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ACCP COMMENTARY

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Decoding pharmacogenomic test interpretation and application to patient care

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Abstract

Pharmacogenomics is a growing area of medicine, and pharmacists across clinical practice settings have the opportunity to individualize medication selection and dosing using genetic data. However, many practicing pharmacists may feel ill-equipped to interpret pharmacogenomic test results because of insufficient education and training. Evidence-based, updated, and freely available resources such as the Clinical Pharmacogenetics Implementation Consortium guidelines can help pharmacists interpret and apply pharmacogenomic test results to patient care. Although gaps for the application of pharmacogenomic information exist, this commentary aims to demystify the interpretation of pharmacogenomic test results and empower pharmacists to apply genetic data alongside other clinical variables to optimize medication-related outcomes for their patients. An "ABCD" framework is proposed to guide pharmacists through the steps: (1) Actionability—Are the gene(s) clinically relevant for the patient? (2) Be Mindful of Limitations—What are the caveats with pharmacogenomic test results and reports? (3) Clinical Practice Guidelines—How do you use pharmacogenomic test results to guide clinical decision-making? and (4) Document and Discuss—How do you educate the patient about their pharmacogenomic test results and

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document the results for future use? Key concepts are illustrated using a psychiatric patient case example.

KEYWORDS
CPIC, gene, pharmacist, pharmacogenetics, pharmacogenomics, pharmacy

1 | INTRODUCTION

Pharmacogenomics is an exciting and growing area of precision medicine, and pharmacists, as key members of a multidisciplinary team, are at the forefront of clinical application. Pharmacogenomic testing provides actionable insight into how patients' genetic profiles influence their response to specific medications. A high percentage of therapeutic failures and adverse drug reactions are attributed to use of the wrong drug(s) or wrong dosage(s), decisions that can be improved by genotype-based prescribing. In fact, a significant percentage of the population will be exposed to at least one drug with pharmacogenomic implications in their lifetime, and more than 95% have at least one high-risk pharmacogenomic variant.[1–3] Furthermore, recent data highlight the powerful ability of panel pharmacogenomic testing not only to significantly decrease the incidence of clinically relevant adverse drug reactions, but also to reduce cost when part of a comprehensive medication management program.[4,5] Pharmacogenomics has broad clinical usefulness across therapeutic areas, including oncology, cardiology, psychiatry, neurology, infectious disease, pain management, and organ and stem cell transplantation.[6] Integration of pharmacogenomics into comprehensive medication management for all patients carries great potential for improving medication-related outcomes.[5] Although pioneers in pharmacogenomics implementation have demonstrated the feasibility of pharmacogenomics in patient care[7–15] and the potential for pharmacogenomics to improve medication use has been clear for decades, significant gaps remain in its routine and broad clinical use.

Because of their expertise in pharmacology and pharmacotherapy, clinical pharmacists are the ideal health care professional to interpret pharmacogenomic test results and provide genotype-guided medication recommendations.[16,17] Genotype is one of many patient-specific factors (e.g., age, renal function, hepatic function, and drug interactions) pharmacists routinely consider in prescribing recommendations. Although pharmacogenomics has become more prominent in pharmacy school curricula and pharmacogenomics-specific competencies and continuing education programs are available,[18] many practicing pharmacists may feel ill-equipped to interpret pharmacogenomic test results. Tertiary resources, such as a textbook chapter[19] or a review article,[20] can provide a helpful starting point for pharmacists new to the topic. However, these resources may not contain the most up-to-date clinical recommendations. For this, clinician-friendly resources for interpreting and applying pharmacogenomics to patient care are freely available (e.g., Clinical Pharmacogenetics Implementation Consortium [CPIC] guidelines).[21] For guided learning, ACCP and other organizations provide pharmacogenomics certificate programs and other educational programming to improve competency and teach strategies for implementing pharmacogenomics into clinical care.

Although gaps for the application of pharmacogenomic information exist, this commentary aims to demystify the interpretation of pharmacogenomic test results and empower clinical pharmacists to apply genetic data alongside other clinical variables to optimize medication-related outcomes for their patients. An "ABCD" framework is proposed to guide pharmacists through the steps: (1) Actionability, (2) Be Mindful of Limitations, (3) Clinical Practice Guidelines, and (4) Document and Discuss (Figure 1). Key concepts are illustrated using a psychiatric patient case example.

Clinical Case: A 21-year-old student with a history of anxiety and depression, treated with paroxetine, presents for a telehealth visit. The student reports good control of symptoms related to anxiety and depression with the current therapy of paroxetine 40 mg per day but has had daily symptoms of nausea since increasing the paroxetine dose from 20 mg per day. The student is concerned about the impact of GI symptoms on the ability to train and compete as a college athlete (tennis player). Pharmacogenomic testing is ordered through a commercial vendor to help guide the student's changes to antidepressant therapy. Genotype results and laboratory interpretations are shown in Table 1 and Figure 2.

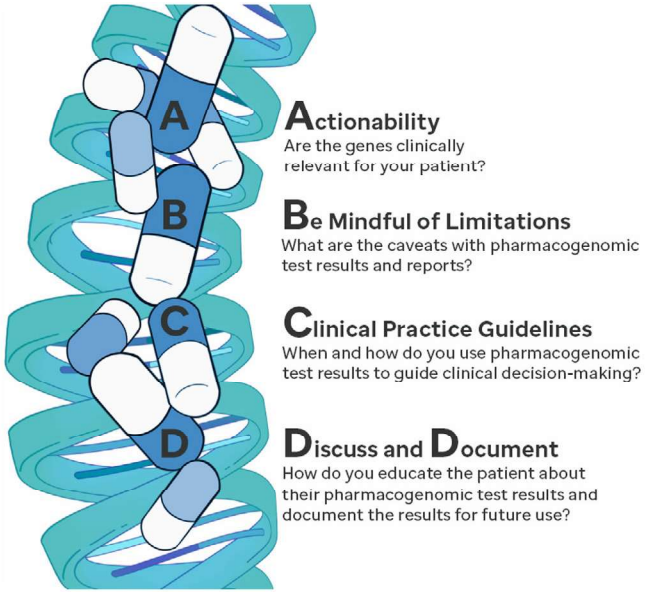

FIGURE 1 ABCDs of interpreting a pharmacogenomic test.

TABLE 1 Interpretation and clinical actionability of the case example patient's pharmacogenomic test results.

Genotype	Reported phenotype	CPIC phenotype	Example medications with CPIC Guidelines[a]
COMT Val/Val	High activity	N/A	None[36]
*CYP2B6*1/*5*	CYP2C9 normal metabolizer	CYP2B6 normal metabolizer	Efavirenz[37]
*CYP2C9*1/*1*	CYP2C9 normal metabolizer	CYP2C9 normal metabolizer	Fluvastatin[35] NSAIDs[38] Phenytoin[39] Warfarin[40]
*CYP2C19*1/*17*	CYP2C19 normal metabolizer	CYP2C19 rapid metabolizer	**Amitriptyline**[30] Clopidogrel[41] **Citalopram**[23] **Escitalopram**[23] **Proton pump inhibitors**[29] **Voriconazole**[42]
*CYP2D6*4/*4*	CYP2D6 poor metabolizer	CYP2D6 poor metabolizer	**Amitriptyline**[30] **Atomoxetine**[43] **Codeine**[36] **Fluvoxamine**[23] **Nortriptyline**[30] Ondansetron[44] **Paroxetine**[23] **Tamoxifen**[45] **Tramadol**[36] **Venlafaxine**[23] **Vortioxetine**[23]
*CYP3A5*3/*3*	CYP3A5 poor metabolizer	CYP3A5 poor metabolizer	Tacrolimus[31]
*HLA-B*15:02*	Negative	Negative	Carbamazepine[46] Oxcarbazepine[46] Phenytoin[39]
HTR2A G/A	Normal response	N/A	None[23]
RYR1 c.982 C>T – CT	Malignant hyperthermia susceptibility	Malignant hyperthermia susceptibility	**Volatile anesthetic agents**[47] **Succinylcholine**[47]
SLC6A4 L(G)/S	Low activity	N/A	None[23]
*SLCO1B1*1/*15*	SLCO1B1 decreased function	SLCO1B1 decreased function	**Statins**[35]

Abbreviation: N/A, not applicable.
[a]Bold = Genotype-guided prescribing indicated for the patient.

The ABCDs of interpreting and applying a pharmacogenomic test report (see Figure 1) will be described and applied to this case.

2 | ACTIONABILITY—ARE THE GENE(S) CLINICALLY RELEVANT FOR THE PATIENT?

Some laboratories test for genes that are not associated with established evidence. To assess the clinical usefulness of the genes reported by the laboratory, clinicians can check to see whether the patient's gene-drug pairs have associated CPIC guidelines (www.cpicpgx.org/guidelines).[22] CPIC has been continuously funded since 2012 by the National Institutes of Health with the goal of creating, curating, publishing, and updating evidence-based gene-drug clinical practice guidelines. CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, and use standardized terminology. These guidelines are published after a peer review process with simultaneous posting to cpicpgx.org, where they are regularly updated. The CPIC recommendations categorize gene-drug pairs as "actionable" and "non-actionable." An "actionable" gene-drug pair occurs when a genotype-guided prescribing action is recommended (CPIC level A—strong or moderate recommendation or CPIC level B—optional recommendation). "Non-actionable" means no action is recommended (CPIC level C—no recommendation). As of early 2024, there are 26 published CPIC guidelines covering 29 genes and over 100 drugs, with new guidelines and updates to the existing guidelines published periodically (see www.cpicpgx.org/guidelines for the most up-to-date information).

In the example patient case, a review of the CPIC website reveals a guideline for serotonin reuptake inhibitor antidepressants and the genes *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, and *HTR2A*.[23] The tables in this guideline present therapeutic recommendations for the following drugs (genes): paroxetine (*CYP2D6*), fluvoxamine (*CYP2D6*), venlafaxine (*CYP2D6*), vortioxetine (*CYP2D6*), citalopram (*CYP2C19*),

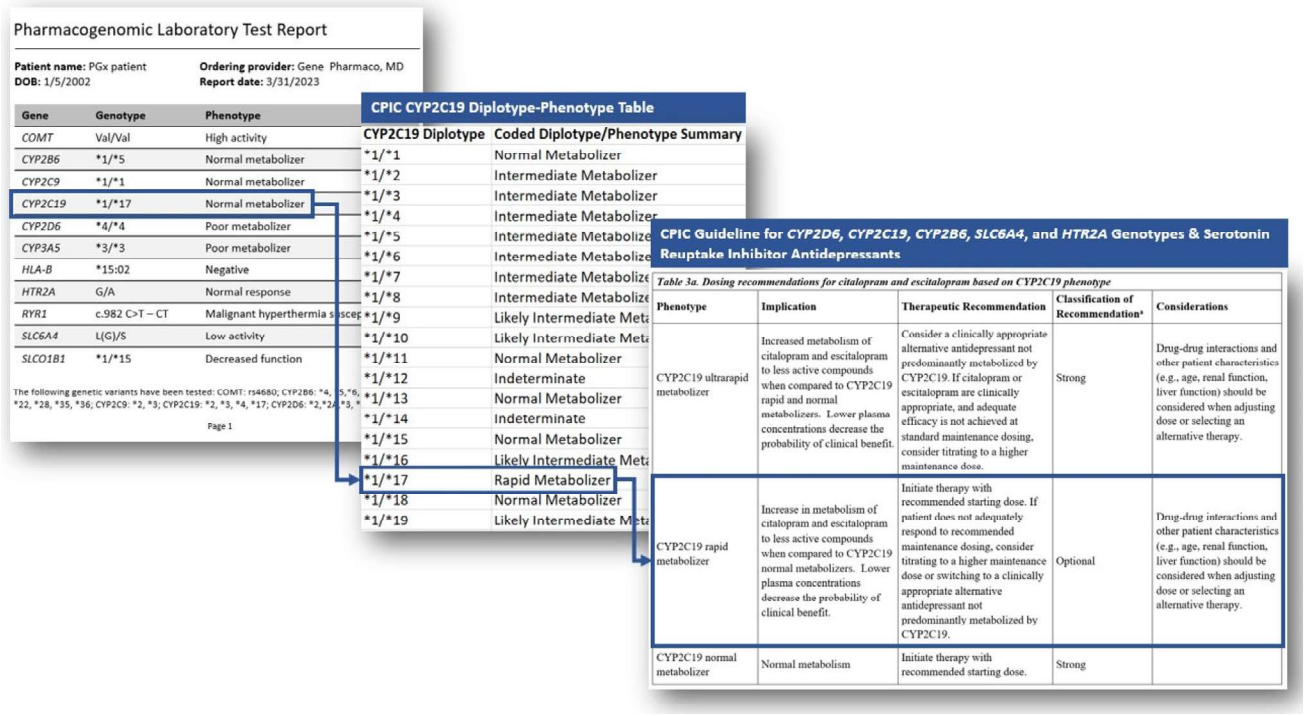

FIGURE 2 Using the CPIC guideline from genotype to phenotype to clinical recommendation. Note the discrepancy in the *CYP2C19*1/*17* phenotype between the CPIC guideline and the pharmacogenomic test laboratory report. In addition, note that the alleles tested for *CYP2C9* are not comprehensive according to the Association for Molecular Pathology recommendations for alleles to test.

escitalopram (*CYP2C19*), and sertraline (*CYP2C19*, *CYP2B6*). Therefore, when considering alternative antidepressant therapy for the patient case, the genes *CYP2D6*, *CYP2C19*, and *CYP2B6* are important to consider. Although *SLC6A4* and *HTR2A* are also included on this patient's pharmacogenomic test report, CPIC determined that the evidence was insufficient to change standard prescribing for antidepressants on the basis of these genotypes (i.e., not actionable).

3 | BE MINDFUL OF LIMITATIONS—WHAT ARE THE CAVEATS WITH PHARMACOGENOMIC TEST RESULTS AND REPORTS?

3.1 | Alleles tested

Pharmacogenomic tests are usually performed using genotyping rather than sequencing, meaning the laboratory is looking for a specific variant(s) in the gene rather than determining each base pair in the gene from start to finish. Therefore, allele selection is an important consideration to ensure adequate representation, especially given that allele frequencies differ among ancestry groups.[24,25] Some variants with important effects on drug response may be common in some ancestry groups and virtually absent in others. The Association for Molecular Pathology (AMP) provides guidance on what alleles should be included for specific pharmacogenomic tests, taking allele frequency differences by ancestry into account (for an updated "must-test" list, see https://www.pharmgkb.org/ampAllelesToTest).[26,27] If none of the variants on the laboratory assay are detected, the laboratory will assign the **1* allele, which is assumed to be wild type/normal function (though the patient could harbor a clinically important variant not included on the assay). For example, our patient was reported to have a *CYP2C9*1/*1* genotype, and the laboratory report indicated that only the *CYP2C9*2* and **3* alleles were tested (see Figure 2). However, *CYP2C9*5*, **6*, **8*, and **11*, which occur predominantly in African ancestry populations, also reduce CYP2C9 enzyme activity and are considered tier 1 (e.g., must-test) alleles by AMP. Although we will assume our patient is a CYP2C9 normal metabolizer on the basis of the reported **1/*1* genotype, they may in fact be a CYP2C9 intermediate or poor metabolizer if they carry the **5*, **6*, **8*, or **11* allele, which went undetected by this particular pharmacogenomic test. Even if a test adheres to the AMP must-test list, it is important to understand that rare variants can still be missed.

3.2 | Clinical interpretation of the result

Pharmacogenomic test results should not be used alone because they only account for genetic variability in drug response. Rather, clinicians should take a precision medicine–based approach and integrate pharmacogenomic information with other clinical data (e.g., age, renal function, liver function, and concomitant medications) when developing a pharmacotherapy plan. Sometimes clinical factors trump the pharmacogenomic data (e.g., if a patient who is a CYP2D6 normal metabolizer on the basis of genotype is taking a medication that is a

strong CYP2D6 inhibitor like fluoxetine, the corresponding genotype result is irrelevant, given there will be limited-to-no CYP2D6 activity because of the drug–drug interaction).[28] Furthermore, if a patient has been stable on a particular medication that is working well without significant adverse effects, in most cases, that medication should not be adjusted on the basis of any pharmacogenomic test result or guideline recommendation, even if the patient has an "actionable" result. However, there are exceptions to this. For example, prolonged use (more than 12 weeks) of proton pump inhibitors (PPIs) in CYP2C19 intermediate and poor metabolizers may place individuals at a higher risk of PPI-related adverse events (e.g., infection, bone fracture), and CPIC recommends considering a 50% dose reduction if efficacy can be maintained.[29]

Of importance, clinicians should not solely rely on a laboratory's interpretation of genotype results or medication recommendations because interpretations may be incorrect and recommendations may not be based on up-to-date evidence. In addition, some laboratories oversimplify medication information by categorizing medications as green, yellow, and red to symbolize minimal, moderate, and major gene-drug interactions. This color-coding can cause patient distress and misinterpretation. Therefore, it is best practice for clinicians to use the genotype results directly and consult clinical practice guidelines (e.g., CPIC guidelines) for interpretation.

4 | CLINICAL PRACTICE GUIDELINES—HOW DO YOU USE PHARMACOGENOMIC TEST RESULTS TO GUIDE CLINICAL DECISION-MAKING?

Pharmacists have long used clinical practice guidelines as a measure of appropriate drug use, and pharmacogenomic guidelines are no different. The CPIC guidelines are designed to provide clear, evidence-based recommendations to guide prescribing decisions on the basis of pharmacogenomic data.[22] The CPIC guidelines do not advise clinicians when they should order pharmacogenomic tests, but rather what they should do if they have the test results in hand. The CPIC guidelines provide tables of all the information a clinician will need to interpret a genetic test result (e.g., genotype to phenotype translation) and apply it to patient care (phenotype to therapeutic recommendation translation).

4.1 | Genotype to phenotype translation

Most pharmacogenomic test results are reported using the "star allele nomenclature" (e.g., *CYP2B6*1/*5*), with each star allele (e.g., **1* and **5*) representing each of the two copies of the gene that was inherited (one maternal allele and one paternal allele). This genotype (also known as the "diplotype") must then be translated to a phenotype because the clinical recommendations are based on phenotype categories (see Figure 2). The CPIC guidelines explain in detail how to interpret pharmacogenomic tests, including translating genotype (e.g., *CYP2D6*4/*4*) into phenotype (e.g., "CYP2D6 poor metabolizer"). For example, the patient in our case has the *CYP2D6*4/*4* genotype. Consulting the CPIC guidelines would show that this genotype is associated with the poor metabolizer phenotype. For a quick reference, CPIC provides a table summarizing genotype to phenotype translation for each gene that is the subject of their guidelines, which lists out every possible genotype result and maps it to a phenotype (see Figure 2). These tables can be found on individual CPIC guideline webpages and at https://www.pharmgkb.org/page/pgxGeneRef. It is essential for clinicians to be aware that not all pharmacogenomic testing laboratories use the same standards for genotype to phenotype translation as CPIC, so checking the laboratory's interpretation is crucial before making medication recommendations on the basis of the CPIC guidelines. For example, the laboratory in the case example reports that the patient is a "CYP2C19 normal metabolizer." However, CPIC's interpretation of the *CYP2C19*1/*17* genotype is "rapid metabolizer," which may have significant implications for medication management. It is also important to note that each gene has its own genotype to phenotype translation table, so the appropriate gene table must be reviewed.

4.2 | Clinical recommendations

Each CPIC guideline contains one or more clinical recommendation tables that provide a specific prescribing action (or lack thereof) for each pharmacogenomic *phenotype* of the gene in question. In each guideline, CPIC also provides pediatric considerations (and sometimes, a separate pediatric recommendation table if data are sufficient to generate one). In our patient case, results from the genetic test show our patient is a CYP2C19 rapid metabolizer and a CYP2D6 poor metabolizer and that the patient has low activity for SLC6A4. According to the CPIC guideline, SLC6A4 is not actionable (CPIC level C—no recommendation), but there is antidepressant guidance for CYP2D6 poor metabolizers and CYP2C19 rapid metabolizers. The CPIC guideline recommends a 50% reduction in the paroxetine maintenance dose in patients who are CYP2D6 poor metabolizers. Because adverse effects occurred after the dose increase and the patient reports good control of anxiety and depression, it might be suitable to change to a medication not metabolized by CYP2D6 such as citalopram or escitalopram. Although CYP2C19 metabolizes both citalopram and escitalopram and this patient is a CYP2C19 rapid metabolizer, the CPIC guideline recommends initiation of the recommended starting dose, with higher doses indicated if the patient is not responding.

Some of these recommendations may depend on the indication of the medication. For example, the CPIC guideline for tricyclic antidepressants (TCAs) has a recommendation table that provides *CYP2D6*- and *CYP2C19*-guided dosing recommendations for TCAs when they are used at doses to treat depression.[30] The recommendations differ if the patient takes a TCA at lower doses to treat neuropathic pain. In addition, a clinician cannot determine whether there is a genotype-guided change from standard prescribing on the basis of the patient's phenotype (i.e., poor metabolism does not always indicate a therapy

adjustment and normal metabolism does not always indicate normal dosing). For example, the patient in our case is a CYP3A5 poor metabolizer, and the CPIC guideline for *CYP3A5*/tacrolimus recommends the standard starting dose in these patients and an increased dose in CYP3A5 normal metabolizers.[31]

In addition to checking the CPIC guidelines for clinical recommendations, clinicians should check the respective guideline webpage on the CPIC website for any pertinent updates to the guideline that have emerged since the guideline was published (e.g., see https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/).

5 | DISCUSS AND DOCUMENT—HOW DO YOU EDUCATE THE PATIENT ABOUT THEIR PHARMACOGENOMIC TEST RESULTS AND DOCUMENT THE RESULTS FOR FUTURE USE?

Pharmacogenomic test results are relevant lifelong, making patient counseling a critical part of returning results to patients. Key counseling points and strategies for discussing the results of a multi-gene pharmacogenomic panel with patients have been described.[32] Although pharmacogenomic test results should be documented in the patient's electronic health record to support continued use of these results over time, patients need to be empowered to share this information with all of their health care providers, especially those outside the health care system where the testing was ordered.[33] In some cases, pharmacogenomic test results may have significant familial or disease implications, in which case referral to a genetic counselor may be warranted.[34] In our case, this patient carries an *RYR1* variant linked to malignant hyperthermia susceptibility; thus, further counseling may be warranted for both the patient and the patient's family members. When counseling the patient, it is also important to discuss the implications for the other drugs (see Table 1) the patient may be prescribed in the future. For example, our patient has SLCO1B1 decreased function, and if ever prescribed a statin, they would likely need a lower dose or selection of a statin less affected by SLCO1B1.[35]

In summary, clinical pharmacists can use freely available, evidence-based resources to guide pharmacogenomic test result interpretation and clinical application. As medication experts, clinical pharmacists must understand both genetics and other patient-specific factors that influence medication response. We recommend that clinical pharmacists review the CPIC guideline webpage and familiarize themselves with the pharmacogenomic associations most relevant to their daily practices. This is a rapidly evolving field, so clinical pharmacists should stay abreast of new CPIC guidelines and updates of previous guidelines. CPIC has a public announcement list, and subscribers to this list receive updates and announcements about CPIC on a regular basis (cpicipgx.org → contact → sign-up). All pharmacists can gain valuable knowledge and skills in pharmacogenomics and can harness this powerful clinical tool to implement precision medicine. Remembering the "ABCDs" of pharmacogenomics outlined in this paper can help guide pharmacists through this process.

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