Evidence and resources to implement pharmacogenetic knowledge for precision medicine

Kelly E. Caudle, Pharm.D., Ph.D., BCPS Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN.

Roseann S. Gammal, Pharm.D., BCPS, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, and Department of Pharmacy Practice, MCPHS University, Boston, MA.

Michelle Whirl-Carrillo, Ph.D., Pharmacogenomics Knowledgebase (PharmGKB), Stanford University School of Medicine, Palo Alto, CA.

James M. Hoffman, Pharm.D., M.S., BCPS, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN.

Mary V. Relling, Pharm.D., Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN.

Teri E. Klein, Ph.D., Pharmacogenomics Knowledgebase (PharmGKB), Stanford University School of Medicine, Palo Alto, CA.

Address correspondence to Dr. Caudle (kelly.caudle@stjude.org).

DOI 10.2146/ajhp150977

Purpose. The current state of pharmacogenetic data curation and dissemination is described, and evidence-based resources for applying pharmacogenetic data in clinical practice are reviewed.

Summary. Implementation of pharmacogenetics in clinical practice has been relatively slow despite substantial scientific progress in understanding linkages between genetic variation and variability of drug response and effect. One factor that has inhibited the adoption of genetic data to guide medication use is a lack of knowledge of how to translate genetic test results into clinical action based on currently available evidence. Other implementation challenges include controversy over selection of appropriate evidentiary thresholds for routine clinical implementation of pharmacogenetic data and the difficulty of compiling scientific data to support clinical recommendations given that large randomized controlled trials to demonstrate the utility of pharmacogenetic testing are not feasible or are not considered necessary to establish clinical utility. Organizations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledgebase (PharmGKB) systematically evaluate emerging evidence of pharmacogenomic linkages and publish evidence-based prescribing recommendations to inform clinical practice. Both CPIC and PharmGKB provide online resources that facilitate the interpretation of genetic test results and provide prescribing recommendations for specific gene–drug pairs.

Conclusion. Resources provided by organizations such as CPIC and PharmGKB, which use standardized approaches to evaluate the literature and provide clinical guidance for a growing number of gene–drug pairs, are essential for the implementation of pharmacogenetics into routine clinical practice.

Keywords: CPIC, evidence, guideline, pharmacogenetics, pharmacogenomics, PharmGKB, precision medicine

Am J Health-Syst Pharm. 2016; 73:1977-85

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 for use of pharmacogenetic test results for medication selection and dosing is one factor that inhibits the routine application of pharmacogenetics in patient care. Another factor is a lack of knowledge of how to translate genetic test results into clinical action.[2] Resources that provide evidence-based recommendations pertaining to a growing number of gene–drug pairs are available. Here we describe the current state of curation and dissemination of pharmacogenetic evidence and evidence-based resources that facilitate the implementation of pharmacogenetic recommendations in clinical practice.

Current practices in evaluation of pharmacogenetic evidence

There are different perspectives regarding evidentiary thresholds for applying pharmacogenetic test results to patient care, taking into account clinical utility and cost-effectiveness.[3,4] For medications in general, recommendations for medication dose adjustments are routinely made with little or no evidence from large population-based studies, often by extrapolating from strong mechanistic evidence for interpatient 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; however, there is typically very little evidence from controlled studies to validate those recommendations.[5] There are many examples of pharmacogenetic variations that ultimately affect the pharmacokinetics of certain drugs (e.g., variations in the genes encoding cytochrome P-450 [CYP] isozymes 2D6, 2C19, and 3A5); thus, adjusting doses using pharmacogenetic information is analogous to making dose adjustments according to underlying renal function—adjustments for which randomized clinical trials to compile supportive data are neither practical nor indicated.

In evaluating the pharmacogenetics literature to make clinical decisions, various perspectives should be considered 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 for measuring 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 a 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 assign patients who are homozygous for nonfunctional variants of the thiopurine *S*-methyltransferase gene (*TPMT*) to receive normal versus reduced doses of thiopurines, as the mechanism of *TPMT* variation is related to 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]

KEY POINTS

- The evidence threshold required for routine clinical implementation of pharmacogenetic data remains controversial.
- 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 the Clinical Pharmacogenetics Implementation Consortium and the Pharmacogenomics Knowledgebase that use standardized approaches to evaluate the literature and provide clinical guidance are essential for the implementation of pharmacogenetics into routine clinical practice.

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 (a vitamin K epoxide reductase involved in blood clotting), as well as variants of *CYP2C9*, the gene coding for the enzyme principally responsible for *S*-warfarin metabolism, are associated with increased sensitivity to warfarin.[10] The European Pharmacogenetics of Anti-coagulant Therapy (EU-PACT) trial indicated that patients who initially received pharmacogenetics-based warfarin dosing were more likely to be in the therapeutic International Normalized Ratio (INR) range than patients who initially received standard warfarin dosing.[8] In contrast, however, the Clarification of Optimal Anticoagulation through Genetics (COAG) trial indicated that genotype-guided warfarin dosing did not improve anticoagulation control when compared with a non–genotype-based dosing algorithm containing other clinical variables and was associated with decreased 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 studies' methods and generalizability.[11,12] For example, one critique of the COAG trial was that the patients involved were in a controlled study environment and could be closely monitored through frequent INR determinations (which is not always the case in a real-world setting), potentially masking a benefit of initial pharmacogenetic dosing. In addition, in the COAG trial genotype-guided dosing was compared with dosing based on a complex clinical algorithm, which is not the standard of care. The EU-PACT study population was nearly 99% Caucasian, in contrast to the COAG study population, which was more diverse (one third of participants were black). With respect to the worse outcomes observed in African-American patients receiving genotype-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 likely explained the outcome difference.[13] Despite the many strengths of an RCT, the COAG and EU-PACT trials highlighted some key limitations that must be considered in the broader context of the current state of pharmacogenetic knowledge.

Due to the challenges of performing pharmacogenetic RCTs (e.g., the high numbers of participants needed, ethical and cost issues), knowledge must be derived from non-RCT sources such as observational studies (e.g., case reports, cross-sectional studies, case-controlled studies) and pharmacokinetic and pharmacodynamic studies, including in vivo and in vitro studies, aimed at linking drug effects 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 and with few ethical concerns.

At this time, implementing pharmacogenetics and genomic medicine often requires a strategic commitment from the healthcare organization, and pharmacists are well positioned to lead implementation efforts.[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 that 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] For example, many hospitals have invested in smart infusion pumps, and this technology is now common. A 2013 evidence assessment from the Agency for Healthcare Research and Quality (AHRQ) indicated that the strength of evidence for the effectiveness of smart pumps is low, and no RCTs were mentioned.[18] With this level of evidence, smart infusion pumps are appropriately becoming widely used to improve medication safety, and the expense is justified.

Evidence-based resources

Over the past decade, advances have been made in synthesizing evidence to guide the use of pharmacogenetic data in patient care. In 2008 and 2011, the Dutch Pharmacogenetics Working Group (DPWG) provided a listing of pharmacogenetics recommendations.[19,20] While such a comprehensive list was useful, the level-of-evidence reviews for the targeted gene–drug pairs were limited. Since the creation of the Clinical Pharmacogenetics Implementation Consortium (CPIC) in 2009, there is now more detailed gene–drug guidance available to assist clinicians in interpreting a genetic test result and altering therapy based on that result.[21] Each guideline group uses different evidence evaluation methodology. Level-of-evidence definitions used in the Pharmacogenomics Knowledgebase (PharmGKB, Stanford University, Palo Alto, CA),[22] by CPIC[23] and DPWG,[19] and in the Centers for Disease Control and Prevention's Evaluation of Genomic Applications in Practice and Prevention initiative[24] are available from open-access resources.

CPIC. CPIC was established as a shared project of PharmGKB[25] and the Pharmacogenomics Research Network (PGRN)[26] 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 National Institutes of Health (NIH)–funded comprehensive online resource established in 2000 and managed by a scientific team at Stanford University that collects, curates, and disseminates knowledge about the impact of human genetic variation on drug responses.[25] PGRN, also founded in 2000 and funded by NIH, is a group of investigators who lead research in the discovery of how genomic variation affects therapeutic and adverse drug effects.[27] The CPIC membership now includes over 160 pharmacogenetics experts (clinicians and scientists) from 86 institutions and 16 countries as well as multiple observers from NIH and the Food and Drug Administration (FDA). To date, CPIC has published 19 gene–drug guidelines,[16,23,27-47] 6 of which were recently updated.

CPIC guidelines are designed to help clinicians understand how available genetic test results should be used to optimize drug therapy—not whether ordering a genetic test is appropriate. This is an important distinction that separates CPIC guidelines from other disease-specific guidelines that address pharmacogenetic testing. For example, CPIC's guideline regarding the *CYP2C19* gene and clopidogrel use offers genotype-based clopidogrel prescribing recommendations for patients with a known *CYP2C19* genotype.[39] In contrast, the American College of Cardiology (ACC) Foundation, the American Heart Association (AHA) Task Force on Practice Guidelines, and the Society for Cardiovascular Angiography and Interventions recommended against routine *CYP2C19* genotyping in a joint 2011 guideline on percutaneous coronary intervention, as did AHA and ACC in a joint 2014 guideline on the management of patients with non-ST-elevation acute coronary syndromes.[48,49] 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.,[23] CPIC guidelines closely follow the National Academy of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" and are created through established methods of guideline development, including rigorous literature review and grading of the scientific literature, solicitation of input from a writing committee of clinicians and researchers with expertise in the guideline subject, presentation of guidelines in a standard format, and the use of an

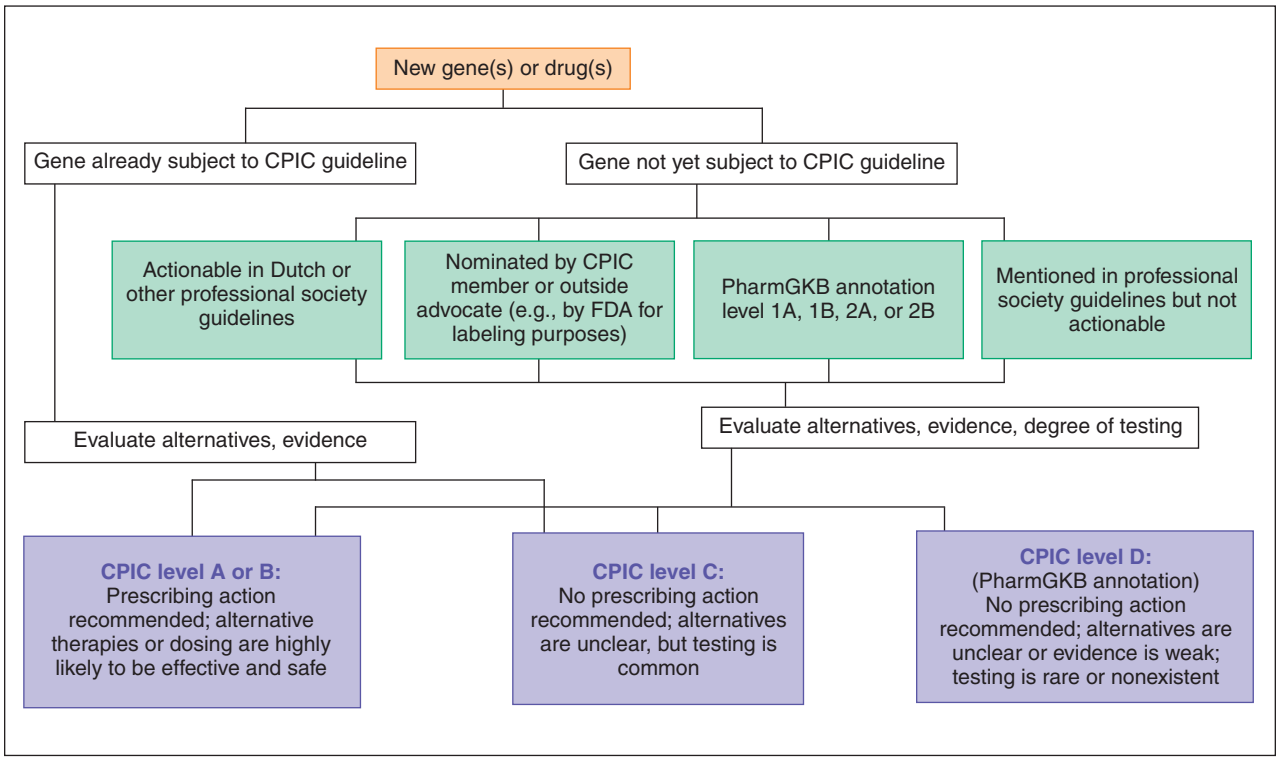
extensive presubmission and postsubmission peer review and approval process. CPIC guidelines also meet the strict criteria for inclusion in AHRQ's National Guideline Clearinghouse (www.guidelines.gov). The American Society of Health-System Pharmacists (ASHP) has endorsed seven CPIC guidelines to date[50] and is in the process of reviewing additional CPIC guidelines for potential endorsement. The American Society of Clinical Pharmacology and Therapeutics has endorsed the CPIC guideline development process, and endorsement review of individual guidelines is underway. CPIC guidelines are freely available at the websites of CPIC (www.cpicpgx.org) and PharmGKB (www.pharmgkb.org) and at PubMed Central.

CPIC guidelines provide the information a clinician needs 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, indicating susceptibility to serious carbamazepine-induced adverse effects due to carriage of a specific allele of the gene coding for human leukocyte antigen B) and provide therapeutic recommendations based on these predicted phenotypes or groupings. Various methods of phenotype and allele function assignment have been described in the literature, but CPIC has recently led an effort to establish standardized terminology.[23] Each guideline contains tables that assign likely functions to relevant alleles and phenotypes, and a comprehensive table that defines all phenotypes for all possible diplotypes (e.g., there are 6668 combinations for the gene encoding CYP2D6) is available from PharmGKB. The text of each CPIC guideline also includes (1) background information for both the gene and the drug, (2) information regarding the interpretation of the applicable genetic test, (3) incidental findings (i.e., diseases or conditions that have or have not been linked to variation of the gene regardless of medication use), (4) other considerations for critical issues about the gene or drug, (5) a description of the evidence linking genetic variability to variability in drug-related phenotypes, and (6) potential patient benefits and harms of using the drug (e.g., the toxicities or adverse reactions that may be avoided by pharmacogenetic-based dosing), as well as any potential risks associated with incidental findings or use of alternative drugs or dosing (e.g., differences in efficacy). Of course, the main purpose of each guideline is the therapeutic recommendation, which is based on the current level of evidence for the gene–drug pair and for alternative therapies.

CPIC's therapeutic recommendations are based on assessing the evidence from a combination of preclinical functional data and clinical data as well as existing consensus guidelines (if available).[23] Examples of the 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."[23] If available, evidence evaluating the outcomes reported when prescribing was altered based on genetic testing is included. As stated previously, for most gene–drug pairs, RCTs comparing clinical outcomes of genotype-guided versus conventional dosing are not available. Furthermore, evidence related to the appropriateness of alternative medications or dosing that may be used on the basis of genetic testing data 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 or, occasionally, in an algorithm. To assign a strength rating to a recommendation, CPIC uses a transparent three-category system.[17,23] Therapeutic recommendations are graded as strong if "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects," as moderate when "there is a close or uncertain balance" as to whether the evidence is of high quality and the desirable effects clearly outweigh the undesirable effects, or as optional when "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.[23]

With community and member feedback, CPIC has learned that there is a critical need to classify gene–drug groupings into those that are likely actionable versus nonactionable and to develop gene–drug guidelines beyond those that contain strong prescribing recommendations. CPIC now classifies gene–drug pairs at levels A, B, C, and D (Figure 1; Table 1). As gene test results pertaining to drugs subject to strong or moderate-strength recommendations (CPIC level A guidelines) are placed into patients' medical records, clinicians are faced with deciding how the same test results should be used in relation to other prescribed drugs for which there may be substantial pharmacogenetic literature references or even clinical laboratory interpretations but for which prescribing actions are deemed optional (CPIC level B) or are not recommended (CPIC level C). Definitive recommendations on lack of actionability can be just as useful to the clinician as recommendations on actionability. There are a few examples of non-CPIC gene–drug pairings that are marketed by companies or advocated for testing in the literature but are not deemed by CPIC to be actionable. In these cases, clinicians also need an unbiased and well-referenced guidance,

Figure 1. Pharmacogenomics Knowledgebase (PharmGKB) initial prioritization considerations for new gene–drug groups. Level-of-evidence assignments may change over time as evidence and experience accumulate. CPIC = Clinical Pharmacogenetics Implementation Consortium, FDA = Food and Drug Administration. Flowchart used with permission of PharmGKB. PharmGKB is a registered trademark of the U.S. Department of Health and Human Services and is financially supported by the National Institute of General Medical Sciences, part of the National Institutes of Health. PharmGKB is managed at Stanford University.



based on standardized criteria, to assist in decision-making and provide the basis for not changing prescribing based on test results. In the CPIC prioritization process, level D gene–drug associations are those for which "there are few published studies . . . little mechanistic basis, mostly weak evidence, or substantial conflicting data"; CPIC deems that guidelines are not currently warranted for these gene–drug pairs (which are generally annotated on the PharmGKB as clinical annotations). It should be noted that the listing of gene–drug pairs and their assignment to guideline levels on CPIC's website are based on current evidence; the process is dynamic, and genes and drugs may be added or CPIC levels may be changed in response to new evidence or available testing options.

PharmGKB. Like CPIC, PharmGKB uses an evidence-based, tiered system of grading pharmacogenetic associations.[22] An annotated pharmacogenetic summary of FDA-approved labeling information and corresponding information developed by the European Medicines Association, Japan's Pharmaceuticals and Medical Devices Agency, and Health Canada (Santé Canada) can also be found on the PharmGKB website.

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

PharmGKB evidence level assignments range from 1A (highest strength) for "annotation[s] for variant-drug combinations in a CPIC or medical society-endorsed pharmacogenetics guidelines, or implemented at a PGRN site or in another major health system" to level 4 (lowest strength) for "annotation[s] based on a case report, non-significant study or in vitro, molecular or functional assay evidence only." The assignment of an evidence level is based on several criteria, including replication of the association, statistical parameters, and

Table 1. Clinical Pharmacogenetics Implementation Consortium (CPIC) Level Definitions for Genes and Drugs[a]

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 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 direct-to-consumer 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.

[a]Used with permission from PharmGKB. PharmGKB® is a registered trademark of the U.S. Department of Health and Human Services and is financially supported by the National Institute of General Medical Sciences, part of the National Institutes of Health; it is managed at Stanford University.

Table 2. Strength of Pharmacogenetic Evidence, Labeling Information, and Guidelines for Selected Gene–Drug Pairs[a]

Gene[b]	Drug	PharmGKB Clinical Association Level[c]	FDA Labeling Information[d]	CPIC Guideline (Reference or Status)
CFTR	Ivacaftor	1A	Genetic testing required	53
CYP2C19	Amitriptyline	1A	NA	36
CYP2C19	Clopidogrel	1A	Genetic testing recommended	39
CYP2C19	Doxepin	3	Actionable pharmacogenetics	36
CYP2C19	Imipramine	2A	NA	36
CYP2C19	Trimipramine	2A	NA	36
CYP2C19	Voriconazole	2A	Actionable pharmacogenetics	In development
CYP2C19	Citalopram	1A	Actionable pharmacogenetics	46
CYP2C19	Escitalopram	1A	NA	46
CYP2C9	Phenytoin	1B	NA	23
CYP2C9	Warfarin	1A	Actionable pharmacogenetics	28
CYP2D6	Amitriptyline	1A	Actionable pharmacogenetics	36
CYP2D6	Codeine	1A	Actionable pharmacogenetics	31
CYP2D6	Desipramine	1A	Actionable pharmacogenetics	36

Continued on next page

Continued from previous page

Table 2. Strength of Pharmacogenetic Evidence, Labeling Information, and Guidelines for Selected Gene–Drug Pairs[a]

Gene[b]	Drug	PharmGKB Clinical Association Level[c]	FDA Labeling Information[d]	CPIC Guideline (Reference or Status)
CYP2D6	Doxepin	1A	Actionable pharmacogenetics	36
CYP2D6	Fluvoxamine	1A	Informative pharmacogenetics	46
CYP2D6	Imipramine	1A	Actionable pharmacogenetics	36
CYP2D6	Nortriptyline	1A	Actionable pharmacogenetics	36
CYP2D6	Paroxetine	1A	Informative pharmacogenetics	46
CYP2D6	Tamoxifen	2A	NA	In development
CYP2D6	Tramadol	1B	Actionable pharmacogenetics	42
CYP2D6	Trimipramine	1A	Actionable pharmacogenetics	36
CYP3A5	Tacrolimus	1A	NA	47
DPYD	Capecitabine	1A	Actionable pharmacogenetics	34
DPYD	Fluorouracil	1A	Actionable pharmacogenetics	34
DPYD	Tegafur	1A	NA	34
G6PD	Rasburicase	1A	Genetic testing required	27
HLA-B	Abacavir	1A	Genetic testing required	32, 43
HLA-B	Allopurinol	1A	NA	16, 35
HLA-B	Carbamazepine	1A	Genetic testing required	37
HLA-B	Phenytoin	1A	Actionable pharmacogenetics	23
IFNL3	Peg interferon alfa-2b	1A	Actionable pharmacogenetics	44
SLCO1B1	Simvastatin	1A	NA	33
TPMT	Azathioprine	1A	Genetic testing recommended	29
TPMT	Mercaptopurine	1A	Genetic testing recommended	29
TPMT	Thioguanine	1A	Actionable pharmacogenetics	29
UGT1A1	Atazanavir	1A	NA	45
UGT1A1	Irinotecan	2A	Actionable pharmacogenetics	Planned
VKORC1	Warfarin	1A	Actionable pharmacogenetics	28

[a]PharmGKB = Pharmacogenomics Knowledgebase, FDA = Food and Drug Administration, CPIC = Clinical Pharmacogenetics Implementation Consortium, *CFTR* = gene encoding cystic fibrosis transmembrane conductance regulator; *CYP2C19* = gene encoding cytochrome P-450 family 2 subfamily C member 19; NA = not applicable; *CYP2C9* = gene encoding cytochrome P-450 family 2 subfamily C member 9; *CYP2D6* = gene encoding cytochrome P-450 family 2 subfamily D member 6; *CYP3A5* = gene encoding cytochrome P-450 family 3 subfamily A member 5; *DPYD* = gene encoding dihydropyrimidine dehydrogenase; *G6PD* = gene encoding glucose-6-phosphate dehydrogenase; *HLA-B* = gene encoding major histocompatibility complex, class I, B; *IFNL3* = gene encoding interferon, lambda 3; *SLCO1B1* = gene encoding solute carrier organic anion transporter family member 1B1; *TPMT* = gene encoding thiopurine *S*-methyltransferase; *UGT1A1* = gene encoding UDP glucuronosyltransferase family 1 member A1; *VKORC1* = gene encoding vitamin K epoxide reductase complex subunit 1.

[b]Assigning CPIC levels to genes and drugs and grouping together genes and drugs for planned CPIC guidelines are dynamic processes that are 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 (www.pharmgkb.org/cpic/pairs).

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

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

population size. The evidence level for a clinical annotation can change over time as new studies are published. Association evidence may accumulate as new literature is annotated by PharmGKB curators and the corresponding clinical annotations are reevaluated. If the clinical annotation meets the criteria for a higher level of evidence, the curator adjusts the level; conversely, a preliminary association may not be replicated by future studies, and so the level of evidence is adjusted downward. Therefore, 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 genomics and precision medicine databases such as ClinGen[51] and ClinVar,[31,52] which are central resources that define the clinical relevance of a gene and variants. These types of relationships unite a relatively new field in developing new standards for clinical pharmacogenetic evidence review and the description of gene and variant functionality—both requirements for implementation into clinical practice. A summary of current CPIC guidelines and PharmGKB annotations can be found in Table 2.

Controversy over the appropriate evidentiary threshold for routine clinical implementation of pharmacogenetics persists, and the level of evidence required to mandate the ordering of genetic tests may differ from the level required for clinicians to act preemptively on available genetic test results.

Conclusion

Resources provided by organizations such as CPIC and PharmGKB, which use standardized approaches to evaluate the literature and provide clinical guidance for a growing number of gene–drug pairs, are essential for the implementation of pharmacogenetics into routine clinical genetic test results.

Disclosures

This work was funded by NIH grants to CPIC (R24GM115264) and PharmGKB (R24 GM61374). Dr. Klein and Dr. Whirl-Carrillo are scientific advisors to Rxight Pharmacogenetics and are funded by NIH grant R24 GM61374 to PharmGKB. Dr. Relling, Dr. Caudle, Dr. Klein, Dr. Hoffman, Dr. Whirl-Carrillo, and Dr. Gammal are funded by NIH grant R24GM115264 to CPIC. Dr. Caudle, Dr. Gammal, Dr. Hoffman, and Dr. Relling are funded by American Lebanese Syrian Associated Charities (ALSAC).

References

1. Relling MV, Evans WE. Pharmacogenomics in the clinic. *Nature.* 2015; 526:343-50.
2. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther.* 2011; 89:464-7.
3. Gillis NK, Innocenti F. Evidence required to demonstrate clinical utility of pharmacogenetic testing: the debate continues. *Clin Pharmacol Ther.* 2014; 96:655-7.
4. Ratain MJ, Johnson JA. Meaningful use of pharmacogenetics. *Clin Pharmacol Ther.* 2014; 96:650-2.
5. Khanal A, Castelino RL, Peterson GM et al. Dose adjustment guidelines for medications in patients with renal impairment: how consistent are drug information sources? *Intern Med J.* 2014; 44:77-85.
6. Young B, Squires K, Patel P et al. First large, multicenter, open-label study utilizing HLA-B*5701 screening for abacavir hypersensitivity in North America. *AIDS.* 2008; 22:1673-5.
7. Filipski KK, Mechanic LE, Long R et al. Pharmacogenomics in oncology care. *Front Genet.* 2014; 5:73.
8. Pirmohamed M, Burnside G, Eriksson N et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med.* 2013; 369:2294-303.
9. Kimmel SE, French B, Kasner SE et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med.* 2013; 369:2283-93.
10. Baker WL, Johnson SG. Pharmacogenetics and oral antithrombotic drugs. *Curr Opin Pharmacol.* 2016; 27:38-42.
11. Zineh I, Pacanowski M, Woodcock J. Pharmacogenetics and coumarin dosing—recalibrating expectations. *N Engl J Med.* 2013; 369:2273-5.
12. Furie B. Do pharmacogenetics have a role in the dosing of vitamin K antagonists? *N Engl J Med.* 2013; 369:2345-6.
13. Drozda K, Wong S, Patel SR et al. Poor warfarin dose prediction with pharmacogenetic algorithms that exclude genotypes important for African Americans. *Pharmacogenet Genomics.* 2015; 25:73-81.
14. Evans WE, Crews KR, Pui CH. A health-care system perspective on implementing genomic medicine: pediatric acute lymphoblastic leukemia as a paradigm. *Clin Pharmacol Ther.* 2013; 94:224-9.
15. Johnson SG. Leading clinical pharmacogenomics implementation: advancing pharmacy practice. *Am J Health-Syst Pharm.* 2015; 72:1324-8.
16. Saito Y, Stamp LK, Caudle KE et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin Pharmacol Ther.* 2016; 99:36-7.
17. Leape LL, Berwick DM, Bates DW. What practices will most improve safety? Evidence-based medicine meets patient safety. *JAMA.* 2002; 288:501-7.
18. Shekelle PG, Wachter RM, Pronovost PJ et al. Making health care safer II: an updated critical analysis of the evidence for patient safety practices. *Evid Rep Technol Assess (Full Rep).* 2013; 211:1-945.
19. Swen JJ, Nijenhuis M, de Boer A et al. Pharmacogenetics: from bench to byte—an update of guidelines. *Clin Pharmacol Ther.* 2011; 89:662-73.
20. Swen JJ, Wilting I, de Goede AL et al. Pharmacogenetics: from bench to byte. *Clin Pharmacol Ther.* 2008; 83:781-7.
21. Clinical Pharmacogenetics Implementation Consortium. https://cpicpgx.org/ (accessed 2016 Mar 16).
22. Whirl-Carrillo M, McDonagh EM, Hebert JM et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2012; 92:414-7.
23. Caudle KE, Klein TE, Hoffman JM et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab.* 2014; 15:209-17.
24. Teutsch SM, Bradley LA, Palomaki GE et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP working group. *Genet Med.* 2009; 11:3-14.
25. The Pharmacogenomics Knowledgebase. www.pharmgkb.org/ (accessed 2016 Mar 16).

26. Pharmacogenomics Research Network. www.pgrn.org/ (accessed 2016 Mar 16).
27. Relling MV, McDonagh EM, Chang T et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. *Clin Pharmacol Ther.* 2014; 96:169-74.
28. Johnson JA, Gong L, Whirl-Carrillo M et al. Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2C9* and *VKORC1* genotypes and warfarin dosing. *Clin Pharmacol Ther.* 2011; 90:625-9.
29. Relling MV, Gardner EE, Sandborn WJ et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther.* 2011; 89:387-91.
30. Scott SA, Sangkuhl K, Gardner EE et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (*CYP2C19*) genotype and clopidogrel therapy. *Clin Pharmacol Ther.* 2011; 90:328-32.
31. Crews KR, Gaedigk A, Dunnenberger HM et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450-2D6 (*CYP2D6*) genotype. *Clin Pharmacol Ther.* 2012; 91:321-6.
32. Martin MA, Klein TE, Dong BJ et al. Clinical Pharmacogenetics Implementation Consortium guidelines for *HLA-B* genotype and abacavir dosing. *Clin Pharmacol Ther.* 2012; 91:734-8.
33. Wilke RA, Ramsey LB, Johnson SG et al. Clinical Pharmacogenetics Implementation Consortium: CPIC guideline for *SLCO1B1* and simvastatin-induced myopathy. *Clin Pharmacol Ther.* 2012; 92:112-7.
34. Caudle KE, Thorn CF, Klein TE et al. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. *Clin Pharmacol Ther.* 2013; 94:640-5.
35. Hershfield MS, Callaghan JT, Tassaneeyakul W et al. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin Pharmacol Ther.* 2013; 93:153-8.
36. Hicks JK, Swen JJ, Thorn CF et al. Clinical Pharmacogenetics Implementation Consortium guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther.* 2013; 93:402-8.
37. Leckband SG, Kelsoe JR, Dunnenberger HM et al. Clinical Pharmacogenetics Implementation Consortium guidelines for *HLA-B* genotype and carbamazepine dosing. *Clin Pharmacol Ther.* 2013; 94:324-8.
38. Relling MV, Gardner EE, Sandborn WJ et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. *Clin Pharmacol Ther.* 2013; 93:324-5.
39. Scott SA, Sangkuhl K, Stein CM et al. Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2C19* genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther.* 2013; 94:317-23.
40. Ramsey LB, Johnson SG, Caudle KE et al. The Clinical Pharmacogenetics Implementation Consortium guideline for *SLCO1B1* and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther.* 2014; 96:423-8.
41. Clancy JP, Johnson SG, Yee SW et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of *CFTR* genotype. *Clin Pharmacol Ther.* 2014; 95:592-7.
42. Crews KR, Gaedigk A, Dunnenberger HM et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther.* 2014; 95:376-82.
43. Martin MA, Hoffman JM, Freimuth RR et al. Clinical Pharmacogenetics Implementation Consortium guidelines for *HLA-B* genotype and abacavir dosing: 2014 update. *Clin Pharmacol Ther.* 2014; 95:499-500.
44. Muir AJ, Gong L, Johnson SG et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *IFNL3* (*IL28B*) genotype and PEG interferon-α-based regimens. *Clin Pharmacol Ther.* 2014; 95:141-6.
45. Gammal RS, Court MH, Haidar CE et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *UGT1A1* and atazanavir prescribing. *Clin Pharmacol Ther.* 2016; 99:363-9.
46. Hicks JK, Bishop JR, Sangkuhl K et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther.* 2015; 98:127-34.
47. Birdwell KA, Decker B, Barbarino JM et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *CYP3A5* genotype and tacrolimus dosing. *Clin Pharmacol Ther.* 2015; 98:19-24.
48. Levine GN, Bates ER, Blankenship JC et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011; 58:e44-122.
49. Amsterdam EA, Wenger NK, Brindis RG et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014; 64:e139-228.
50. American Society of Health-System Pharmacists. Endorsed documents. www.ashp.org/menu/PracticePolicy/PolicyPositionsGuidelinesBestPractices/BrowsebyDocumentType/EndorsedDocuments.aspx (accessed 2016 Mar 16).
51. Clinical Genome Resource. www.clinicalgenome.org/ (accessed 2016 Mar 16).
52. ClinVar. www.ncbi.nlm.nih.gov/clinvar/ (accessed 2016 Mar 16).
53. Clancy JP, Johnson SG, Yee SW et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of *CFTR* genotype. *Clin Pharmacol Ther.* 2014; 95:592-7.