

CYP2D6 and CYP2C19 Polymorphisms as Predictors of Antidepressant Response

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Abstract

Precision medicine aims to tailor therapeutic interventions to individual patients by integrating genetic, environmental, and lifestyle factors. In the context of Major Depressive Disorder (MDD), traditional antidepressant prescribing is hindered by variable drug response and a high prevalence of treatment resistance. Pharmacogenomic (PGx) testing, particularly for the cytochrome P450 enzymes *CYP2D6* and *CYP2C19*, offers a clinically actionable approach to guide drug selection and dosing. This review synthesizes current evidence on the role of *CYP2D6* and *CYP2C19* polymorphisms in antidepressant metabolism, the resulting metabolic phenotypes, and their implications for efficacy and adverse drug reactions. PGx-guided therapy has been shown to improve response and remission rates compared to conventional treatment, while reducing the risks of under- or overexposure. Challenges to widespread implementation include cost, clinician training, and multi-gene interpretation complexity, though integration into electronic health records and emerging polygenic risk scores may facilitate broader adoption. Overall, PGx testing represents a validated, practical tool to individualize antidepressant therapy, offering a pathway toward more effective and safer treatment strategies for MDD.

Keywords: Pharmacogenomics, CYP2D6, CYP2C19, Antidepressants, Major Depressive Disorder (MDD), Precision Medicine, Personalized Therapy, Treatment-Resistant Depression (TRD), Drug Metabolism, Genetic Polymorphism

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1. Introduction

1.1. Context and Background

Genetics plays a foundational role in modern medicine by explaining why individuals differ in their susceptibility to disease and in their responses to therapeutic interventions. Together with environmental exposures and lifestyle influences, these genetic differences shape the considerable variability seen in drug effectiveness and safety. Precision medicine is an emerging approach that aims to optimize patient care by accounting for individual variability rather than applying uniform, standardized treatment strategies. It incorporates multiple sources of variation, including genetic makeup, environmental exposures, and lifestyle components, to support more accurate diagnoses and more precisely targeted therapies. By moving beyond

the traditional one-size-fits-all model, precision medicine seeks to improve overall treatment outcomes and reduce the likelihood of therapeutic failure [1]. Pharmacogenetics, a central component of precision medicine, focuses on identifying genetic variants that shape drug response [2].

Treating Major Depressive Disorder (MDD) remains challenging because initial antidepressant response rates are low and vary widely among patients. MDD is often underdiagnosed, complicated by somatic symptoms, and commonly co-occurs with chronic medical conditions, delaying accurate treatment. Even with proper diagnosis, many patients do not respond to first-line therapy. Large clinical datasets, such as STAR*D, show that roughly 30% of patients do not achieve remission even after several antidepressant trials, underscoring the presence of a substantial treatment-resistant subgroup [3]. These outcomes reflect the biological and social variability within MDD, making standardized, trial-and-error prescribing inadequate. This gap underscores the need for more individualized strategies such as pharmacogenomic (PGx)-guided therapy to optimize initial drug selection and reduce repeated treatment failures.

1.2. Scope and Thesis

This review examines the clinical role of PGx in guiding antidepressant prescribing, with a particular emphasis on its potential to improve treatment selection and patient outcomes. The central argument of this paper is that

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PGx testing of key Cytochrome P450 enzymes, particularly *CYP2D6* and *CYP2C19*, can significantly enhance the prediction of drug response and optimize therapeutic outcomes for individuals undergoing antidepressant therapy.

2. Materials & Methods

2.1. Literature Search Strategy

To gather the materials for this review, our team conducted a literature search across several major scientific databases, including PubMed, Google Scholar, and Web of Science. We used a range of search terms related to the topic, such as “pharmacogenomics and antidepressants,” “*CYP2D6/CYP2C19* polymorphisms,” “*CYP2D6* and *CYP2C19* dose adjustments,” “Major Depressive Disorder (MDD),” “drug metabolism genetics,” “precision medicine,” “CPIC guidelines,” “DPWG guidelines,” “tricyclic antidepressants,” and “SSRIs.” These articles were selected based on the following criteria: peer-reviewed publications, clinical guidelines, and review papers published between 2000 and 2025, with a clear focus on PGx and antidepressant therapy. Non-peer-reviewed sources, including conference abstracts and opinion pieces, were excluded to ensure that only reliable and clinically relevant evidence informed the review.

2.2. Data Extraction and Synthesis

We extracted and synthesized data from the selected sources, focusing on key PGx elements such as the specific genes involved (e.g., *CYP2D6*, *CYP2C19*), the corresponding antidepressant drug classes (e.g., Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs)), and the predicted metabolic phenotypes including ultrarapid, normal, intermediate, and poor metabolizers. Clinical recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) were also collected, along with comparative findings evaluating treatment-as-usual versus PGx-guided antidepressant therapy in patients with MDD.

After extraction, the information was systematically synthesized and organized into three central thematic categories: Genetics in Etiology and Diagnosis, Applications in Therapy, and Clinical Challenges and Future Directions. This structure provides a coherent framework that guides the development of the Discussion section and enables clear integration of the evidence across studies.

3. Discussion

3.1. Genetics in Etiology and Diagnosis

3.1.1. Introduction to Pharmacogenomics and Genetic Variation

The most common form of DNA variation among individuals is the single-nucleotide polymorphism (SNP). SNPs

are fundamentally a substitution of a single nucleotide that occurs at a specific position in the genome. These common variants occur approximately once in every 1 000 nucleotides on average or, more broadly, every 300–2 000 base pairs, meaning a person’s genome contains roughly 4–5 million SNPs [4]. SNPs are responsible for conferring genomic diversity and generating phenotypic differences among individuals. Although most SNPs do not affect health, those in functionally relevant regions can significantly alter gene function. Functional changes resulting from SNPs include influencing promoter activity (gene expression) and affecting messenger RNA (mRNA) conformation and stability. This inherited variability is a crucial factor, accounting for $\approx 15–30\%$ of inter-individual variability in drug disposition and response, though for certain drugs, this variability can reach up to 95%. The identification and analysis of these variations provide a starting point for developing safer, individualized medication [5, 6].

3.1.2. Genetic Basis of Drug Metabolism: Cytochrome P450 System

The genetic foundation of PGx directly intersects with drug elimination through the Cytochrome P450 (CYP) enzyme system, which functions as the cornerstone of drug metabolism. Genetic factors, specifically the inherited variability in drug-metabolizing enzymes, have a major impact on drug disposition and are responsible for a significant degree of interpatient variability [7]. Variations closely linked to drug metabolism are predominantly observed in Phase I metabolism, particularly within the gene polymorphisms of *CYP2C19* and *CYP2D6* [5]. The CYP enzyme system is central to psychiatric PGx because CYP enzymes are recognized as the primary liver enzymes responsible for drug metabolism.

3.1.3. *CYP2D6* and *CYP2C19* in Antidepressant Metabolism

In the context of antidepressant therapy, polymorphisms in *CYP2D6* and *CYP2C19* are the most clinically relevant pharmacogenes influencing drug disposition and response. These highly polymorphic enzymes are centrally involved in the metabolism of numerous psychiatric drugs, including SSRIs and TCAs [7].

3.1.3.1. *CYP2D6* Overview.

CYP2D6 is one of the most extensively studied PGx biomarkers and plays an essential role in antidepressant metabolism, participating in the clearance of roughly 20% of all therapeutic drugs. *CYP2D6* extensively metabolizes several antidepressants, including paroxetine, fluvoxamine, venlafaxine, and vortioxetine, typically converting the active parent compound into less active metabolites [8, 9, 7].

3.1.3.2. *CYP2C19* Overview.

CYP2C19 is highly involved in antidepressant metabolism, alongside *CYP2D6*. It is responsible

for metabolizing about 5 – 10% of all drugs. Importantly, it extensively metabolizes several SSRIs, such as citalopram, escitalopram, and sertraline, usually converting them to much less potent metabolites. The antidepressant escitalopram, for instance, is metabolized by *CYP2D6*, *CYP2C19*, and *CYP3A4* [10, 9, 7].

The extensive polymorphism of these two enzymes dictates that individuals possess different metabolic capacities, impacting the clearance, half-life, and plasma concentrations of most antidepressants. Consequently, genetic testing focuses on these two key enzymes to classify a patient’s metabolic status and predict pharmacokinetic variability associated with standard dosing [7].

3.1.4. Diagnostic Metabolic Categories

The inherent functional capacity of these CYP enzymes is determined by the patient’s unique combination of inherited alleles, or diplotype. PGx testing utilizes this information to categorize individuals into distinct metabolic phenotypes, which act as diagnostic tools to predict the efficacy and safety profile of standard drug dosages [11, 12]. The resulting phenotypes include poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs), rapid metabolizers (RMs), and ultrarapid metabolizers (UMs) [7]. Tables 1 and 2 summarize the relationship between *CYP2D6*/*CYP2C19* diplotypes and the resulting metabolic phenotypes. These phenotypes determine whether a patient under- or over-metabolizes a drug, forming the basis for clinical dose adjustments.

3.1.5. Conceptual Summary

The analysis of *CYP2D6* and *CYP2C19* polymorphisms functions as a preemptive diagnostic tool to classify the individual’s metabolic phenotype (UM, RM, NM, IM, or PM). This diagnostic classification is critical for predicting drug exposure levels (pharmacokinetics), which then guides clinical decisions regarding optimal drug selection or necessary dosage adjustments for standard maintenance therapy. This helps personalize treatment and move away from ineffective trial-and-error methods [8, 7, 5].

3.2. Application in Therapy

PGx testing translates genomic variation into actionable therapeutic choices, shifting antidepressant therapy away from trial-and-error and toward a model in which mechanism, exposure, and clinical effect are linked in a predictable way. In practice, this means that the patient’s metabolic capacity is used as a starting point for drug selection, dose setting, and interpretation of nonresponse.

3.2.1. Guiding Drug Selection

The primary application of PGx in antidepressant therapy is the initial selection of a medication that matches the patient’s metabolic profile. This process aims to maximize efficacy while alleviating the risk of adverse drug reactions (ADRs). The CPIC and the DPWG

provide guidelines for specific gene–drug pairs, particularly involving *CYP2D6* and *CYP2C19*, and operationalize this by mapping genotype→phenotype→expected serum concentration→likelihood of response or toxicity [8, 15, 13]. When a patient is predicted to have non-normal metabolism, selection of an antidepressant with a metabolic pathway that avoids the affected enzyme is often the simplest, safest strategy to preserve therapeutic exposure.

For UMs, who carry duplications or increased-function alleles that markedly accelerate metabolic clearance, guidelines generally emphasize selecting an alternative agent rather than increasing the dose of the original drug. Dose escalation in UMs may be insufficient to overcome rapid clearance and may increase risk without ensuring efficacy. Several antidepressants are metabolized largely by pathways other than *CYP2D6* or *CYP2C19*, making them suitable alternatives when UM status is known. These include medications primarily metabolized by *CYP3A4* or *CYP2B6* (e.g., vilazodone, levomilnacipran, trazodone, bupropion) as well as agents with minimal *CYP2D6*/*CYP2C19* involvement, such as desvenlafaxine or milnacipran [8, 16, 17]. Selection, however, must still consider the medication’s broader clinical profile, including side-effect risks, comorbidities, and drug–drug interactions.

Population-level differences in *CYP2D6* and *CYP2C19* allele frequencies further illustrate why genotype-guided selection matters. For instance, *CYP2D6* gene duplications occur in approximately 20–30% of individuals in Ethiopia and Saudi Arabia (see Fig. 1), predisposing a substantial proportion of these populations to treatment failure with standard doses of drugs metabolized by *CYP2D6* [18]. For TCAs such as amitriptyline and nortriptyline, this increased clearance results in subtherapeutic serum levels and apparent nonresponse despite good adherence. In such cases, guidelines recommend avoiding *CYP2D6*-dependent antidepressants entirely [19]. A similar issue arises for *CYP2C19* UMs, for whom citalopram and escitalopram are discouraged due to a high likelihood of subtherapeutic exposure [13].

3.2.2. Dosage Adjustment

When a patient must remain on a particular antidepressant despite a predicted non-normal metabolic phenotype, PGx testing provides evidence-based guidance for dosage modification to preserve clinical safety and effectiveness. Standard dosing regimens—derived from population averages—may produce toxic drug accumulation in PMs or lack efficacy in UMs. CPIC offers specific dose adjustments based on *CYP2D6*/*CYP2C19* phenotypes:

- SSRIs: For *CYP2C19* PMs taking citalopram, escitalopram, or sertraline, CPIC recommends reducing the initial dose by 50% to avoid excessive serum levels and potential complications such as QT prolongation

Table 1: Assignment of predicted *CYP2D6* phenotypes based on diplotypes

Phenotype	Activity score	Genotypes	Example diplotypes
<i>CYP2D6</i> Ultrarapid metabolizer	> 2.25	Carries duplications of functional alleles	$(\ast 1/\ast 1) \times N$, $(\ast 1/\ast 2) \times N$, $(\ast 2/\ast 2) \times N$
<i>CYP2D6</i> Normal metabolizer	$1.25 \leq x \leq 2.25$	Allele combinations yielding an activity score of 1.0–2.0	$\ast 1/\ast 1$, $\ast 1/\ast 2$, $\ast 2/\ast 2$, $\ast 1/\ast 9$, $\ast 1/\ast 41$, $\ast 41/\ast 41$, $\ast 1/\ast 5$, $\ast 1/\ast 4$
<i>CYP2D6</i> Intermediate metabolizer	$0 < x < 1.25$	One decreased-function allele and one no-function allele	$\ast 4/\ast 41$, $\ast 5/\ast 9$, $\ast 4/\ast 10$
<i>CYP2D6</i> Poor metabolizer	0	Carries only no-function alleles	$\ast 4/\ast 4$, $(\ast 4/\ast 4) \times N$, $\ast 3/\ast 4$, $\ast 5/\ast 5$, $\ast 5/\ast 6$
<i>CYP2D6</i> Indeterminate	n/a	One or two uncertain or unknown-function alleles	$\ast 1/\ast 22$, $\ast 1/\ast 25$, $\ast 22/\ast 25$

Note. Phenotype assignments were synthesized from the DPWG guideline on *CYP2C19* and *CYP2D6* interactions with SSRIs [13], the CPIC Guideline for Selective Serotonin Reuptake Inhibitors (2023) [8], and the CPIC Guideline for Tricyclic Antidepressants (2016) [14].

Table 2: Assignment of predicted *CYP2C19* phenotypes based on diplotypes

Phenotype	Activity score	Genotypes	Example diplotypes
<i>CYP2C19</i> Ultrarapid metabolizer	n/a	Two increased-function alleles	$\ast 17/\ast 17$
<i>CYP2C19</i> Rapid metabolizer	n/a	One normal-function and one increased-function allele	$\ast 1/\ast 17$
<i>CYP2C19</i> Normal metabolizer	n/a	Two normal-function alleles	$\ast 1/\ast 1$
<i>CYP2C19</i> Likely intermediate metabolizer	n/a	One normal and one decreased-function allele; or one increased and one decreased-function allele; or two decreased-function alleles	$\ast 1/\ast 9$, $\ast 9/\ast 17$, $\ast 9/\ast 9$
<i>CYP2C19</i> Intermediate metabolizer	n/a	One normal and one no-function allele; or one no-function and one increased-function allele	$\ast 1/\ast 2$, $\ast 1/\ast 3$, $\ast 2/\ast 17$
<i>CYP2C19</i> Likely poor metabolizer	n/a	One decreased-function allele and one no-function allele	$\ast 2/\ast 9$, $\ast 3/\ast 9$
<i>CYP2C19</i> Poor metabolizer	n/a	Two no-function alleles	$\ast 2/\ast 2$, $\ast 2/\ast 3$, $\ast 3/\ast 3$
<i>CYP2C19</i> Indeterminate	n/a	One or two uncertain-function alleles	$\ast 1/\ast 12$, $\ast 2/\ast 12$, $\ast 12/\ast 14$

Note. Phenotype assignments were synthesized from the DPWG guideline on *CYP2C19* and *CYP2D6* interactions with SSRIs [13], the CPIC Guideline for Selective Serotonin Reuptake Inhibitors (2023) [8], and the CPIC Guideline for Tricyclic Antidepressants (2016) [14].

or serotonin toxicity [8, 13, 20].

-TCAs: For *CYP2D6** PMs, dose reductions of up to 50% are recommended to prevent toxicity, while IMs may require more modest reductions of approximately 25% depending on the agent and clinical context [14].

These tailored dosing strategies help maintain drug concentrations within the therapeutic window, reducing the time patients spend on ineffective or harmful regimens and improving the likelihood of early clinical benefit [21].

3.2.3. Treatment of Resistant Cases

PGx testing is particularly valuable in the management of Treatment-Resistant Depression (TRD), generally defined as failure to respond to at least two adequate antidepressant trials [22]. In routine clinical settings, PGx testing is often initiated only after multiple unsuccessful treatments or unexpected ADRs.

In such cases, genetic testing can clarify whether prior treatment failures reflect true pharmacodynamic resistance or previously unrecognized pharmacokinetic issues. For example, a patient classified as “treatment-resistant” may actually be a *CYP2D6* UM who never achieved therapeutic drug levels, or a PM who discontinued therapy after



Fig. 1: Interethnic distribution of alleles containing duplicated active *CYP2D6* genes. Reproduced from Ingelman-Sundberg M [2].

experiencing intolerable side effects misinterpreted as non-adherence [23, 24]. An illustrative case involves *CYP2D6* PMs receiving standard nortriptyline doses, where excessive serum levels cause anticholinergic toxicity and cardiac risks, leading to early discontinuation that may be mistaken for clinical nonresponse [25].

Evidence increasingly supports that PGx-guided therapy improves treatment outcomes in TRD. Meta-analyses and controlled trials report higher response and remission rates among patients receiving PGx-tailored treatment compared to treatment-as-usual [26, 27, 28]. By uncovering actionable genetic contributors to poor response, clinicians can select alternative medications whose metabolism or mechanism bypasses the source of prior failure, enabling effective treatment even after multiple unsuccessful trials.

3.3. Clinical Challenges and Future Directions

3.3.1. Challenges

High costs of PGx testing represent a primary barrier to implementation in antidepressant therapy, with multi-gene panels often exceeding affordable thresholds in resource-limited settings and lacking consistent reimbursement from insurers [29]. Physician training remains a sig-

nificant barrier. Many clinicians report inadequate preparation for interpreting PGx results or applying them in prescribing decisions, which limits adoption despite the existence of guidelines [30]. The complexity of multi-gene interpretation further complicates use, since antidepressant response involves interacting variants in genes like *CYP2D6* and *CYP2C19*, where phenotypes such as UMs or PMs require nuanced assessment amid variable evidence strength [31]. Additional obstacles include workflow disruptions, inconsistent clinical guidelines, and data privacy issues that hinder routine PGx application [32].

3.3.2. Future Directions

Future directions in PGx for antidepressant therapy aim to resolve key clinical challenges, such as interpretation complexity, physician education deficits, and workflow inefficiencies, through technological and analytical advancements. Integration of PGx data into Electronic Health Records (EHRs) enables automated clinical decision support [33]. For instance, an EHR system can scan a patient's genotype and flag a *CYP2D6* UM status, prompting clinicians to consider switching to an antidepressant not primarily metabolized by *CYP2D6*; only when alternatives are unsuitable would the system suggest a higher

starting dose for agents such as nortriptyline. Polygenic Risk Scores (PRS) will enhance precision by combining multiple loci to predict treatment response, surpassing single-gene limitations and supporting stratified dosing in depression care [34]. Although promising, these scores remain early-stage research tools for antidepressant response, and no clinical guidelines currently support their routine use, so they should be viewed as a longer-term direction rather than an imminent component of standard care [35]. The aforementioned innovations, alongside expanded guidelines and training, promise broader equitable access.

4. Conclusion

This review has demonstrated that PGx testing, particularly focusing on inherited variations in the key drug-metabolizing enzymes Cytochrome P450 *CYP2D6* and *CYP2C19*, is an essential strategy for improving how we prescribe antidepressants for MDDs. Our main conclusion—that PGx testing can markedly improve the prediction of how a patient will respond to medication—is strongly supported by its established role in clinical practice.

The significant genetic differences found within *CYP2D6* and *CYP2C19* directly lead to distinct metabolic profiles in patients (for example, poor, intermediate, and ultrarapid metabolizers). These profiles, in turn, critically affect the actual amount of an antidepressant (like SSRIs and TCAs) that reaches the bloodstream. To address this, organizations such as the CPIC and the DPWG have developed guidelines that turn this genetic data into practical advice for choosing the right drug or adjusting its dose. This systematic approach allows clinicians to move beyond the traditional, often frustrating, trial-and-error method. For PMs, this means significantly reducing the risk of ADRs; for UMs, it helps ensure the drug is not cleared too quickly, leading to nonresponse. Importantly, PGx testing also provides a valuable tool for addressing TRD, helping clinicians identify biological reasons for nonresponse and guiding more effective alternative therapies.

Despite the clear benefits, certain roadblocks remain today. These hurdles include the substantial expense of testing, the need for improved training for medical professionals in interpreting these results, and the difficulty inherent in analyzing multiple genes whose effects interact. Nonetheless, the outlook for the future is quite encouraging. We anticipate a smoother, automated process as PGx results are integrated directly into Electronic Health Records (EHRs). Furthermore, the creation of more advanced PRS is expected to make tailored depression treatment both more successful and more widely available to patients. The key takeaway is this: testing for *CYP2D6* and *CYP2C19* is no longer a developing theory; it is now an increasingly validated, reliable clinical tool. It offers

the most direct and practical path to genuinely individualize antidepressant therapy, which is the most critical factor for enhancing patient results.

5. Author Contributions

- Tran Quoc Hoang: Conceived the study and developed the overall methodology (Conceptualization, Methodology). Managed the project and compiled the manuscript in Quarto (Project Administration, Software). Performed literature synthesis and wrote *Section 3.2* “Application in Therapy” (Investigation, Writing – Original Draft). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Nguyen Hoang Thanh Ngan: Conducted literature review and synthesized evidence for *Section 3.1* “Genetics in Etiology and Diagnosis” (Investigation, Writing – Original Draft). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Pham Gia Han: Collected and analyzed background information for *Section 1* “Introduction” and *Section 2* “Materials & Methods” (Investigation, Methodology). Wrote these sections (Writing – Original Draft) and contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Pham Ngo Phuong Thao: Investigated and summarized clinical challenges and future directions for *Section 3.3* “Clinical Challenges and Future Directions” (Investigation, Writing – Original Draft). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Nguyen Hoang Tuong Vy: Summarized the manuscript to prepare presentation slides (Data Curation, Visualization). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Nguyen Le Ngoc Vy: Summarized the manuscript to prepare presentation slides (Data Curation, Visualization). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).

6. Declaration of Competing Interest

The authors declare no competing interests.

7. Abbreviations

8. Data/Code Availability

The Quarto project underlying this paper—including the manuscript, figures, and bibliography—is available at <https://github.com/ht2905/pgx-antidepressant-response-article>.

Abbreviation	Full Term
ADR	Adverse Drug Reaction
CPIC	Clinical Pharmacogenetics Implementation Consortium
DPWG	Dutch Pharmacogenetics Working Group
EHR	Electronic Health Record
IM	Intermediate Metabolizer
MDD	Major Depressive Disorder
PGx	Pharmacogenomic
PM	Poor Metabolizer
PRS	Polygenic Risk Scores
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TRD	Treatment-Resistant Depression
UM	Ultrarapid Metabolizer

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