NEJM Evidence

Published September 23, 2025
NEJM Evid 2025;4(10)
DOI: 10.1056/EVIDra2400343

REVIEW ARTICLE | UPDATES IN GENETICS

Pharmacogenetic Testing — Evidence, Challenges, and Pathways to Adoption

Nihal El Rouby, Pharm.D., Ph.D.,[1,2] and Julie A. Johnson, Pharm.D.[3,4]

Abstract

Genetics plays an important role in the response to some drugs. Clinical pharmacogenetic testing can be used to guide pharmacotherapy selection or dosing to optimize outcomes. Growing evidence over the past decade has led to the identification of numerous pharmacogenetic associations, which have been integrated across multiple clinical areas, including cardiology, primary care, pain management, surgery, and oncology. Increased access to pharmacogenetic testing via national laboratories and pharmacogenetic testing companies has facilitated uptake and heightened public interest. While clinical adoption of pharmacogenetics has increased, challenges remain, including a lack of clinician confidence in navigating the logistics of testing and applying pharmacogenetics results in patient care; limited reimbursement for testing in some cases; the need for extensive outcomes and economic data; and limited inclusion of testing in clinical guidelines. Future opportunities include the broader use of multigene panels, enhanced clinician training, the integration of pharmacogenetic data within electronic health records, and increased documentation of outcomes data from real-world implementation to support insurance coverage.

Sonja A. Rasmussen, M.D., and C. Corey Hardin, M.D., Ph.D., Editors

Introduction

Pharmacogenetics, the study of how genetic variation impacts patients' drug responses, emerged from early observations of variable susceptibility to drug-related adverse events.[1] The influence of genetics on variability in drug response has now been clearly documented to extend to many commonly prescribed medications.[2] The terms pharmacogenetics and pharmacogenomics are often used interchangeably, but can be used to distinguish gene-specific versus genome-wide data, respectively. Both focus on the use of genetic data to improve drug therapy outcomes.[1,3]

Pharmacogenetics has advanced through numerous U.S. National Institutes of Health (NIH)–funded initiatives, including the Pharmacogenomics Global Research Network and pharmacogenetic consortia[4-6] (Fig. 1). Key pharmacogenetic resources, such as the NIH-funded Implementing Genomics in Practice Network, helped drive pharmacogenetic discoveries into clinical practice.[7-10]

The author affiliations are listed at the end of the article.

Julie A. Johnson can be contacted at julie.johnson@osumc.edu.

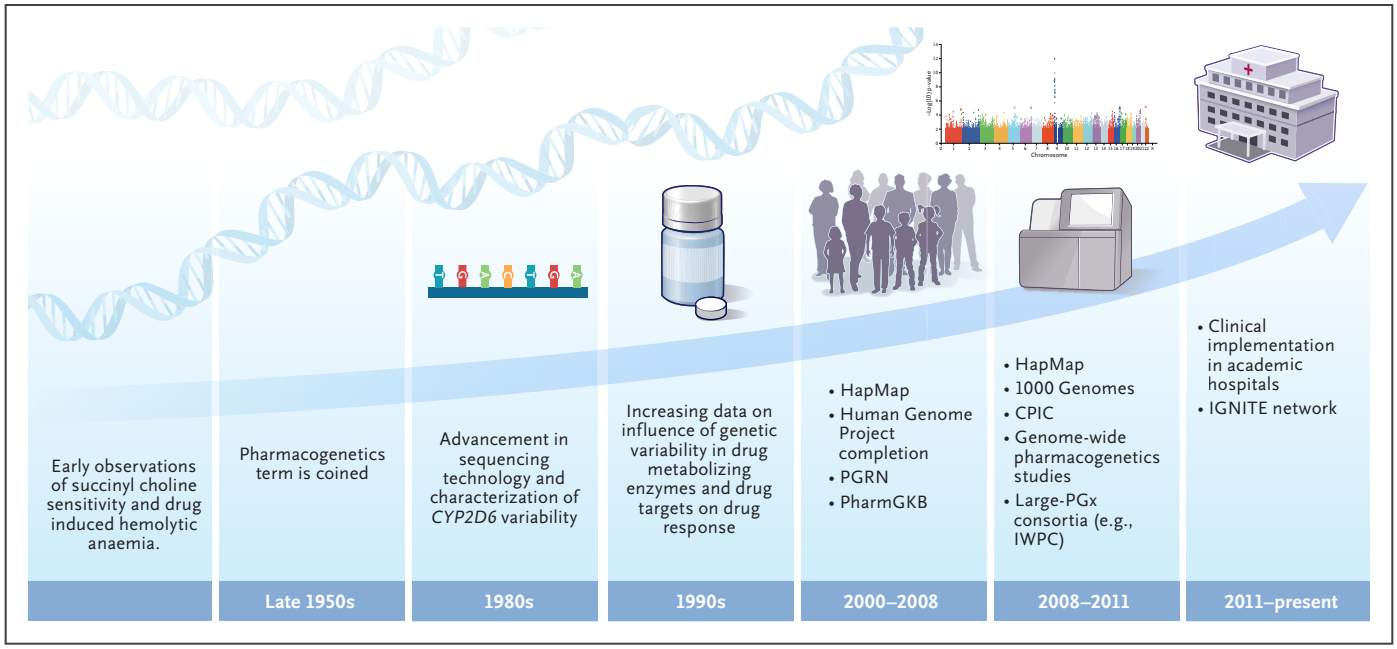

Figure 1. Evolution of Pharmacogenomics from Discovery to Implementation.

CPIC denotes Clinical Pharmacogenetics Implementation Consortium; HapMap, International HapMap Project; IGNITE, Implementing Genomics in Practice; IWPC, International Warfarin Pharmacogenetics Consortium; PGRN, Pharmacogenomics Global Research Network; PGx, pharmacogenomics; and PharmGKB, Pharmacogenomics Knowledge Base.

Advances in Pharmacogenetic Implementation

The past decade has seen successful clinical pharmacogenetics testing at numerous institutions, with most efforts centering on drug-metabolizing enzymes that possess common genetic variations with large effect sizes. Among these, the most common pharmacogenetic applications are with the cytochrome P450 enzymes CYP2C19 and CYP2D6. The genes encoding these proteins have variations that lead to absent protein function, reduced protein function, or increased protein function, and variations in these genes are common in populations all across the world (Table 1).[11] The potential impact of genetic variation for drug-metabolizing enzymes depends on whether the drug is an active drug or a prodrug, as highlighted in Figure 2.

Medications for which there is pharmacogenetic guidance span a wide range of therapeutic areas and represent many of the most commonly prescribed drugs (Table 2).[12-28] For instance, among medications with Clinical Pharmacogenetics Implementation Consortium (CPIC) clinical practice recommendations, 16 are among the top 50 most prescribed drugs in the United States, accounting for over 500 million prescriptions filled for 162 million individuals in 2022.[29] The common use of drugs with CPIC guidance means that they are routinely encountered within health systems. For example, prescribing data from the period between 2011 and 2016 from electronic health records (EHRs) of 11 U.S. health systems estimated that more than 15,000 out of every 100,000 adults treated at these health systems were prescribed at least one drug with a CPIC recommendation.[30] Similarly, University of Michigan Health System data showed that 75% of adult patients were prescribed at least one medication with a CPIC recommendation between 2014 and 2021.[31] Furthermore, over 95% of individuals carry an actionable pharmacogenetic variant that may impact a prescribing action.[32] Collectively, the potential population impact of implementing pharmacogenetics is high.

This review focuses on pharmacogenetic germ-line variations and their impact on drug dosing and response. We summarize pharmacogenetics resources and examples of drugs and genes with the widest clinical implementation and/or most extensive literature.[33] Testing for *HLA-B*57:01* before the prescription of abacavir is common, although we do not discuss this example herein. Interested readers are referred to key citations for more information.[34,35]

Table 1. Phenotype Frequency of *CYP2C19* and *CYP2D6* Metabolic Phenotypes across Multiple Populations.*

Population/Continental ancestry†	Poor Metabolizers	Intermediate Metabolizers	Normal Metabolizers	Rapid Metabolizer	Ultrarapid Metabolizers
CYP2D6					
African American/Afro-Caribbean	0.02	0.36‡	0.57	NA	0.05
European	0.07	0.38‡	0.52		0.03
Central/South Asian	0.02	0.28‡	0.68		0.02
East Asian	0.01	0.38‡	0.59		0.02
Latino	0.03	0.29‡	0.63		0.05
CYP2C19					
African American/Afro-Caribbean	0.05	0.34	0.33	0.24	0.04
European	0.02	0.26	0.40	0.27	0.05
Central/South Asian	0.08	0.41	0.30	0.19	0.03
East Asian	0.13	0.46	0.38	0.03	0.00
Latino	0.01	0.19	0.53	0.24	0.03

* The rapid metabolizer phenotype is not applicable to *CYP2D6*. The *CYP2D6* phenotype is based on activity scores (ASs). AS is calculated based on genetic variants of *CYP2D6*. Each copy of the variant is assigned a score of 0, 0.25, 0.5, or 1, where no-function variants are assigned a score of 0; decreased function variants are assigned scores of 0.25 or 0.5; and normal function variants are assigned a score of 1. If a person has more than one copy of a variant, the score for that variant is multiplied by the number of copies. The total AS is the sum of all variant scores. Poor metabolizer, AS=0; intermediate metabolizer (IM), AS>0 but ≤1; normal metabolizer, AS>1 but ≤2.25; ultrarapid metabolizer, AS>2.25.[11] NA, not applicable.

† Population grouping is defined by CPIC based on geographic origin or self-identified race/ethnicity, as reported in the source publications or databases from which allele frequencies were derived.

‡ The prevalence of *CYP2D6* IM phenotype in this table is based on a newer definition for the *CYP2D6* IM. In the newer definition, IM is based on an AS of *CYP2D6*>0≤1. The phenotype frequency of *CYP2C19* and *CYP2D6* was obtained from the Clinical Pharmacogenetics Implementation Consortium.

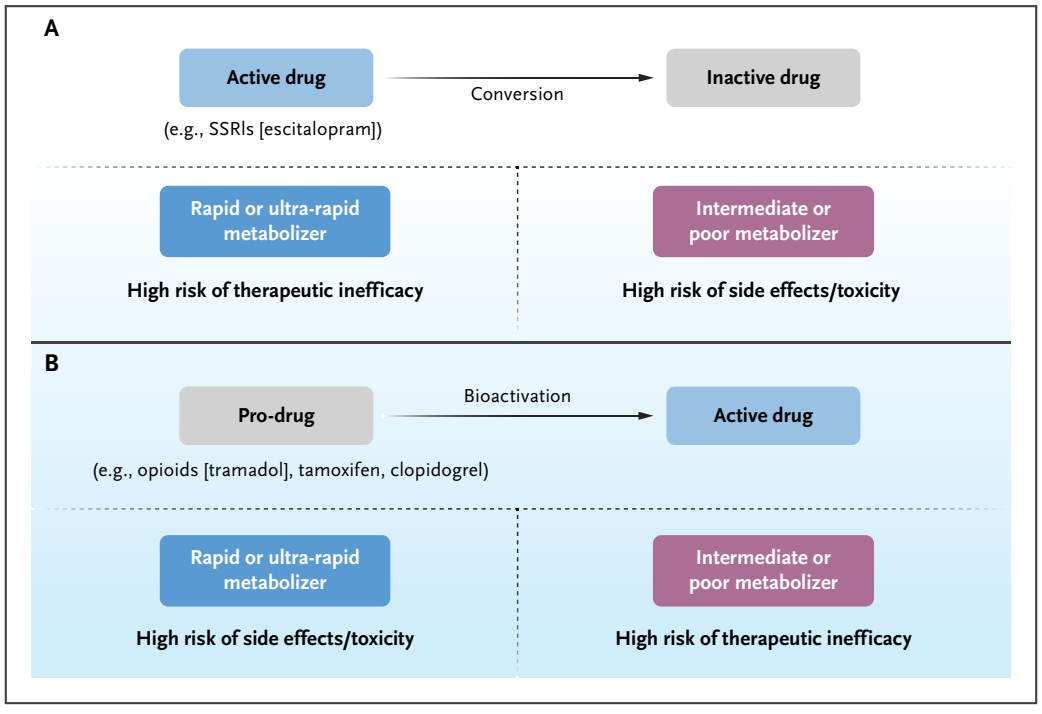

Figure 2. Impact of Metabolism Phenotypes on Drug Response.

Panel A shows the impact of metabolism phenotypes on response of active drugs, while Panel B shows the impact on prodrugs. SSRI denotes selective serotonin reuptake inhibitor.

Table 2. Drugs and Genes with Clinical Pharmacogenetics Implementation Consortium Recommendations.*

Indication and Drug or Drug Class	Gene(s)	Actionable Phenotype(s) or Variants	Implication	Recommendation†
Cardiovascular				
Clopidogrel[12]	*CYP2C19*	IM, PM	Decreased active metabolite, impaired efficacy	Use an alternative antiplatelet
Warfarin[13]†	*VKORC1*	*VKORC1-1639 A* carrier	Warfarin sensitive	Use a pharmacogenetic algorithm as described in the CPIC guideline
	CYP2C9	IM, PM		
Atorvastatin[14]	*SLCO1B1*‡	Decreased Function or poor function	Statin-associated muscle symptoms	Select appropriate statin potency per clinical indication and dose based on *SLCO1B1*
Rosuvastatin[14]‡	*SLCO1B1*	Decreased or poor function		Select appropriate statin potency and dose based on two genes (*SLCO1B1*; *ABCG2*)
	ABCG2	rs2231142 A carrier		
Metoprolol[15]	*CYP2D6*	PM	Increased active drug concentration, safety risk	Start with the lowest recommended dose, with a slow titration and close monitoring
Pain				
Codeine Tramadol[16]	*CYP2D6*	PM	Decreased active metabolite, impaired efficacy	Select a non-*CYP2D6* alternative (e.g., morphine)
		UM	Increased active metabolite, safety risk	
Ibuprofen Celecoxib[17]	*CYP2C9*§	PM	Increased active drug concentration, safety risk	Start at 25–50% of the minimum dose; titrate to effect or 25–50% of the maximum dose or select an alternative (e.g., naproxen)
Meloxicam[17]	*CYP2C9*	IM (activity score=1)	Increased active drug concentration, safety risk	Start at 50% of the minimum dose; titrate to effect or 50% of the maximum dose, or select an alternative (e.g., naproxen)
		PM (activity score=0.5 or 0)	Increased active drug concentration, safety risk	Select an alternative (e.g., naproxen)
Psychiatry				
Escitalopram Citalopram[18]	*CYP2C19*	PM	Increased active drug concentration, safety risk	Select a non-*CYP2C19* alternative or adjust the dose
		UM	Decreased active drug concentration, impaired efficacy	
Sertraline[18]†	*CYP2C19*	PM	Increased active drug concentration, safety risk	Use the two genes for decisions. Start a lower dose with slow titration and lower maintenance dose or select a non-*CYP2C19*, non-*CYP2B6* alternative
	CYP2B6	PM		
Paroxetine[18]	*CYP2D6*	PM	Increased active drug concentration, safety risk	Select a non-*CYP2D6* alternative (UM), or use a lower starting and maintenance dose (PM)
		UM	Decreased active drug concentration, impaired efficacy	
Fluvoxamine[18]	*CYP2D6*	PM	Increased active drug concentration, safety risk	Use a lower starting dose or select a non-*CYP2D6* alternative
Venlafaxine[18]	*CYP2D6*	PM	Increased active drug concentration, safety risk	Select a non-*CYP2D6* alternative

(*Continued*)

Table 2. Drugs and Genes with Clinical Pharmacogenetics Implementation Consortium Recommendations.*

Indication and Drug or Drug Class	Gene(s)	Actionable Phenotype(s) or Variants	Implication	Recommendation†
Vortioxetine[18]	*CYP2D6*	PM	Increased active drug concentration, safety risk	Use a lower starting and maintenance dose or select a non-*CYP2D6* alternative
		UM	Decreased active drug concentration, impaired efficacy	Select a non-*CYP2D6* or use a higher maintenance dose
Tertiary TCA† (amitriptyline, clomipramine, trimipramine, imipramine)[19]¶	*CYP2D6*	PM, IM, UM	Increased or decreased concentration of the parent drug and/or the metabolite, impaired efficacy, or safety risk	Use the two genes for decisions. Select a non-*CYP2C19*, non-*CYP2D6* alternative antidepressant in case of UM or PM or use therapeutic drug monitoring (TDM). Use lower dose (IM) and TDM‖
	CYP2C19	PM, UM		
Desipramine Nortriptyline[19]	*CYP2D6*	PM, IM	Increased active drug concentration, safety risk	Select a non-*CYP2D6* alternative (PM), lower dose, and use TDM (IM)‖
		UM	Decreased active drug concentration, impaired efficacy	Select a non-*CYP2D6* alternative or use TDM, if TCA is warranted‖
Atomoxetine[20]	*CYP2D6*	PM	Increased active drug concentration, safety risk	Use a normal starting dose, monitor side effects, and consider a lower dose if side effects emerge
		UM	Decreased active drug concentration, impaired efficacy	Use a normal starting dose, consider a dose increase to achieve a drug level of 400 ng/ml
Neurology				
Carbamazepine[21]	*HLA-A*31:01* or *HLA-B*15:02*	Positive	Severe cutaneous reaction	Select an alternative agent
Oxcarbazepine	*HLA-B*15:02*	Positive	Severe cutaneous reaction	Select an alternative agent
Phenytoin[22]†	*CYP2C9*	PM (AS=0 or 0.5), IM (AS=1)	Increased active drug concentration, safety risk	Use a lower maintenance dose if *HLA-B*15:02* is negative
	*HLA-B*15:02*	Positive	Severe cutaneous reaction	Select an alternative agent
Chemotherapy, Anti-Inflammatory, and Supportive Care				
5-fluorouracil Capecitabine[23]	*DPYD*	PM	Increased active drug concentration, safety risk	Use an alternative, non-fluoropyrimidine agent
		IM		Use a lower starting dose and titrate as tolerated
Tamoxifen[24]	*CYP2D6*	PM, IM	Decreased active metabolite, impaired efficacy	Use an alternative aromatase inhibitor or higher FDA doses, if tamoxifen is warranted
Mercaptopurine† Thioguanine† Azathioprine[25]†	*TPMT*	PM, IM	Increased active drug concentration, safety risk	Use the two genes for decisions. Use lower doses or alternative non-thiopurine in noncancer conditions (e.g., *TPMT* PM, *NUDT15* PM)
	NUDT15	PM, IM	Increased active drug concentration, safety risk	
Ondansetron[26]	*CYP2D6*	UM	Decreased active drug concentration, impaired efficacy	Use an alternative agent such as granisetron
Allopurinol[27]	*HLA-B *58:01*	Positive	Severe cutaneous reaction	Use an alternative agent

(*Continued*)

Table 2. Drugs and Genes with Clinical Pharmacogenetics Implementation Consortium Recommendations.*

Indication and Drug or Drug Class	Gene(s)	Actionable Phenotype(s) or Variants	Implication	Recommendation†
Gastrointestinal Disorders				
Omeprazole Pantoprazole Lansoprazole Dexlansoprazole[28]	*CYP2C19*	PM, IM	Increased active drug concentration, safety risk	Use a lower dose (for chronic therapy) (>12 weeks)
		RM	Decreased active drug concentration, impaired efficacy	Use a higher dose (e.g., 50–100% increase) for *Helicobacter pylori* infection and erosive esophagitis
		UM		Use a higher dose (e.g., 100% increase)

* CPIC denotes Clinical Pharmacogenetics Implementation Consortium; *DPYD*, dihydropyrimidine dehydrogenase; FDA, Food and Drug Administration; IM, intermediate metabolizer; NM, normal metabolizer; *NUDT15*, nudix hydrolase 15; PM, poor metabolizer; RM, rapid metabolizer; *SLCO1B1*, solute carrier organic anion transporter family member 1B1; TCA, tricyclic antidepressant; TDM, therapeutic drug monitoring; *TPMT*, thiopurine methyltransferase; and UM, ultrarapid metabolizer.

† Whenever two genes or more are involved (e.g., tricyclic antidepressants, sertraline), we refer the reader to the respective Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for recommendations; details on recommendations are not listed in the table.

‡ Atorvastatin and rosuvastatin were included as examples of statins impacted by solute carrier organic anion transporter family member 1B1 (*SLCO1B1*). Other less commonly used statins, such as fluvastatin, lovastatin, and pitavastatin, are impacted by *SLCO1B1* and addressed in the same CPIC guideline (PMID:35152405).[14] Fluvastatin is impacted by both *CYP2C9* and *SLCO1B1*.

§ *CYP2C9* activity score is mapped to the *CYP2C9* phenotype as follows: those with an activity score of 0 or 0.5 are classified as poor metabolizers, and those with a score of 1 or 1.5 as intermediate metabolizers.

¶ Tertiary amine tricyclic antidepressants are active drugs that are metabolized by *CYP2C19* and *CYP2D6*. For example, *CYP2C19* converts amitriptyline into another active metabolite (nortriptyline), while *CYP2D6* further metabolizes nortriptyline into less active or inactive compounds.

‖ The tricyclic antidepressant recommendations apply to the higher doses used in the context of depression and not to lower doses used for other indications, such as sleep or neuropathic pain. For a detailed magnitude of dose adjustments, we refer the reader to the respective CPIC guideline.

Pharmacogenetics Resources

Rigorous and systematic assessment of evidence is essential to inform clinicians on how to interpret and act upon their patients' pharmacogenetic results. Two U.S.-based resources are crucial here, CPIC and the Pharmacogenomics Knowledge Base (PharmGKB), both of which are NIH-funded resources.[7,8,36,37] As of July 2025, it was announced that PharmGKB will be transitioning to ClinPGx, a unified platform that integrates PharmGKB, CPIC, and other resources.

CPIC is an international consortium, the authors of which grade evidence on the association between genetics and drug dose or response (often called drug–gene pairs), and then make recommendations about whether or not the evidence supports using the genetic information in the clinical setting.[38] Importantly, CPIC recommends what to do when pharmacogenetic data are available, not when and whom to test. To date, CPIC has issued 28 clinical guidelines, assessing 168 drugs and making recommendations for changes in drug therapy based on genotypes for ~80 of them. CPIC publishes open-access guidelines in the *Journal of Clinical Pharmacology and Therapeutics*, and all guidelines are freely available on the CPIC website.[36] In addition, pharmacogenetic guidelines are generated by other groups such as the Dutch Pharmacogenetics Working Group (DPWG).[9]

PharmGKB systematically synthesizes the evidence of pharmacogenetic associations and provides data on pharmacogenetic variants and their associated drug responses.[8] While CPIC and DPWG provide peer-reviewed clinical recommendations, PharmGKB serves as a centralized resource that links to all these pharmacogenetic resources, including CPIC, DPWG, and the U.S. Food and Drug Administration (FDA) package labels, providing clinicians with access to a wide range of pharmacogenetic information. PharmGKB has user-friendly tools to further support clinicians, which include the Genotype Selection Interface, a Web-based tool that allows clinicians to input a patient's genetic information to obtain prescribing recommendations. Its DNA-Driven Prescribing is a mobile application tool that provides prescribing guidance based on user-provided genotypes.

Other important resources include the Pharmacogene Variation Consortium (PharmVar) and the Association for Molecular Pathology's (AMP) pharmacogenetics working group.[39,40] The Pharmacogene Variation Consortium is a repository for pharmacogene variation focused on cataloging high-quality pharmacogenetic variation and standardizing allele designation for pharmacogenes. The

Association for Molecular Pathology's pharmacogenetics working group publishes guidance to standardize clinical pharmacogenetic testing, including recommendations on the alleles and variants to be tested by laboratories.

FDA package labeling provides information on the impact of genetic variations on drug efficacy and safety, including whether testing is required, recommended, actionable, or informative. In addition, the FDA maintains a table of pharmacogenetic associations related to metabolizing enzymes, human leukocyte antigen markers, and transporters.[41] Although the table includes information on genetic associations with pharmacokinetic changes or therapeutic effects, it does not include citations for the evidence supporting these associations. In addition, the FDA has a separate pharmacogenomic biomarker table, which includes germline and somatic genetic variants, used to guide treatment decisions.[42]

Selected Examples of Pharmacogenetics Implementation

CARDIOLOGY

Clopidogrel is a commonly prescribed antiplatelet therapy in acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), and neurovascular settings. *CYP2C19* is one of the most extensively studied genes and was included in the earliest CPIC guidelines to guide clopidogrel use.[12] Data supporting the role of *CYP2C19* in clopidogrel response span pharmacokinetic, pharmacodynamic, observational, and retrospective analyses of genetic data from randomized controlled trials (RCTs), meta-analyses, RCTs of pharmacogenetic-guided approaches, and outcomes associated with clinical implementation of clopidogrel pharmacogenetics.[43-48]

The CYP2C19 enzyme, encoded by *CYP2C19*, is the key metabolizing enzyme that bioactivates clopidogrel to the active metabolite that inhibits P2Y12 receptors. *CYP2C19* demonstrates common loss-of-function genetic variability, with the **2* and **3* haplotypes being the most common no-function variants. Patients with two no-function variants (poor metabolizers) have no functional CYP2C19 enzyme, and those with one no-function variant (intermediate metabolizers) have half-normal CYP2C19 protein — and both lead to the impaired formation of the active metabolite and an increased risk of cardiovascular events.[43] CPIC recommends alternative antiplatelet therapies for patients identified as intermediate or poor metabolizers, especially in the context of PCI, ACS, and neurovascular indications such as ischemic stroke.[12]

There is an extensive body of literature on the impacts on cardiovascular outcomes that are associated with a *CYP2C19*-guided approach to antiplatelet therapy, including RCTs and the evaluation of cardiovascular outcomes following clinical implementation of clopidogrel pharmacogenetics. These are best summarized through two recent meta-analyses and the CPIC guideline, where citations for all but the most recent individual studies can be found.[12,45,46] One meta-analysis included seven RCTs that encompassed ~16,000 patients who had predominantly ACS and PCI. Compared with clopidogrel, ticagrelor or prasugrel led to 30% reduction of major adverse cardiovascular events in patients with reduced *CYP2C19* function (relative risk [RR], 0.70; 95% confidence interval [CI], 0.59 to 0.83); outcomes were not different between clopidogrel and the alternative P2Y12 inhibitors in patients with normal *CYP2C19*, with a statistically significant interaction for *CYP2C19* genotype and antiplatelet therapy.[45] These data provide clear evidence of the risk that treating patients with reduced *CYP2C19* function with clopidogrel poses.

Aligned with a *CYP2C19*-guided approach, a 2021 meta-analysis included ~21,000 patients from 11 RCTs and 3 observational studies where guided therapy (through pharmacogenetic or platelet reactivity testing) was compared with standard of care, with pharmacogenetic testing representing the guided approach in most participants. The analysis demonstrated that guided escalation of antiplatelet therapy compared with standard of care resulted in a 26% reduction (RR, 0.74; 95% CI, 0.57 to 0.95) in major adverse cardiovascular events among patients with PCI. Furthermore, a guided de-escalation of therapy led to a 19% reduction (RR, 0.81; 95% CI, 0.68 to 0.96) in bleeding without increasing the risk of ischemic events.[46] These data suggest that personalized antiplatelet therapy, including pharmacogenetic testing, improves outcomes for patients.

Observational outcomes data from pharmacogenetics-guided antiplatelet therapy implementations at multiple institutions across the United States provide further supportive evidence. For example, an Implementing Genomics in Practice Network analysis included 3342 patients treated at sites using *CYP2C19* testing and CPIC guidance. It confirmed that patients with ACS with reduced *CYP2C19* activity treated with alternatives had significantly lower atherothrombotic event rates than those treated with clopidogrel (17.8 vs. 46.3 events per 100 patient-years; adjusted hazard ratio, 0.49; 95% CI, 0.32 to 0.76).[47] Conversely, among the patients with ACS with

normal *CYP2C19* function, there was no significant difference in the event rates between clopidogrel and alternative P2Y12 inhibitors–treated patients (adjusted hazard ratio, 1.05; 95% CI, 0.67 to 1.66).[47]

Collectively, the evidence suggests that patients with reduced *CYP2C19* function should be treated with ticagrelor or prasugrel, whereas in those with normal *CYP2C19* function, clopidogrel performs as well as the more potent alternative P2Y12 inhibitors, which are associated with higher bleeding risks. Based on the strong evidence base for *CYP2C19*-guided antiplatelet therapy, the American Heart Association recently published a scientific statement supporting *CYP2C19* genotyping for patients undergoing PCI, with or without ACS.[49]

CANCER AND INFLAMMATORY DISORDERS

Thiopurines (azathioprine, mercaptopurine, and thioguanine) are antimetabolite medications commonly used for various indications, including pediatric cancers and autoimmune disorders, such as inflammatory bowel diseases (IBD).[50] The therapeutic efficacy of thiopurines predominantly relies on the availability of the active metabolite, 6-thioguanine nucleotides, which are incorporated into deoxyribonucleic acid and ribonucleic acid, inhibiting replication and translation processes, respectively.[51] While higher levels of the 6-thioguanine nucleotides metabolites improve therapeutic outcomes, they can also lead to severe bone marrow toxicity, often leading to treatment discontinuation.[51]

The thiopurine methyltransferase (TPMT) enzyme is important in inactivating the active metabolites.[52] Three key *TPMT* genetic variants (**2, *3A*, and **3C*) are associated with an increased risk of thiopurine-induced myelosuppression. The three variants are common in those of European ancestry and account for 25% of thiopurine-related toxicity cases.[50] As is the case with *CYP2C19*, those who carry a normal function and a no-function genotype are described as intermediate metabolizers. Complete *TPMT* deficiency, as in patients with two no-function variants, can lead to fatal toxicity if given standard doses.[25]

The nudix hydrolase 15 (*NUDT15*) gene emerged in 2014 as a significant predictor of thiopurine toxicity in patients with acute lymphoblastic leukemia and IBD.[53] Variations in *NUDT15* are more common in patients of Asian and Hispanic descent, contributing to myelotoxicity that cannot be explained by *TPMT* alone.[25] *NUDT15* facilitates the conversion of thioguanine triphosphate, a cytotoxic metabolite, into thioguanine monophosphate, which is less toxic.[25] While less common, in those of European ancestry, *NUDT15* variants can also lead to hematological toxicity.[54]

The role of *TPMT* deficiency in thiopurine toxicity, dose reduction, and treatment discontinuation is well documented for both cancer and IBD.[55-59] While the relationship between *NUDT15* and thiopurine toxicity is also well established, the literature on *NUDT15* association is less extensive due to its recent discovery. Nevertheless, a 2023 meta-analysis of 24 studies with 3374 patients documented that *NUDT15* intermediate metabolizers or poor metabolizers had a significantly higher risk of 6-mercaptopurine–induced leukopenia (odds ratio, 9.0; 95% CI, 3.7 to 21.7) and neutropenia (odds ratio, 2.5; 95% CI, 1.7 to 3.7) than those patients with normal *NUDT15* function.[60]

CPIC recommends genetics-guided dose reduction of thiopurines for patients who are intermediate metabolizers for *TPMT* or *NUDT15*, with consideration for alternative non-thiopurine treatments for nonmalignant conditions in patients with poor metabolizer phenotypes.[25] The FDA-approved labels for thiopurines recommend testing for *TPMT* and *NUDT15* in patients experiencing severe myelosuppression, and dose reductions or alternative therapy for patients with partial metabolizer phenotypes. Similarly, the National Comprehensive Cancer Network recommends genetic testing for *TPMT* and *NUDT15* variants before initiating thiopurine.[61]

TPMT genotype-based dosing has been shown to reduce thiopurine-induced hematological toxicity without compromising the anticancer or anti-inflammatory effectiveness across several clinical indications.[62-64] The literature on the outcomes of *TPMT*-based testing up to 2019 is detailed in the CPIC guideline.[25] Studies have also shown that pharmacogenetics-guided thiopurine dosing reduces hematological toxicity in gastrointestinal indications without compromising outcomes.[57] Similar to studies showing that *TPMT*-guided treatment does not compromise efficacy in acute lymphoblastic leukemia, a 2021 meta-analysis confirmed that *TPMT*- and *NUDT15*-guided therapy do not reduce effectiveness in IBD.[65] A meta-analysis of four RCTs (N=1710) demonstrated that pharmacogenetics-based therapy was associated with a significantly lower incidence of leukopenia and neutropenia (RR, 0.71; 95% CI, 0.56 to 0.90) with no difference in clinical efficacy outcomes between the pharmacogenetics and standard of care treatment groups.[65]

The findings of these studies highlight the strong association between *TPMT*/*NUDT15* and thiopurine-induced toxicity while demonstrating that the use of these pharmacogenetic

data to guide treatment decisions does not reduce treatment efficacy. It is also likely that the endorsement of professional organizations, clinical guidelines, and the FDA is necessary for wider adoption. Clinical *TPMT* testing is now routinely performed in major cancer centers and has become a part of standard treatment protocols for pediatric leukemia.

ANTIDEPRESSANTS

The effectiveness of antidepressants is highly variable, with approximately 42 to 53% of patients responding to treatment.[66] Prescribers typically rely on a trial-and-error approach to therapy selection. Given the challenge of identifying effective therapy in many patients with anxiety or depression, pharmacogenetics-guided approaches have had appeal.

Escitalopram and citalopram are metabolized by CYP2C19; paroxetine, fluvoxamine, and venlafaxine are metabolized by CYP2D6; and sertraline is metabolized by both CYP2C19 and CYP2B6 — all of them have CPIC pharmacogenetics guidance. Patients with a poor metabolizer phenotype may have higher drug concentrations, increasing the risk of side effects and treatment discontinuation, while a patient with a rapid or ultrarapid metabolizer phenotype may have lower concentrations, potentially leading to suboptimal efficacy.[18]

Currently, CPIC guidelines cover the selective serotonin reuptake inhibitors escitalopram, citalopram, sertraline, paroxetine, fluvoxamine, and fluoxetine; the tricyclic antidepressants amitriptyline, clomipramine, doxepin, trimipramine, nortriptyline, and desipramine; the selective serotonin and norepinephrine reuptake inhibitors, such as venlafaxine; and the selective norepinephrine reuptake inhibitor atomoxetine (used for attention deficit hyperactivity disorder treatment), based on *CYP2C19*, *CYP2D6*, and *CYP2B6* genotypes, as noted in Table 2.[18,19]

Data on the impact of pharmacogenetic testing on depression outcomes have predominantly come from studies using commercial gene panels, where the basis for the recommendations is unclear. In addition, many of these commercially available panels test for pharmacodynamic genes (e.g., *HTR2A* and *SLC6A4*) despite limited evidence supporting the impact of these genes on treatment response. In general, these studies have demonstrated variable results, likely due to the use of proprietary algorithms, the inclusion of low-evidence genes, and small sample sizes.[67] Nevertheless, recent systematic reviews and meta-analyses suggest a positive impact of industry-led, pharmacogenetic panel–guided antidepressant treatment.[68]

A 2018 meta-analysis of 1737 participants showed that a pharmacogenetic panel–guided approach was associated with improved remission rates compared with nonguided approaches (RR, 1.71; 95% CI, 1.17 to 2.48).[69] A more recent meta-analysis of 4767 patients also suggested a benefit for the pharmacogenetic panel–guided approaches, where patients in the pharmacogenetics group were 41% more likely to achieve remission (odds ratio, 1.41; 95% CI, 1.15 to 1.74) than patients receiving nonguided treatment.[68] The Precision Medicine in Mental Health Care trial evaluated the impact on remission rates of a commercial pharmacogenetic panel on 1944 veterans with major depressive disorder.[70] The trial showed those in the pharmacogenetic panel–guided group were 28% more likely to achieve remission (odds ratio, 1.28; 95% CI, 1.05 to 1.57) over 8 and 12 weeks. However, this was not sustained in later follow-ups.[70]

The Depression and Opioid Pragmatic Trial in Pharmacogenetics is investigating the impact of CPIC pharmacogenetic guidance for antidepressant therapy on clinical outcomes. Results from this trial are expected later in 2025.[71]

Landscape of Pharmacogenetic Testing, Current Challenges, and Future Opportunities

Pharmacogenetic testing in clinical practice was initially adopted and led by large academic health systems with substantial resources, often starting with single-gene drug testing and gradually expanding to additional clinical areas. Given that polypharmacy is common and genetic information remains unchanged, multigene panels are advocated as an efficient and cost-effective approach.[30] The rise of direct-to-consumer pharmacogenetic testing, which tests multiple genes, has increased patient access to testing.[72] Furthermore, community hospitals are leveraging commercial laboratories and third-party clinical decision support solutions to integrate pharmacogenetic information as discrete data within the EHR, an important facilitator of the clinical use of pharmacogenetics.[73] The increasing accessibility of testing is likely to improve patient engagement and may offer more opportunities for patients to engage with their health care providers.[74]

Studies have demonstrated improved health care utilization, including reductions in hospitalization rates, emergency department visits, and overall health care costs,

when multigene pharmacogenetics panels are used.[75] The Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions trial was a prospective implementation trial involving 6944 European participants whose data were generated using a 12-gene panel. The trial documented a lower occurrence of clinically relevant adverse drug reactions in the genotype-guided group than in the control group (21% vs. 28%) among the patients with an actionable genotype, resulting in a 30% lower risk in the genotype group. In addition, data suggest an economic benefit of multigene panels, particularly when combined with clinical decision support.[75]

Although adoption of testing has improved, it remains lower than anticipated and is still largely the exception, not the norm. Many clinicians report a lack of confidence in ordering tests and applying results as a barrier to adoption.[76] Although RCTs are often considered the gold standard, conducting RCTs for every gene–drug pair may not be feasible or realistic, in part because many of the drugs are available generically and, thus, pharmaceutical companies are not likely to support such research. Furthermore, RCTs could raise ethical concerns if patients are exposed to potentially ineffective or harmful drug therapies, especially when guidelines exist for well-established genetic variations. Some have proposed the concept of genetic exceptionalism, where genetics is treated with unusually high standards.[77] It can be argued that this should not be true if pharmacogenetics is viewed as a tool for optimizing therapy, much like the use of serum creatinine to adjust dosing in patients with renal impairment. In the case of renal function and drug dosing, there is no expectation of conducting an RCT to document the benefit of renal dosing. Alternative investigative designs, such as pragmatic clinical trials, hybrid implementation–effectiveness trials, and real-world data from implementation studies, can provide practical and valuable alternatives for documenting the outcomes of the use of pharmacogenetics in clinical practice.

The absence of clear guidelines on when and who should undergo pharmacogenetic testing, along with the limited endorsement of the clinical guidelines, remains a significant barrier to widespread adoption. The established guidelines for *TPMT/NUDT15*–thiopurine testing, as in the National Comprehensive Cancer Network, were pivotal in increasing adoption, and similar guidelines for other drugs could help expand pharmacogenetic testing.

Finally, limited insurance coverage has generally slowed the adoption of testing. In July 2020, the Medicare Administrative Contractors began implementing policies to cover pharmacogenetic testing. The U.S. Centers for Medicare and Medicaid Services has established guidelines to determine the medical necessity of pharmacogenetic testing for Medicare beneficiaries, including the use of *International Classification of Diseases* codes to document medical necessity.[78] To date, most Medicare Administrative Contractors cover pharmacogenetic testing if the results are actionable, meaning they can guide medication selection, avoidance, or dosing. While reimbursement policies have generally improved, the overall inconsistency and limited coverage of multigene panels continue to influence provider hesitancy to test.[78]

Summary and Conclusion

Pharmacogenetic testing holds significant promise for improving patients' outcomes through precision pharmacotherapy. Although adoption has been relatively slow, evidence for the clinical utility of pharmacogenetic testing is growing. Several challenges have slowed the widespread adoption of pharmacogenetic testing, including clinicians' lack of training, difficulties with integration into health systems, limited endorsement of testing by clinical guidelines, and insurance coverage.

To achieve routine adoption of pharmacogenetics, several steps are necessary (Fig. 3). First, educating and training clinicians on the use of pharmacogenetics data is important, as clinicians are likely to encounter increasing numbers of patients with pharmacogenetic data or who are requesting testing. In addition, integrating pharmacogenetic data into the EHR as discrete variables, which can then be used for clinical decision support, is critical. Building the evidence base for pharmacogenetics and documenting its impact on patient outcomes, and health care economics is essential to drive adoption by guidelines and improve coverage and reimbursement policies — all of these steps are needed to ensure equitable access to testing.

In a 2009 commentary, Francis Collins, then Director of the National Institutes of Health, highlighted key challenges in the use of pharmacogenetics and stated that it is a critical component of medical practice.[79] The main challenge, he noted, is the delay in obtaining genetic information. However, if these data were readily available in medical records and supported by strong clinical evidence, it would be difficult to argue against their use, especially as the costs of genetic sequencing decline.[79] Sixteen years later, we have not achieved the vision Francis Collins laid out, yet it still

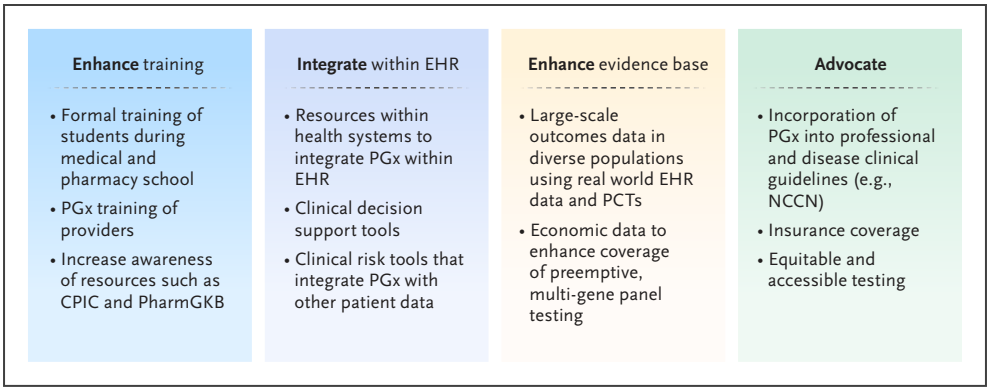

Figure 3. Efforts Needed to Enhance Pharmacogenetics Implementation.

CPIC denotes Clinical Pharmacogenetics Implementation Consortium; EHR, electronic health record; NCCN, National Comprehensive Cancer Network; PCTs, Pragmmatic Clinical Trials; PGx, pharmacogenomics; and PharmGKB, Pharmacogenomics Knowledge Base.

seems a realistic ideal for the future. Addressing these challenges and leveraging available resources will help realize the full potential of pharmacogenetics.

Disclosures

Author disclosures are available at evidence.nejm.org.

Author Affiliations

[1] Division of Pharmacy Practice and Administrative Sciences, James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati

[2] St. Elizabeth Healthcare, Edgewood, KY

[3] Colleges of Medicine and Pharmacy, The Ohio State University, Columbus

[4] Clinical and Translational Science Institute, The Ohio State University, Columbus

References

1. Pirmohamed M. Pharmacogenetics and pharmacogenomics. Br J Clin Pharmacol 2001;52:345-347. DOI: 10.1046/j.0306-5251.2001.01498.x.

2. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med 2001;7:201-204. DOI: 10.1016/S1471-4914(01)01986-4.

3. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 1999;286:487-491. DOI: 10.1126/science.286.5439.487.

4. Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009;360:753-764. DOI: 10.1056/NEJMoa0809329.

5. Relling MV, Krauss RM, Roden DM, et al. New pharmacogenomics research network: an open community catalyzing research and translation in precision medicine. Clin Pharmacol Ther 2017;102:897-902. DOI: 10.1002/cpt.755.

6. Giacomini KM, Karnes JH, Crews KR, et al. Advancing precision medicine through the new Pharmacogenomics Global Research Network. Clin Pharmacol Ther 2021;110:559-562. DOI: 10.1002/cpt.2340.

7. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther 2011;89:464-467. DOI: 10.1038/clpt.2010.279.

8. Whirl-Carrillo M, Huddart R, Gong L, et al. An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther 2021;110:563-572. DOI: 10.1002/cpt.2350.

9. Swen JJ, Wilting I, de Goede AL, et al. Pharmacogenetics: from bench to byte. Clin Pharmacol Ther 2008;83:781-787. DOI: 10.1038/sj.clpt.6100507.

10. Cavallari LH, Beitelshees AL, Blake KV, et al. The IGNITE pharmacogenetics working group: an opportunity for building evidence with pharmacogenetic implementation in a real-world setting. Clin Transl Sci 2017;10:143-146. DOI: 10.1111/cts.12456.

11. Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing *CYP2D6* genotype to phenotype translation: consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. Clin Transl Sci 2020;13:116-124. DOI: 10.1111/cts.12692.

12. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium guideline for *CYP2C19* genotype and clopidogrel therapy: 2022 update. Clin Pharmacol Ther 2022;112:959-967. DOI: 10.1002/cpt.2526.

13. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther 2017;102:397-404. DOI: 10.1002/cpt.668.

14. Cooper-DeHoff RM, Niemi M, Ramsey LB, et al. The Clinical Pharmacogenetics Implementation Consortium guideline for *SLCO1B1*, *ABCG2*, and *CYP2C9* genotypes and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther 2022;111:1007-1021. DOI: 10.1002/cpt.2557.

15. Duarte JD, Thomas CD, Lee CR, et al. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for *CYP2D6*, *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5* genotypes and beta-blocker therapy. Clin Pharmacol Ther 2024;116:939-947. DOI: 10.1002/cpt.3351.

16. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium guideline for *CYP2D6*, *OPRM1*, and *COMT* genotypes and select opioid therapy. Clin Pharmacol Ther 2021;110:888-896. DOI: 10.1002/cpt.2149.

17. Theken KN, Lee CR, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for *CYP2C9* and nonsteroidal anti-inflammatory drugs. Clin Pharmacol Ther 2020;108:191-200. DOI: 10.1002/cpt.1830.

18. Bousman CA, Stevenson JM, Ramsey LB, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, and *HTR2A* genotypes and serotonin reuptake inhibitor antidepressants. Clin Pharmacol Ther 2023;114:51-68. DOI: 10.1002/cpt.2903.

19. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017;102:37-44. DOI: 10.1002/cpt.597.

20. Brown JT, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium guideline for cytochrome P450 (*CYP*)*2D6* genotype and atomoxetine therapy. Clin Pharmacol Ther 2019;106:94-102. DOI: 10.1002/cpt.1409.

21. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. Clin Pharmacol Ther 2018;103:574-581. DOI: 10.1002/cpt.1004.

22. Karnes JH, Rettie AE, Somogyi AA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C9* and *HLA-B* genotypes and phenytoin dosing: 2020 update. Clin Pharmacol Ther 2021;109:302-309. DOI: 10.1002/cpt.2008.

23. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther 2018;103:210-216. DOI: 10.1002/cpt.911.

24. Goetz MP, Sangkuhl K, Guchelaar HJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and tamoxifen therapy. Clin Pharmacol Ther 2018;103:770-777. DOI: 10.1002/cpt.1007.

25. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105. DOI: 10.1002/cpt.1304.

26. Bell GC, Caudle KE, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther 2017;102:213-218. DOI: 10.1002/cpt.598.

27. 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;99:36-37. DOI: 10.1002/cpt.161.

28. Lima JJ, Thomas CD, Barbarino J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C19* and proton pump inhibitor dosing. Clin Pharmacol Ther 2021;109:1417-1423. DOI: 10.1002/cpt.2015.

29. ClinCalc. The Top 200 of 2022. 2022 (https://clincalc.com/DrugStats/Top200Drugs.aspx).

30. Hicks JK, El Rouby N, Ong HH, et al. Opportunity for genotype-guided prescribing among adult patients in 11 US health systems. Clin Pharmacol Ther 2021;110:179-188. DOI: 10.1002/cpt.2161.

31. Pasternak AL, Ward K, Irwin M, et al. Identifying the prevalence of clinically actionable drug-gene interactions in a health system biorepository to guide pharmacogenetics implementation services. Clin Transl Sci 2023;16:292-304. DOI: 10.1111/cts.13449.

32. Haddad A, Radhakrishnan A, McGee S, et al. Frequency of pharmacogenomic variation and medication exposures among All of Us Participants. June 13, 2024 (https://www.medrxiv.org/content/10.1101/2024.06.12.24304664). Preprint.

33. Cavallari LH, Hicks JK, Patel JN, et al. The Pharmacogenomics Global Research Network Implementation Working Group: global collaboration to advance pharmacogenetic implementation. Pharmacogenet Genomics 2025;35:1-11. DOI: 10.1097/FPC.0000000000000547.

34. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-579. DOI: 10.1056/NEJMoa0706135.

35. Martin MA, Klein TE, Dong BJ, Pirmohamed M, Haas DW, Kroetz DL. Clinical pharmacogenetics implementation consortium guidelines for *HLA-B* genotype and abacavir dosing. Clin Pharmacol Ther 2012;91:734-738. DOI: 10.1038/clpt.2011.355.

36. Clinical Pharmacogenetics Implementation Consortium. What Is CPIC? September 10, 2025 (https://cpicpgx.org/).

37. ClinPGx. The evolution of PharmGKB. September 10, 2025 (https://www.clinpgx.org/).

38. 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;15:209-217. DOI: 10.2174/1389200215666140130124910.

39. Gaedigk A, Casey ST, Whirl-Carrillo M, Miller NA, Klein TE. Pharmacogene variation consortium: a global resource and repository for pharmacogene variation. Clin Pharmacol Ther 2021;110:542-545. DOI: 10.1002/cpt.2321.

40. Pratt VM, Del Tredici AL, Hachad H, et al. Recommendations for clinical *CYP2C19* genotyping allele selection: a report of the Association for Molecular Pathology. J Mol Diagn 2018;20:269-276. DOI: 10.1016/j.jmoldx.2018.01.011.

41. Deb S, Hopefl R, Reeves AA, Cvetkovic D. *ADME* gene-related pharmacogenomic labeling of FDA-approved drugs: comparison with Clinical Pharmacogenetics Implementation Consortium (CPIC) evidence levels. Medicines (Basel) 2024;11:6. DOI: 10.3390/medicines11030006.

42. Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labeling. September 23, 2024 (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling).

43. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-362. DOI: 10.1056/NEJMoa0809171.

44. Mega JL, Simon T, Collet JP, et al. Reduced-function *CYP2C19* genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA 2010;304:1821-1830. DOI: 10.1001/jama.2010.1543.

45. Pereira NL, Rihal C, Lennon R, et al. Effect of *CYP2C19* genotype on ischemic outcomes during oral P2Y. JACC Cardiovasc Interv 2021;14:739-750. DOI: 10.1016/j.jcin.2021.01.024.

46. Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Lancet 2021;397:1470-1483. DOI: 10.1016/S0140-6736(21)00533-X.

47. Beitelshees AL, Thomas CD, Empey PE, et al. Genotype-guided antiplatelet therapy after percutaneous coronary intervention in diverse clinical settings. J Am Heart Assoc 2022;11:e024159. DOI: 10.1161/JAHA.121.024159.

48. Wang Y, Meng X, Wang A, et al. Ticagrelor versus clopidogrel in *CYP2C19* loss-of-function carriers with stroke or TIA. N Engl J Med 2021;385:2520-2530. DOI: 10.1056/NEJMoa2111749.

49. Pereira NL, Cresci S, Angiolillo DJ, et al. Genetic testing for oral P2Y12 inhibitor therapy: a scientific statement from the American Heart Association. Circulation 2024;150:e129-e150. DOI: 10.1161/CIR.0000000000001257.

50. Daniel LL, Dickson AL, Chung CP. Precision medicine for rheumatologists: lessons from the pharmacogenomics of azathioprine. Clin Rheumatol 2021;40:65-73. DOI: 10.1007/s10067-020-05258-2.

51. Lennard L, Gibson BE, Nicole T, Lilleyman JS. Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. Arch Dis Child 1993;69:577-579. DOI: 10.1136/adc.69.5.577.

52. Lennard L, Van Loon JA, Lilleyman JS, Weinshilboum RM. Thiopurine pharmacogenetics in leukemia: correlation of erythrocyte thiopurine methyltransferase activity and 6-thioguanine nucleotide concentrations. Clin Pharmacol Ther 1987;41:18-25. DOI: 10.1038/clpt.1987.4.

53. Yang SK, Hong M, Baek J, et al. A common missense variant in *NUDT15* confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014;46:1017-1020. DOI: 10.1038/ng.3060.

54. Schaeffeler E, Jaeger SU, Klumpp V, et al. Impact of *NUDT15* genetics on severe thiopurine-related hematotoxicity in patients with European ancestry. Genet Med 2019;21:2145-2150. DOI: 10.1038/s41436-019-0448-7.

55. Relling MV, Hancock ML, Rivera GK, et al. Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. J Natl Cancer Inst 1999;91:2001-2008. DOI: 10.1093/jnci/91.23.2001.

56. Derijks LJ, Gilissen LP, Engels LG, et al. Pharmacokinetics of 6-mercaptopurine in patients with inflammatory bowel disease: implications for therapy. Ther Drug Monit 2004;26:311-318. DOI: 10.1097/00007691-200406000-00016.

57. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of patients with variants in *TPMT* and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. Gastroenterology 2015;149:907-917.e7. DOI: 10.1053/j.gastro.2015.06.002.

58. Ansari A, Arenas M, Greenfield SM, et al. Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel disease. Aliment Pharmacol Ther 2008;28:973-983. DOI: 10.1111/j.1365-2036.2008.03788.x.

59. Dong XW, Zheng Q, Zhu MM, Tong JL, Ran ZH. Thiopurine S-methyltransferase polymorphisms and thiopurine toxicity in treatment of inflammatory bowel disease. World J Gastroenterol 2010;16:3187-3195. DOI: 10.3748/wjg.v16.i25.3187.

60. Du S, Huang X, He X, et al. Association of *NUDT15* gene polymorphism with adverse reaction, treatment efficacy, and dose of 6-mercaptopurine in patients with acute lymphoblastic leukemia: a systematic review and meta-analysis. Haematologica 2024;109:1053-1068. DOI: 10.3324/haematol.2023.282761.

61. Shah B, Mattison RJ, Abboud R, et al. Acute lymphoblastic leukemia, version 2.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2024;22:563-576. DOI: 10.6004/jnccn.2024.0051.

62. Relling MV, Pui CH, Cheng C, Evans WE. Thiopurine methyltransferase in acute lymphoblastic leukemia. Blood 2006;107:843-844. DOI: 10.1182/blood-2005-08-3379.

63. Lennard L, Cartwright CS, Wade R, Vora A. Thiopurine methyltransferase and treatment outcome in the UK acute lymphoblastic leukaemia trial ALL2003. Br J Haematol 2015;170:550-558. DOI: 10.1111/bjh.13469.

64. Stanulla M, Schaeffeler E, Flohr T, et al. Thiopurine methyltransferase (*TPMT*) genotype and early treatment response to mercaptopurine in childhood acute lymphoblastic leukemia. JAMA 2005;293:1485-1489. DOI: 10.1001/jama.293.12.1485.

65. Gutiérrez-Valencia M, Leache L, Saiz LC, et al. Role of pharmacogenomics in the efficacy and safety of thiopurines in inflammatory bowel disease: a systematic review and meta-analysis. J Clin Gastroenterol 2023;57:671-685. DOI: 10.1097/MCG.0000000000001791.

66. Taliaz D, Spinrad A, Barzilay R, et al. Optimizing prediction of response to antidepressant medications using machine learning and integrated genetic, clinical, and demographic data. Transl Psychiatry 2021;11:381. DOI: 10.1038/s41398-021-01488-3.

67. Tesfamicael KG, Zhao L, Fernández-Rodríguez R, et al. Efficacy and safety of pharmacogenomic-guided antidepressant prescribing in patients with depression: an umbrella review and updated meta-analysis. Front Psychiatry 2024;15:1276410. DOI: 10.3389/fpsyt.2024.1276410.

68. Brown LC, Stanton JD, Bharthi K, Maruf AA, Müller DJ, Bousman CA. Pharmacogenomic testing and depressive symptom remission: a systematic review and meta-analysis of prospective, controlled clinical trials. Clin Pharmacol Ther 2022;112:1303-1317. DOI: 10.1002/cpt.2748.

69. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics 2019;20:37-47. DOI: 10.2217/pgs-2018-0142.

70. Oslin DW, Lynch KG, Shih MC, et al. Effect of pharmacogenomic testing for drug–gene interactions on medication selection and remission of symptoms in major depressive disorder: the PRIME care randomized clinical trial. JAMA 2022;328:151-161. DOI: 10.1001/jama.2022.9805.

71. Hines LJ, Wilke RA, Myers R, et al. Rationale and design for a pragmatic randomized trial to assess gene-based prescribing for SSRIs in the treatment of depression. Clin Transl Sci 2024;17:e13822. DOI: 10.1111/cts.13822.

72. Gammal RS, Smith DM, Wiisanen KW, et al. The pharmacist's responsibility to ensure appropriate use of direct-to-consumer genetic testing. J Am Coll Clin Pharm 2021;4:652-658. DOI: 10.1002/jac5.1437.

73. Muldoon M, Beck M, Sebree N, et al. Real-world implementation of DPYD and UGT1A1 pharmacogenetic testing in a community-based cancer center. Clin Transl Sci 2024;17:e13704.DOI: 10.1111/cts.13704.

74. Carere DA, VanderWeele TJ, Vassy JL, et al. Prescription medication changes following direct-to-consumer personal genomic testing: findings from the Impact of Personal Genomics (PGen) study. Genet Med 2017;19:537-545. DOI: 10.1038/gim.2016.141.

75. Jarvis JP, Peter AP, Keogh M, et al. Real-world impact of a pharmacogenomics-enriched comprehensive medication management program. J Pers Med 2022;12:421. DOI: 10.3390/jpm12030421.

76. Haga SB, Burke W, Ginsburg GS, Mills R, Agans R. Primary care physicians' knowledge of and experience with pharmacogenetic testing. Clin Genet 2012;82:388-394. DOI: 10.1111/j.1399-0004.2012.01908.x.

77. Green MJ, Botkin JR. "Genetic exceptionalism" in medicine: clarifying the differences between genetic and nongenetic tests. Ann Intern Med 2003;138:571-575. DOI: 10.7326/0003-4819-138-7-200304010-00013.

78. Rogers SL. The current state of pharmacoeconomics and reimbursement for pharmacogenomics. Adv Mol Pathol 2023;6:87-97. DOI: 10.1016/j.yamp.2023.06.002.

79. Collins F. Opportunities and challenges for the NIH–an interview with Francis Collins. Interview by Robert Steinbrook. N Engl J Med 2009;361:1321-1323. DOI: 10.1056/NEJMp0905046.