Evidence and resources to implement Pharmacogenetic Knowledge for Precision Medicine

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Abstract

Purpose—Implementation of pharmacogenetics into clinical practice has been relatively slow despite substantial scientific progress over the last decade. One barrier that inhibits uptake of pharmacogenetics into routine clinical practice is the lack of knowledge of how to translate a genetic test into a clinical action based on current evidence. The purpose of this paper is to describe the current state of pharmacogenetic evidence and evidence-based resources that facilitate the uptake of pharmacogenetics into clinical practice.

Summary—Controversy exists over the required evidence threshold needed for routine clinical implementation of pharmacogenetics. Large randomized controlled trials are not clinically feasible or necessary for many pharmacogenetic applications. Online resources exist like the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledgebase (PharmGKB) that provide freely available, evidence-based resources that facilitate the translation of genetic laboratory test results into actionable prescribing recommendations for specific drugs.

Conclusion—Resources provided by organizations such as CPIC and PharmGKB that use standardized approaches to evaluate the literature and provide clinical guidance are essential for the implementation of pharmacogenetics into routine clinical practice.

Introduction

The implementation of pharmacogenetic knowledge from the bench to the bedside has been relatively slow despite a growing body of evidence that supports using select pharmacogenetic test results to optimize medication outcomes.[1] Controversy over the required level of evidence to use pharmacogenetic test results for medication selection and dosing is one barrier that inhibits the routine application of pharmacogenetics to patient care. Another barrier is the lack of knowledge of how to translate a genetic test into a clinical action.[2] Resources are available that provide evidence-based gene-drug recommendations. Here we describe the current state of pharmacogenetic evidence and evidence-based resources that facilitate the uptake of pharmacogenetics into clinical practice.

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Current Practice of Evaluating Pharmacogenetic Evidence

Different perspectives exist regarding the required evidence thresholds for applying pharmacogenetic test results to patient care, taking into account clinical utility and cost-effectiveness.[3, 4] In general, recommendations for dose adjustments are routinely made with little or no large population-based studies on outcomes of those dose adjustments, often extrapolating from strong mechanistic evidence for inter-patient variability in drug response (i.e. pharmacokinetic studies). Furthermore, drug resources and drug labeling often provide recommendations for dose adjustments based on renal function assessment as evidenced by creatinine clearance calculation; however, very few controlled studies validate those recommendations.[5] Since many examples of pharmacogenetic variation ultimately affect pharmacokinetics (e.g., cytochrome P450 2D6 [*CYP2D6*], *CYP2C19, CYP3A5*) of certain drugs, adjusting doses using pharmacogenetic information is analogous to using drug doses adjusted according to underlying renal function, adjustments for which randomized clinical trials would neither be practical nor indicated.

When evaluating the pharmacogenetic literature to make implementation decisions, various perspectives should be considered, including clinicians and researchers, and evidence standards must be defined. Although randomized controlled trials (RCTs) are recognized as the 'gold standard' by which to evaluate the clinical utility of a new drug, this study design is not ideal to measure the benefit of pharmacogenetic testing, as clinically significant genetic variants are often present in only a small percentage of a given patient population. Furthermore, depending on the current body of evidence linking genotype to drug response, RCTs in patients with specific genetic polymorphisms may be precluded on ethical grounds.[6] For example, it would be unethical to randomize patients who are homozygous for non-functional thiopurine S-methyltransferase (*TPMT)* variants to normal vs. reduced doses of thiopurines, as the mechanism of the *TPMT* variation is related to drug pharmacokinetics, and it is known that normal doses of the drugs could result in lethal toxicity. Therefore, alternative study designs are often necessary to explore the clinical utility of pharmacogenetic testing.[7]

One drug for which RCTs have been conducted to assess the clinical utility of pharmacogenetic testing is warfarin.[8, 9] Genetic variants in *VKORC1,* the gene that codes for warfarin's target (vitamin K epoxide reductase), as well as variants in *CYP2C9*, the gene coding for the enzyme that is principally responsible for S-warfarin metabolism, are associated with increased sensitivity to warfarin.[10] The European Pharmacogenetics of Anti-coagulant Therapy (EU-PACT) trial concluded that patients who initially received pharmacogenetic-based warfarin dosing were more likely to be in the therapeutic international normalized ratio (INR) range compared to patients who initially received standard warfarin dosing.[8] In contrast, however, the Clarification of Optimal Anticoagulation through Genetics (COAG) trial concluded that genotype-guided warfarin dosing did not improve anticoagulation control compared to a non-genotype based dosing algorithm containing other clinical variables and was associated with less time in the therapeutic INR range among African American patients.[9]

These RCTs ignited a conversation about the clinical utility of genotype-guided warfarin therapy and prompted a critical evaluation of the methods and generalizability of each.[11, 12] For example, one critique of these trials is that in the controlled study environment, patients are closely monitored with frequent INRs, which is not always the case in a real-world setting and could therefore mask the benefit of initial pharmacogenetic dosing. In addition, in the COAG trial, genotype-guided dosing was compared to a complex clinical algorithm in the control group, which is not the standard of care. With respect to the worse outcome for African American patients receiving gene-based dosing in the COAG trial, experts were quick to point out that relevant genetic variants common in the African American population that result in increased warfarin sensitivity were not accounted for and could likely explain that outcome.[13] Despite the many strengths of a RCT, these warfarin trials highlight some key limitations that must be considered in the broader context of the current state of pharmacogenetic knowledge.

Due to the limitations of performing pharmacogenetic RCTs (i.e., number of participants needed, ethical issues, cost, etc.), knowledge must be derived from non-RCT sources, including observational studies (e.g, case reports, cross-sectional studies, case-control studies), and pharmacokinetic/pharmacodynamic studies, including in vivo and in vitro studies, linking drug effect to genetic variation. Although observational studies are more susceptible to bias, these studies offer advantages over RCTs for studying pharmacogenetic associations including the ability to compare larger numbers of subjects at a lower cost with few ethical concerns.

At this time, implementing pharmacogenetics and genomic medicine often requires a strategic commitment from the organization, and pharmacists are well-positioned to lead the implementation.[14-16] In this context, pharmacogenetic testing can be viewed as a patient safety strategy, and the evidence for the use of pharmacogenetic testing can be compared with the evidence threshold needed for other safety strategies an organization pursues. Other medication safety technologies are becoming widely used without RCT evidence, and persuasive arguments have been made for implementing patient safety interventions without waiting for RCTs.[17]

Evidence-based resources for pharmacogenetics implementation: CPIC and PharmGKB

Clinical Pharmacogenetics Implementation Consortium (CPIC)

CPIC™ was established as a shared project between PharmGKB[18] and the Pharmacogenomics Research Network (PGRN)[19] to address the need for clinical practice guidelines that facilitate the translation of genetic laboratory test results into actionable prescribing recommendations for specific drugs. PharmGKB is a comprehensive online resource established in 2000 whose scientific team at Stanford University collects, curates, and disseminates knowledge about the impact of human genetic variation on drug responses.[18] The PGRN, also founded in 2000, is a National Institutes of Health (NIH) - funded group of investigators that lead research in the discovery of how genomic variation impacts therapeutic and adverse drug effects.[20] CPIC membership has grown to over 160

pharmacogenetics experts (clinicians and scientists) from 86 institutions and 16 countries with multiple observers from the NIH and the U.S. Food and Drug Administration (FDA). To date, CPIC has published 19 gene-drug guidelines, six of which have recently been updated[16, 18-39] (Table 1).

CPIC guidelines are designed to help clinicians understand how available genetic test results should be used to optimize drug therapy and not whether to order a genetic test. This is an important distinction that separates CPIC guidelines from other disease-specific guidelines that may address pharmacogenetic testing. For example, CPIC's guideline for *CYP2C19*/ clopidogrel offers genotype-based clopidogrel prescribing recommendations for patients with a known *CYP2C19* genotype.[30] In contrast, the American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, and the Society for Cardiovascular Angiography and Interventions recommended against routine *CYP2C19* genotyping in their 2011 guideline for percutaneous coronary intervention, as did the American Heart Association and the American College of Cardiology in their 2014 guideline for the management of patients with non-ST-elevation acute coronary syndromes. [40, 41] The underlying assumption governing CPIC guidelines is that genomic testing results will increasingly be available and clinicians will be faced with having a patient's relevant pharmacogenetic genotype available, even if they did not order a test with a specific gene or drug in mind. Therefore, the question will become not whether to test, but how to effectively use the pharmacogenetic information that is becoming increasingly available.

As described by Caudle et al.[31], CPIC guidelines closely follow the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines and have established methods for guideline development, including a rigorous literature review and grading of the scientific literature, input of a writing committee of clinicians and researchers with expertise in the guideline subject, a standard format, and extensive pre- and post-submission peer review approval process. CPIC guidelines also meet the strict criteria for inclusion into the National Guideline Clearinghouse or guidelines.gov. The American Society of Health-System Pharmacists (ASHP) has endorsed seven CPIC guidelines to date[42] and is in the process of endorsing more. The American Society of Clinical Pharmacology and Therapeutics has also endorsed the CPIC guideline development process and endorsement of individual guidelines is underway. CPIC guidelines are freely available at the CPIC and PharmGKB websites and at PubMed Central.

CPIC guidelines provide the information a clinician would need to translate patient-specific diplotypes for each gene into clinical phenotypes (e.g., CYP2C19 poor metabolizer) or drug prescribing groups (e.g., *HLA-B*15:02* positive) and provide therapeutic recommendations based on these predicted phenotypes or groupings. Phenotype and allele function assignment has been variable in the literature, but CPIC has recently led an effort to establish standardized terminology for these assignments.[31] Each guideline contains tables that assign likely function to relevant alleles and phenotypes, and a comprehensive table is posted on PharmGKB that defines all phenotypes for all possible diplotypes (e.g., 6,668 diplotype combinations for *CYP2D6*). The guideline text also includes 1) background information for both the gene and drug, 2) information regarding the interpretation of the genetic test, 3)

incidental findings (i.e., diseases or conditions that have or have not been linked to variation of the gene, unrelated to medication use), 4) other considerations for critical issues about the gene or drug, and 5) description of the evidence linking genetic variability to variability in drug-related phenotypes, and 6) potential benefits and harm for the patient (i.e., the toxicities or adverse reactions that may be avoided by pharmacogenetic-based dosing) as well as any potential risks from incidental findings or use of alternative drugs or dosing (e.g., differences in efficacy). Of course, the "heart" of the guideline is the therapeutic recommendation which is based on the current level of evidence for the gene/drug pair, as well as evidence for alternative therapies.

CPIC's therapeutic recommendations are based on assessing the evidence from a combination of preclinical functional and clinical data, as well as on any existing consensus guidelines.[31] Examples of types of evidence reviewed include, but are not limited to, "randomized clinical trials with pharmacogenetic-based prescribing versus dosing not based on genetics, pre-clinical and clinical studies demonstrating that drug effects or concentration are linked to functional pharmacogenetic loci, case studies associating rare variants with drug effects, in vivo pharmacokinetic/pharmacodynamics studies for drug or reference drug plus variant type, and in vitro metabolic and/or transport capacity for the drug plus variant type".[31] Where available, evidence evaluating the outcomes when prescribing has been altered based on genetic testing is included. As stated previously, for most genes/drugs, RCTs comparing clinical outcomes with genotype-guided dosing versus conventional dosing are not available. Furthermore, evidence related to the appropriateness of alternative medications or dosing that may be used based on genetics must be weighed in assigning the strength of the recommendation. Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians and are presented in a guideline table and occasionally in an algorithm. To assign strength to a recommendation, CPIC uses a transparent three category system for rating recommendations.[17, 31] Therapeutic recommendations are graded as strong where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, in which the desirable effects of pharmacogenetic-based dosing are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action. Each recommendation also includes an assessment of its usefulness in pediatric patients.[31]

With community and member feedback, CPIC has learned that there is a critical need to provide classification of gene/drug groupings into those that are likely actionable versus not, and to develop gene/drug guidelines beyond those with strong prescribing recommendations. CPIC now classifies genes/drugs as CPIC level A, B, C, or D (Figure 1; Table 2). As gene results are placed into patients' medical records for those primary drugs with strong or moderate recommendations (termed CPIC level A guidelines), clinicians are faced with deciding how the same gene test results should (or should not) be used for secondary drugs for which there may be substantial literature references or even clinical laboratory interpretations, but drugs which CPIC's experts have deemed actionability as "optional" (termed CPIC level B guidelines) or not actionable (termed CPIC level C) (Figure 1, Table 2). Definitive recommendations on lack of actionability (CPIC level C) can be just as useful

to the clinician as actionable recommendations. There are a few examples of other "non-CPIC" genes/drugs that are marketed by companies or advocated for testing in the literature, yet CPIC does not deem as actionable (CPIC level C). In these cases, clinicians also need an unbiased and well-referenced guidance, based on standardized criteria, to assist in decision making and provide the basis for not changing prescribing based on the test results. Level D gene/drug associations are considered in the CPIC prioritization process, and are generally annotated on the PharmGKB as clinical annotations, but CPIC deems that guidelines are not currently warranted for these genes/drugs. It should be noted that the posted list of genes and drugs and their assignment to CPIC guideline levels is based on current evidence; the process is dynamic and genes and drugs may be added or change CPIC levels in response to new evidence or available testing options. The full list of gene-drug pairs is available on the CPIC website.[34]

The Pharmacogenomics Knowledgebase (PharmGKB)

Like CPIC, PharmGKB uses an evidence-based, tiered system of grading pharmacogenetic associations.[43] An annotated pharmacogenetic summary of FDA-approved labeling, European Medicines Association (EMA), the Pharmaceuticals and Medical Devices Agency, Japan (PMDA), and Health Canada (Santé Canada) (HCSC) can also be found on the PharmGKB website.

Scientific curators annotate published literature with variant-drug phenotypes, capturing information such as statistical significance, population size and association type (e.g., drug efficacy, toxicity, etc.). Curators group together like associations across publications and summarize the impact of each genotype on the drug phenotype in what PharmGKB calls "clinical associations". Clinical associations are assigned a level of evidence to indicate the strength of the literature support, and therefore the confidence in the association as determined by PharmGKB curators.

PharmGKB assigns a level from 1A (highest strength) for annotations for variant-drug combinations in a CPIC or medical society-endorsed PGx guidelines, or implemented at a PGRN site or in another major health system, to level 4 (lowest strength) for annotations based on a case report, non-significant study or in vitro, molecular or functional assay evidence only. The assignment of evidence level is based on several criteria, including replication of the association, statistical parameters and population size. The evidence level for a clinical annotation can change over time as new studies are published. Association evidence may accumulate and as new literature is annotated by PharmGKB curators, the corresponding clinical annotations are re-evaluated. If the clinical annotation meets the criteria for a higher level of evidence with the new literature, the curator adjusts the level. Conversely, a preliminary association may not be replicated by future studies, and so the level of evidence would be adjusted down. Therefore, the level of evidence assignment is dynamic.

Organizations such as CPIC and PharmGKB that use standardized approaches to evaluate the literature are becoming important to other areas of genomic and precision medicine such as ClinGen[44] and ClinVar[23, 45] which are central resources that define the clinical relevance of gene and variants. These types of relationships unite a relatively new field in developing

gold standards for clinical pharmacogenetic evidence review and the description of gene and variant functionality, all requirements for implementation into clinical practice.

Conclusion

Controversy exists over the required evidence threshold needed for routine clinical implementation of pharmacogenetics, and the level of evidence required to mandate ordering genetic tests vs. the level required to act on preemptively available evidence may differ. Resources provided by organizations such as CPIC and PharmGKB that use standardized approaches to evaluate the literature and provide clinical guidance are essential for the implementation of pharmacogenetics into routine clinical practice.

Acknowledgments

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Key Points

- Controversy exists over the required evidence threshold needed for routine clinical implementation of pharmacogenetics.

- One barrier that inhibits uptake of pharmacogenetics into routine clinical practice is the lack of knowledge of how to translate a genetic test into a clinical action based on current evidence.

- Resources provided by organizations such as CPIC and PharmGKB that use standardized approaches to evaluate the literature and provide clinical guidance are essential for the implementation of pharmacogenetics into routine clinical practice.

Initial prioritization considerations for new gene/drug groups
(may change over time as evidence and experience accumulates)

New gene(s) / drug(s)

Gene already subject to CPIC guideline

Gene not yet subject to CPIC guideline

Actionable in Dutch or other professional society guidelines

Nominate by CPIC member or outside advocate like FDA labeling

PharmGKB annotation level 1A, 1B, 2A or 2B

Mentioned in professional society guidelines but not actionable

Evaluate alternatives, evidence

Evaluate alternatives, evidence, degree of testing

CPIC level A or B: prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe

CPIC level C: no prescibing acti on recommended; alternatives are unclear, but testing is common

CPIC level D: (PharmGKB annotation) no prescribing action recommended; alternatives are unclear or evidence is weak; testing is rare or nonexistent
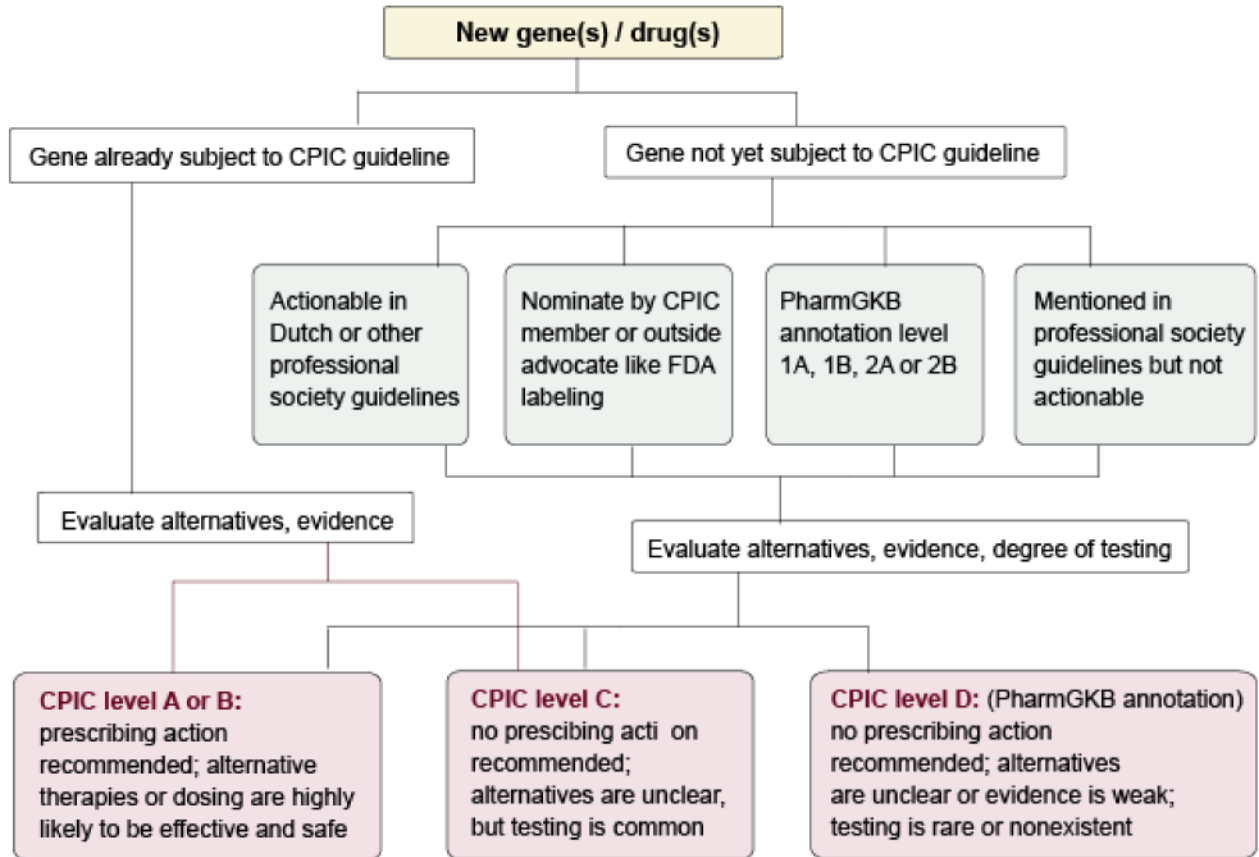
Figure 1. Initial prioritization considerations for new gene/drug groups
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Table 1

Current CPIC guidelines and associated PharmGKB clinical annotation levels and FDA label information

Gene[a,b]	Drug	PharmGKB clinical associations[c]	Pharmacogenetics on FDA Label[d]	CPIC guideline reference
CFTR	ivacaftor	1A	Genetic testing required	[46]
CYP2C19	amitriptyline	1A		[27]
CYP2C19	clopidogrel	1A	Genetic testing recommended	[30]
CYP2C19	doxepin	3	Actionable pharmacogenetics	[27]
CYP2C19	imipramine	2A		[27]
CYP2C19	trimipramine	2A		[27]
CYP2C19	voriconazole	2A	Actionable pharmacogenetics	In progress
CYP2C19	citalopram	1A	Actionable pharmacogenetics	[38]
CYP2C19	escitalopram	1A		[38]
CYP2C9	phenytoin	1B		[31]
CYP2C9	warfarin	1A	Actionable pharmacogenetics	[21]
CYP2D6	amitriptyline	1A	Actionable pharmacogenetics	[27]
CYP2D6	codeine	1A	Actionable pharmacogenetics	[23]
CYP2D6	desipramine	1A	Actionable pharmacogenetics	[27]
CYP2D6	doxepin	1A	Actionable pharmacogenetics	[27]
CYP2D6	fluvoxamine	1A	Informative pharmacogenetics	[38]
CYP2D6	imipramine	1A	Actionable pharmacogenetics	[27]
CYP2D6	nortriptyline	1A	Actionable pharmacogenetics	[27]
CYP2D6	paroxetine	1A	Informative pharmacogenetics	[38]
CYP2D6	tamoxifen	2A		In progress
CYP2D6	tramadol	1B	Actionable pharmacogenetics	[34]
CYP2D6	trimipramine	1A	Actionable pharmacogenetics	[27]
CYP3A5	tacrolimus	1A		[39]
DPYD	capecitabine	1A	Actionable pharmacogenetics	[25]
DPYD	fluorouracil	1A	Actionable pharmacogenetics	[25]
DPYD	tegafur	1A		[25]
G6PD	rasburicase	1A	Genetic testing required	[20]
HLA-B	abacavir	1A	Genetic testing required	[18, 47]
HLA-B	allopurinol	1A		[16, 26]
HLA-B	carbamazepine	1A	Genetic testing required	[28]
HLA-B	phenytoin	1A	Actionable pharmacogenetics	[31]
IFNL3	peg interferon alfa-2b	1A	Actionable pharmacogenetics	[36]
SLCO1B1	simvastatin	1A		[24]
TPMT	azathioprine	1A	Genetic testing recommended	[19]
TPMT	mercaptopurine	1A	Genetic testing recommended	[19]
TPMT	thioguanine	1A	Actionable pharmacogenetics	[19]
UGT1A1	atazanavir	1A		[37]

Gene[a,b]	Drug	PharmGKB clinical associations[c]	Pharmacogenetics on FDA Label[d]	CPIC guideline reference
UGT1A1	irinotecan	2A	Actionable pharmacogenetics	planned
VKORC1	warfarin	1A	Actionable pharmacogenetics	[21]

[a]Assigning CPIC levels to genes and drugs and grouping together genes and drugs for planned CPIC guidelines is a dynamic process that is continually updated. CPIC levels are ultimately decided by the guideline writing committees, who may modify dosing recommendations only after a detailed review of the evidence for genes and drugs. This list was current as of November 2015. The list posted on PharmGKB is the most current list http://www.pharmgkb.org/cpic/pairs.

[b]*CFTR* = cystic fibrosis transmembrane conductance regulator; *CYP2C19* = cytochrome P450 family 2 subfamily C member 19; *CYP2C9* = cytochrome P450 family 2 subfamily C member 9; *CYP2D6* = cytochrome P450 family 2 subfamily D member 6; *CYP3A5* = cytochrome P450 family 3 subfamily A member 5; *DPYD* = dihydropyrimidine dehydrogenase; *G6PD* = glucose-6-phosphate dehydrogenase; *HLA-B* = major histocompatibility complex, class I, B; *IFNL3* = interferon, lambda 3; *SLCO1B1* = solute carrier organic anion transporter family member 1B1; *TPMT* = thiopurine S-methyltransferase; *UGT1A1* = UDP glucuronosyltransferase family 1 member A1; *VKORC1* = vitamin K epoxide reductase complex subunit 1

[c]PharmGKB Clinical Annotation Levels of Evidence as defined at https://www.pharmgkb.org/page/clinAnnLevels.

[d]FDA Label categories created and assigned by PharmGKB, defined at https://www.pharmgkb.org/page/drugLabelLegend#PGxLevel.

Table 2

CPIC Level Definitions for Genes and Drugs

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

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