorphisms will affect this drug's metabolism differently in children compared to adults).

Biogeographic groups.

Describes population(s) primarily studied for the specific gene(s). If specific populations are not studied or minimally studied can make a statement similar to this, "Although studies including individuals from other ancestry groups are needed, there is no reason to

suspect that the effects of CYPXXX genetic variation on drug/drug class exposure or treatment outcomes will not apply across biogeographic groups."

Recommendations for incidental findings

Example wording from previous guidelines (copy/paste and edit as necessary):

No recommendations for incidental findings have been provided given the lack of consistent evidence supporting associations between any of the assessed variants and inherited diseases or conditions independent of drug metabolism and response. For recommendations pertaining to other drugs potentially affected by CYPXXX variation, visit https://cpicpgx.org/guidelines/ to review the applicable CPIC guidelines.

Other considerations

This section may include, but is not limited to (this section may also end up in supplement depending on word count of manuscript):

- *Patient already receiving current therapy and recommended adjustments, if applicable*
- *Drug-drug interactions and phenoconversion*

Implementation of this guideline.

Copy/paste into manuscript and edit reference(s):

The guideline supplement and CPIC website (insert reference) contain resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* in the **Supplemental Material**).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

A brief discussion of the consequences, toxicities or adverse drug reactions that may be avoided or caused by PGx dosing is included. This is also a section to discuss possible risks from incidental findings, and risks from use of alternative drugs and dosing.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

This section allows discussion of predictive limitations of the test, which may include a mention of non-genetic factors affecting drug response for this drug.

The CPIC guideline, however, is not meant to be a comprehensive resource for drug prescribing, but rather a guideline of how to use genetic information to inform prescribing.

Analyses of cost effectiveness are not in scope; CPIC guidelines are meant to guide prescribers how to use genetic information, not whether they should order a test.

Copy/paste into manuscript using similar wording:

One of the limitations inherent in a genotype-only test is that very rare or *de novo* variants will not generally be included in any commercially available genotyping test.

ACKNOWLEDGEMENTS

(Copy and paste as is):

We acknowledge the critical input of Dr. Mary Relling and members of the Clinical Pharmacogenetics Implementation Consortium (CPIC), funded by the National Institutes of Health. CPIC members are listed here: https://cpicpgx.org/members/.

DISCLAIMER

(Copy and paste into manuscript as is):

Clinical Pharmacogenetics Implementation Consortium (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, as well as 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 variation 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 the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

REFERENCES

Insert references

TABLE 1. Assignment of likely metabolism phenotypes based on CYPXXX diplotypes

Edit table as necessary by including activity score, activity score range, etc, if applicable.

Likely phenotype	Genotypes	Examples of diplotypes

TABLE 2. Dosing recommendations for drug based on CYPXXX phenotype

Edit table as necessary by including activity score, considerations, etc, if applicable.

CYPXXX Phenotype	Implications	Therapeutic recommendation	Classification of recommendations[a]

[a]Rating scheme described in Supplemental Materials

Guideline Supplement Template (Appendix B)

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for [gene(s)] and [drug/class]

Authors

[1]Affiliations

Corresponding Author:

_____; cpic@pharmgkb.org

GUIDELINE UPDATES

Example wording from previous guidelines (copy/paste and edit):

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for insert genotype(s) genotypes and the dosing of insert drug(s)/drug class is published in full on http://www.pharmgkb.org and https://cpicpgx.org/guidelines/. Relevant information will be reviewed periodically and updated guidelines published online.

LITERATURE REVIEW

Following application of predetermined inclusion and exclusion criteria, the number of papers included in the Prescribing Evidence Table should also be noted in the guideline supplement. Citations will go into the Evidence Table in the supplement and underlies the key prescribing recommendations. Additionally, a PRISMA diagram will be added to the supplement detailing the inclusion/exclusion criteria.

Example wording from previous guideline (copy/paste and edit):

The PubMed® database (1966 to *insert date*) was search for the following keywords: *insert keywords*. The search was limited to studies conducted in humans or relevant experimental models and written in the English language. Review articles and studies only published as abstracts were excluded. Using these search terms, *insert number*

publications were identified. Inclusion criteria included *insert inclusion criteria*. Following application of the inclusion criteria, *insert number* publications were reviewed and included in the Prescribing Evidence table (**Table *SX***).

> *The following links can be utilized to create a PRISMA diagram for each supplement:*
> https://www.prisma-statement.org/prisma-2020-flow-diagram
> https://www.eshackathon.org/software/PRISMA2020.html

GENE: CYPXXX

Genetic Test Interpretation

Example wording from previous guideline (copy/paste and edit):

Reference Beta-blocker guideline if dealing with CYP2D6 to add additional language about activity score and copy number variants.

CYPXXX genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis. Haplotypes are described using star (*) allele nomenclature to allow for the standardization of genetic polymorphism annotation (insert reference: Robarge, J.D., Li, L., Desta, Z., Nguyen, A. & Flockhart, D.A. The star-allele nomenclature: retooling for translational genomics. Clin Pharmacol Ther 82, 244-8 (2007)). A complete list of CYPXXX star (*) alleles along with the genetic variants that define each star (*) allele is available at *insert PharmVar hyperlink and reference*, and the **CYPXXX Allele Definition Table** may be found at *insert CPIC guideline page hyperlink*. Knowing which SNPs or other genetic variants a particular pharmacogenomic test interrogates is important because the inclusion or exclusion of certain variants in the test could affect the reported star allele result.

Clinical laboratories typically report a diplotype (often referred to as a genotype), which is the summary of inherited maternal and paternal star alleles (e.g., CYPXXX*X/*X, where an

individual inherited a *X allele and a *X allele). Commonly reported CYPXXX star alleles are categorized into function groups (e.g., increased function, normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme (**CYPXXX Allele Functionality Table**) (*insert reference for CPIC guideline and PharmGKB Gene-specific Information Tables for CYPXXX*). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype.

Available Genetic Test Options

Example wording from previous guideline (copy/paste and edit):

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by providers and is available at: http://www.ncbi.nlm.nih.gov/gtr. Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (*insert reference*: Kalman, L.V. et al. Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. Clin Pharmacol Ther 99, 172-85 (2016)) as well as the American College of Medical Genetics and Genomics (ACMG) (*insert reference*: Tayeh, M.K. et al. Clinical pharmacogenomic testing and reporting: A technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med 24, 759-68 (2022)). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (**Allele Definition Table**, **Allele Functionality Table**, and **Allele Frequency Table**) may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles (*insert reference*: CPIC guideline and PharmGKB Gene-Specific Information Tables for CYPXXX). Further, the Association for Molecular Pathology (AMP) has published recommendations for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for CYPXXX (*insert reference*).

Depending on manuscript word count, you may find additional sections in the supplemental such as “Other Considerations” and “Incidental Findings”.

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

Example wording from previous guideline (copy/paste and edit):

The evidence summarized in Tables SX-SX is graded on a scale of high, moderate, and weak based upon the level of evidence:

> **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 the indirect nature of the evidence.
>
> **Weak:** Evidence is insufficient to assess the effects on health outcomes because of the limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

STRENGTH OF RECOMMENDATIONS

Copy and paste and edit gene information:

CPIC’s therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type/reference or non-reference CYPXXX, *in vitro* CYPXXX enzyme activity from tissues isolated from individuals of known CYPXXX genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for

recommendations adopted from the rating scale for evidence-based guidelines on the use of antiretroviral agents (*insert reference:* Guidelines for the use of antiretroviral agents in adults and adolescents with HIV: Introduction. U.S. Department of Health and Human Services. Accessed March 28, 2025. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/introduction#:~:text=Basis%20for%20Recommendations,(see%20Table%202%20below):

- **Strong** recommendation for the statement (CPIC Level A): The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Moderate** recommendation for the statement (CPIC Level A)**:** There is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement (CPIC Level B)**:** 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** (CPIC Level C): There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Example wording from previous guidelines (copy/paste and edit as necessary):

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenomics at the point of care (*insert references: Hicks, J.K., Dunnenberger, H.M., Gumpper, K.F., Haidar, C.E. & Hoffman, J.M. Integrating pharmacogenomics into electronic health records with clinical decision support. Am J Health Syst Pharm 73, 1967-76 (2016), Hoffman, J.M. et al. Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics*

Implementation Consortium (CPIC). J Am Med Inform Assoc 23, 796-801 (2016), Liu, M. et al. A Tutorial for Pharmacogenomics Implementation Through End-to-End Clinical Decision Support Based on Ten Years of Experience from PREDICT. Clin Pharmacol Ther 109, 101-15 (2021)). See https://cpicpgx.org/guidelines/cpic-guideline-for-XXX/ (*insert appropriate hyperlink*) for resources to support the adoption of CPIC guidelines within an EHR (*insert CPIC guideline reference and* Hoffman, J.M. et al. Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC). J Am Med Inform Assoc 23, 796-801 (2016)). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating CYPXXX genotype results in an EHR to guide insert drug(s)/drug class (*insert CPIC guideline reference)* therapy.

Effective incorporation of pharmacogenomic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenomic test results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR. To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted drug metabolism phenotype (**Table 1**, **main manuscript; CYPXXX Diplotype to Phenotype Table**) (*insert CPIC guideline reference and* PharmGKB Gene-Specific Information Tables for CYPXXX*)*. Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient's summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Insert drug(s)/drug class Pre- and Post-Test Alerts and Flow Chart**, for example, CDS alerts; https://cpicpgx.org/guidelines/cpic-guideline-for-XXX/ *(insert updated hyperlink for CPIC guideline) (insert CPIC guideline reference)*.

Because pharmacogenomic test results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible

independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include complete diplotype to phenotype translation tables, diagram(s) that illustrate how CYPXXX pharmacogenomic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see https://cpicpgx.org/guidelines/cpic-guideline-for-XXX/) *(insert updated hyperlink for CPIC guideline) (insert CPIC guideline reference and Caudle, K.E. et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med 19, 215-23 (2017)*.

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (see https://cpicpgx.org/guidelines/cpic-guideline-for-XXX/ *(insert updated hyperlink for CPIC guideline) (insert CPIC guideline reference)*.

CONFLICT OF INTEREST (COI)

Detailed information about COI should be provided in the supplement to be transparent.

TABLE S1. EVIDENCE LINKING *CYPXXX* TO INSERT DRUG/DRUG CLASS PHENOTYPE

Type of Experiment	Major Finding	Reference(s)	Level of Evidence

There may be additional tables and figures in the supplement. These may include, but are not limited to:

- *Pharmacological properties of a drug class for the guideline*
- *PharmGKB pathways*

REFERENCES

Insert references