

Pharmacogenetic (PGx) Testing

*Advanced insights
for optimised drug
treatment outcomes*

Pharmacogenetic Testing

Pharmacogenetics (PGx), an important part of precision medicine, is the study of how genetic variability influences drug treatment outcomes. Recommended by Guidelines, many medications currently prescribed have pharmacogenetic data to support appropriate dosing or selection. Like all diagnostic tests, pharmacotherapeutic genotyping is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient.



Clinical Labs offers a comprehensive range of pharmacogenetic testing in order to provide clinicians and healthcare providers with important information to help decide on the most appropriate treatment for each individual, particularly in areas such as mental health, pain management, cardiology and oncology.

PGx test utility

Implementation of clinical pharmacogenetics, allele function and inferred phenotypes is a crucial step toward optimal patient health. Identifying responders and non-responders to medications can reduce morbidity, avoid adverse events and optimise drug dosing.

Literature has shown that a large number of people are injured or die in hospitals each year due to adverse drug events (ADEs), resulting in millions of dollars in healthcare costs. The field of genomic medicine presents one potential solution to reduce healthcare costs associated with ADEs and poor response to pharmacotherapy.

PGx guidelines

Evidence-based guidelines with pharmacotherapeutic recommendations for combinations of specific drugs and genotypes or predicted phenotypes are essential for implementing acquired pharmacogenetics knowledge in daily clinical practice.

The Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have been developing guidelines for more than a decade (Swen *et al.* 2011a; Caudle *et al.* 2017).

Recommendations are preferably made available at the time of drug prescribing and dispensing for a patient with a genotype that requires an action, such as a dose reduction (Swen *et al.* 2011a; Deneer and van Schaik, 2013).

When to order the test

Physicians may order the pharmacogenetic testing per drug at the point of care, or an alternative approach is the use of pre-emptive testing, perhaps as part of an annual exam in young adults or even children who require multiple treatments. As a result of the increasing number of drugs with pharmacogenetic data, the pre-emptive use of testing could significantly optimise drug outcomes (Schildcrout *et al.* 2012).

Regardless of when ordered (at time of treatment or prior), due to the continuing decline in the costs of genomic testing technologies, a broad-based pharmacogenetic screen may yield the greatest cost savings.



Identifying responders and non-responders to medications can reduce morbidity, avoid adverse events and optimise drug dosing.

The cytochrome P450 (CYP450) and differences in drug metabolism

A family of enzymes (Figure 1), catalyses the metabolism of many drugs and xenobiotics. The genes that code for cytochrome P450 enzymes are highly polymorphic, which can significantly affect drug metabolism in certain individuals. Differences in drug metabolism due to CYP450 gene variants influence plasma levels of both the active drug and its metabolites.

For example, CYP2D6, CYP2C19 and CYP2C9 are responsible for the metabolism of a large number of commonly prescribed drugs, including warfarin, analgesics, clopidogrel, codeine, tamoxifen, some antidepressants, statins, proton pump inhibitors (PPIs) and anti-emetics (See Table 1). CYP3A5 genotype results can be used to guide dosing of tacrolimus in organ transplant patients (Birdwell *et al.* 2015).



DIFFERENT CYP ENZYMES

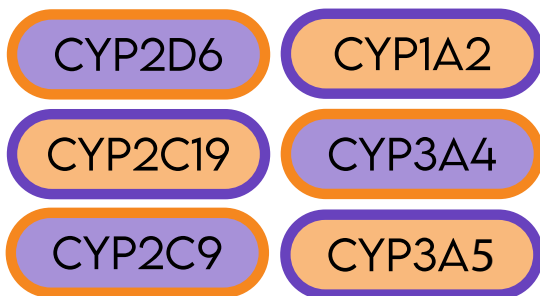


Figure 1. CYP Cytochrome P450 enzyme nomenclature and examples chart.

CYP2D6

CYP2D6 is the primary enzyme responsible for the metabolism of many commonly-used medications especially in mental health, oncology (tamoxifen and 5-HT₃ receptor antagonists) (Goetz *et al.* 2018) and pain management (Crews *et al.* 2021) (Table 1). CYP2D6 is highly polymorphic with over 130 identified allelic variants and sub-variants identified (www.PharmVar.org; CYP2D6 Allele Definition).

CYP2D6 alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups, and significant differences in allele frequencies have been observed. It is important to note that variation in CYP2D6 may have implications for many therapies that may not be listed in this report (Gaedigk *et al.* 2017).

CYP2C19

The hepatic CYP2C19 enzyme contributes to the metabolism of a large number of clinically relevant drugs, such as antidepressants, benzodiazepines, some proton pump inhibitors (Lima *et al.* 2021), clopidogrel (Scott *et al.* 2013) and the anti-fungal medication voriconazole (Moriyama *et al.* 2017) (Table 1). Like many other CYP450 superfamily members, the CYP2C19 gene is highly polymorphic, with >25 known variant alleles.

CYP2C9

Variants in the CYP2C9 gene modify the rate at which some medications are metabolised. When considering antidepressant therapy, such as tricyclic anti-depressants (TCAs), CYP2C9 testing is often combined with analysis of the CYP2C19 and CYP2D6 genes (Attia *et al.* 2014 and Hicks *et al.* 2017). When considering warfarin therapy, this test is often combined with analysis of VKORC1.

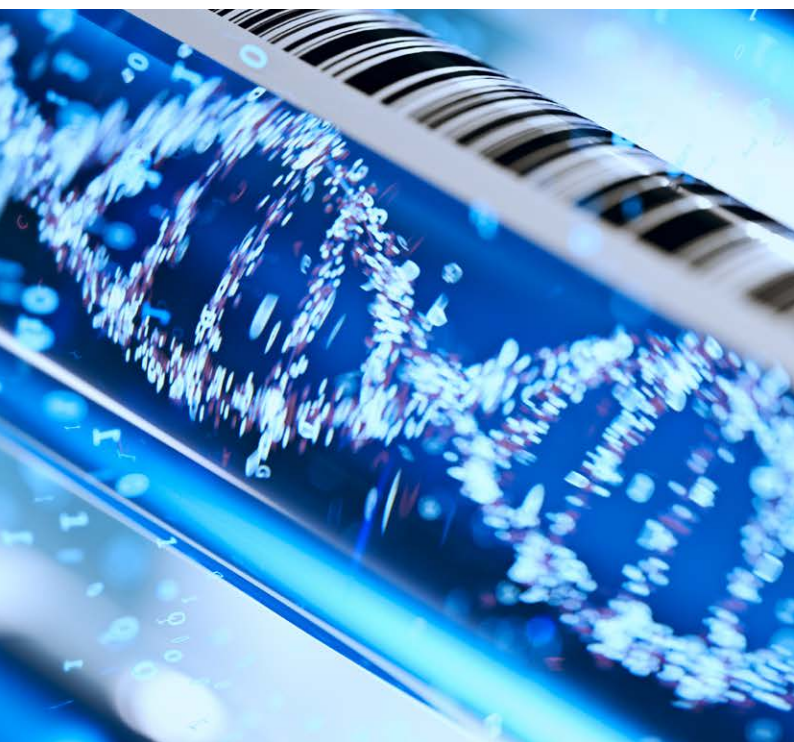
VKORC1, CYP2C9 and warfarin

Warfarin is one of the most commonly prescribed medications worldwide, used for many indications, including prophylaxis and treatment of thromboembolic disorders, atrial fibrillation, cardiac valve replacement and prevention of systemic embolism after myocardial infarction (MI). Approved in the US in 1954, the high efficacy of warfarin is challenged by the high risk of ADEs due to its narrow therapeutic window, requiring careful monitoring and strict compliance.

While CYP2C9 is predominantly involved in the metabolism of warfarin subtypes, VKORC1 is the molecular target of the drug. In 2017, an international collaboration published an updated landmark paper defining appropriate warfarin doses based on a validated dosing algorithm of clinical biomarkers and VKORC1/CYP2C9 genotypes (Johnson *et al.* 2017).

SLCO1B1 and statins

SLCO1B1 gene testing is clinically important in clearance of statins, especially simvastatin. Myopathy is reported in poor metabolisers of this gene. Alternative lipid-lowering statins can be prescribed in lower doses such as atorvastatin, pravastatin and rosuvastatin (Ramsey *et al.* 2014).





Pharmacogenetic markers in oncology

In addition to *RAS*, *BRAF*, *EGFR*, *ERBB2 (HER2)*, *PK3CA* and *KIT* mutation and *PD-1*, *ROS*, *ALK* and *BCR-ABL* fusion genes, other genetic pharmacogenetic biomarkers play a role in patients' responses to oncology therapy.

UDP-glucuronosyltransferase gene (*UGT1A1*)

UGT1A1 is involved in the metabolism of *irinotecan*, a topoisomerase I inhibitor. *UGT1A1* gene polymorphisms are associated with toxicity and clinical efficacy of irinotecan-based chemotherapy in patients with advanced solid tumours, including colorectal, rectal and lung cancer (Fujii *et al.* 2019).

Thiopurine methyltransferase (*TPMT*)

TPMT is the primary enzyme responsible for thiopurine drugs (azathioprine, 6-mercaptopurine and 6-thioguanine) metabolism. These drugs are converted in the body to thioguanine nucleotides (TGNs).

Thiopurine therapy targets the replicating cells without overly harming normal cells. Several studies have established Single Nucleotide Polymorphisms (SNPs) in the *TPMT* gene that may lead to enzyme inactivity, and therefore, haematopoietic toxicity due to thiopurine therapy. It is recommended that physicians order *TPMT* genotyping before prescribing thiopurines to avoid bone marrow toxicity and consequent neutropenia (Relling *et al.* 2018).

Dihydropyrimidine dehydrogenase gene (*DPYD*)

DPD stands for dihydropyrimidine dehydrogenase, an enzyme made by the liver that breaks down uracil and thymine. The molecules created when pyrimidines are broken down (5,6-dihydrouracil and 5,6-dihydrothymine) are excreted by the body or used in other cellular processes. *DPYD* gene mutations result in excess quantities of the breakdown molecules in the blood, urine and cerebrospinal fluid.

Mutations in the *DPYD* gene also interfere with the breakdown of drugs with structures similar to the pyrimidines, such as the cancer drugs 5-fluorouracil and capecitabine (two common chemotherapy drugs used as treatments for a number of different cancers). As a result, these drugs accumulate in the body and cause the severe reactions and neurological manifestations as a result of DPD deficiency (Amstutz *et al.* 2017).

Genetic variations can render some medications ineffective or toxic

Pharmacogenetic variants result in four distinct phenotypes: normal metabolisers (NMs), intermediate metabolisers (IMs), poor metabolisers (PMs), and ultrarapid metabolisers (UMs), which provide guidance for drug dosing and selection.

Overall, wild-type alleles are usually associated with functional enzyme-mediated metabolism. *Ultrarapid metabolisers* may not achieve therapeutic plasma levels due to decreased trough drug concentrations, whereas *poor metabolisers* treated with drugs that are metabolised by these enzymes are at increased risk of prolonged therapeutic effect or toxicity due to increased trough levels of therapeutic drugs.

Some anti-psychotic and SSRI medications can be contraindicated in intermediate *CYP2D6* metabolisers due to increased risk of adverse effects and so alternative agents must be prescribed.

CYP2D6 ultrarapid metabolisers treated with codeine may exhibit symptoms such as extreme sleepiness, confusion or shallow breathing; the lowest possible dose should be prescribed to these patients. Meanwhile, patients who are *CYP2D6 poor metabolisers* may not achieve sufficient pain control due to their inability to convert the drug to its active form, morphine (Crews *et al.* 2021).

CYP2C19 ultrarapid metabolisers should be prescribed alternative therapeutic agents other than benzodiazepines, such as citalopram (Celexa), escitalopram (Lexapro), and TCAs such as imipramine (Tofranil) and clomipramine (Anafranil), due to possible decreases in the efficacy of these medications.

Conclusion

The incorporation of genetic information obtained from pharmacogenetic testing holds substantial promise for improving therapeutic decision-making through enhanced efficacy and reduced adverse events. Considerations for clinical implementation, such as optimal laboratory workflows, electronic health record integration, and stakeholder engagement, as well as provider education, are crucial to patient health.

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- **174 medications** across **19 genes** and multiple therapeutic areas
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- **User-friendly report** developed by psychiatrists
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CNSDose® is a pharmacogenetic (PGx) blood test and clinical decision support tool developed by Australian psychiatrists to support more informed medication selection and dosing in mental health care. Unlike conventional pharmacogenomic tests that analyse only liver metabolic genetics, CNSDose was developed to assess both liver and blood–brain barrier genetics.

This approach identifies potential genetic barriers to psychotropic drug penetration, as well as the doses that ultimately reach the central nervous system and their targets, making CNSDose a uniquely informative tool.

In a retrospective analysis of 1,100 CNSDose test results, 19% of patients with mental illness had normal liver metabolic genetics, which would not assist clinicians in psychotropic medication selection. Of these patients, 40% had blood-brain barrier genetic variants affecting medication transport into the brain. This highlights the clinical value of CNSDose beyond metabolism-only pharmacogenetic testing.

For further information, including a sample report, pricing and educational resources, visit clinicallabs.com.au/doctor/cnsdose.

The CNSDose Report

- **PSYCHOTROPIC DOSE GUIDANCE:** Clear guidance on whether lower, average or higher doses may be required.
- **INTERNATIONAL CLINICAL RECOMMENDATIONS:** Bespoke annotations aligned with FDA (US Food and Drug Administration), CPIC (Clinical Pharmacogenetics Implementation Consortium) or DPWG (Dutch Pharmacogenetics Working Group) guidelines.
- **MEDICATION SAFETY ALERTS:** Highlights medications with significant drug–gene interactions where avoidance may be warranted.

PGx Testing at Clinical Labs

Comprehensive PGx	CNSDose (Comprehensive+) PGx
<ul style="list-style-type: none"> • 8 genes analysed • 97 medications covered • Avoidance and cautionary recommendations in line with FDA, CPIC & DPWG • Prescribing guidance for mental health, cardiology, oncology, pain management, gastroenterology and other clinical areas 	<ul style="list-style-type: none"> • 19 genes analysed • 174 medications covered • Avoidance and cautionary recommendations in line with FDA, CPIC & DPWG • Prescribing guidance for mental health, cardiology, oncology, pain management, gastroenterology and other clinical areas • Dose predictions (low, average, high) for psychotropic medications
Other Smaller PGx Genotyping Panels*	Single Gene PGx Tests*
<ul style="list-style-type: none"> • Statins Predictor: <i>SLCO1B1</i> • Warfarin Panel: <i>CYP2C9</i> and <i>VKORC1</i> • Organ Transplant (Tacrolimus Immunosuppressant) PGx: <i>CYP3A5</i> • PPIs PGx: <i>CYP2C19</i> • Tamoxifen Predictor: <i>CYP2D6</i> • Clopidogrel Predictor: <i>CYP2C19</i> • Voriconazole Predictor: <i>CYP2C19</i> • Anti-Psychotics Predictor: <i>CYP2D6</i> • Anti-Depressants Predictor: <i>CYP2D6</i> and <i>CYP2C19</i> 	<ul style="list-style-type: none"> • <i>TPMT</i> (Medicare rebate available for eligible patients) • <i>DPYD</i> (Medicare rebate available for eligible patients) • <i>UGT1A1</i>

* Report for smaller and single PGx gene panels: You will receive an individual report indicating the genotype and predicted phenotypes for the ordered small gene panels or single gene(s), including metaboliser status and guideline recommendations where applicable.

How to Order Pharmacogenetic (PGx) Testing at Clinical Labs

Request Form Instructions: Before commencing therapy, or in cases of adverse reaction or resistance.

How to order: Fill out our routine Clinical Labs testing request form. List the gene(s) or group of genes required, and prescribed medications if available. **Please note:** CNSDose is only available through Australian Clinical Labs.

Collection locations: Patients can visit any of our convenient locations for their blood test. For locations, please visit clinicallabs.com.au/location.

Turnaround time: Please see our website for current turnaround times for each PGx panel.

Specimen required: 2x EDTA blood samples.

Report for smaller and single PGx gene panels:* You will receive an individual report indicating the genotype and predicted phenotypes for the ordered small gene panels or single gene(s), including metaboliser status and guideline recommendations where applicable.

Test cost: Apart from the *TPMT* and *DPYD* genes, Clinical Labs' PGx gene panels are non-Medicare rebatable (an out-of-pocket fee applies). For more information, including pricing, visit clinicallabs.com.au/pharmacogeneticstesting.

Please note: depending on the PGx panel(s) ordered, testing may be performed and reported in collaboration with an external provider.



For more information about PGx testing options available at Clinical Labs, scan the QR code or visit clinicallabs.com.au/pharmacogeneticstesting.

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CPIC 2022, Guideline for SCL01B1, CYP2C9 and Statins

CPIC 2022, Guideline for CYP2C19 and Clopidogrel Dosing

CPIC 2020 Guideline for CYP2C19 and Proton Pump

Inhibitor Dosing

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Table 1. Clinical Labs Pharmacogenetic (PGx) Testing Medication List

COMPREHENSIVE
COMPREHENSIVE+
(CNSDOSE)



MEDICATION	GENE(S) INVOLVED		
PSYCHOTROPICS			
ANTI-ADHD			
Atomoxetine	CYP2D6	✓	✓
Clonidine	Multi-gene algorithm		✓
Dextroamphetamine	Multi-gene algorithm		✓
Guanfacine	Multi-gene algorithm		✓
Lisdexamfetamine	Multi-gene algorithm		✓
Methylphenidate	Multi-gene algorithm		✓
Modafinil	Multi-gene algorithm		✓
Viloxazine	CYP2D6	✓	✓
ANTI-DEMENTIA			
Donepezil	CYP2D6	✓	✓
ANTIDEPRESSANTS			
Agomelatine	Multi-gene algorithm		✓
Amitriptyline	CYP2C19, CYP2D6	✓	✓
Bupropion	Multi-gene algorithm		✓
Citalopram	CYP2C19	✓	✓
Clomipramine	CYP2C19, CYP2D6	✓	✓
Desipramine	CYP2C19, CYP2D6	✓	✓
Desvenlafaxine	Multi-gene algorithm		✓
Dothiepin	Multi-gene algorithm		✓
Doxepin	CYP2D6	✓	✓
Duloxetine	Multi-gene algorithm		✓
Escitalopram	CYP2C19	✓	✓
Fluoxetine	Multi-gene algorithm		✓
Fluvoxamine	CYP2D6	✓	✓
Imipramine	CYP2C19, CYP2D6	✓	✓
Levomilnacipran	Multi-gene algorithm		✓
Mianserin	Multi-gene algorithm		✓
Milnacipran	Multi-gene algorithm		✓
Mirtazapine	Multi-gene algorithm		✓
Moclobemide	Multi-gene algorithm		✓
Nortriptyline	CYP2D6	✓	✓
Paroxetine	CYP2D6	✓	✓
Protriptyline	CYP2D6	✓	✓
Reboxetine	Multi-gene algorithm		✓
Sertraline	CYP2C19, CYP2B6	✓	✓
Trazodone	Multi-gene algorithm		✓
Trimipramine	CYP2C19, CYP2D6	✓	✓
Venlafaxine	CYP2D6	✓	✓
Vilazodone	Multi-gene algorithm		✓
Vortioxetine	CYP2D6	✓	✓
ANTIPSYCHOTICS			
Amisulpride	Multi-gene algorithm		✓
Aripiprazole	CYP2D6	✓	✓
Asenapine	Multi-gene algorithm		✓
Brexpiprazole	CYP2D6	✓	✓
Cariprazine	Multi-gene algorithm		✓

MEDICATION	GENE(S) INVOLVED		
Chlorpromazine	Multi-gene algorithm		✓
Clozapine	Multi-gene algorithm		✓
Haloperidol	CYP2D6	✓	✓
Iloperidone	CYP2D6	✓	✓
Lurasidone	Multi-gene algorithm		✓
Olanzapine	Multi-gene algorithm		✓
Paliperidone	Multi-gene algorithm		✓
Perphenazine	CYP2D6	✓	✓
Pimozide	CYP2D6	✓	✓
Quetiapine	CYP3A4	✓	✓
Risperidone	CYP2D6	✓	✓
Thioridazine	CYP2C9	✓	✓
Ziprasidone	Multi-gene algorithm		✓
Zuclopenthixol	CYP2D6	✓	✓
ANXIOLYTICS & HYPNOTICS			
Alprazolam	Multi-gene algorithm		✓
Bromazepam	Multi-gene algorithm		✓
Buspirone	Multi-gene algorithm		✓
Clobazam	CYP2C19	✓	✓
Clonazepam	Multi-gene algorithm		✓
Diazepam	CYP2C19	✓	✓
Diphenhydramine	Multi-gene algorithm		✓
Flunitrazepam	Multi-gene algorithm		✓
Melatonin	Multi-gene algorithm		✓
Midazolam	Multi-gene algorithm		✓
Nitrazepam	Multi-gene algorithm		✓
Propranolol	CYP2D6	✓	✓
Suvorexant	Multi-gene algorithm		✓
Temazepam	Multi-gene algorithm		✓
Zolpidem	Multi-gene algorithm		✓
Zopiclone	Multi-gene algorithm		✓
MOOD STABILISERS/ANTICONVULSANTS			
Brivaracetam	CYP2C19	✓	✓
Carbamazepine	Multi-gene algorithm		✓
Lamotrigine	Multi-gene algorithm		✓
Oxcarbazepine	Multi-gene algorithm		✓
Perampanel	Multi-gene algorithm		✓
Phenytoin	CYP2C9	✓	✓
Rufinamide	Multi-gene algorithm		✓
Topiramate	Multi-gene algorithm		✓
Valproic Acid	Multi-gene algorithm		✓
OTHER PSYCHOTROPICS			
Amphetamine	CYP2D6	✓	✓
Bromocriptine	Multi-gene algorithm		✓
Cabergoline	Multi-gene algorithm		✓
Dapoxetine	Multi-gene algorithm		✓
Deutetrabenazine	CYP2D6	✓	✓
Disulfiram	Multi-gene algorithm		✓

MEDICATION	GENE(S) INVOLVED		
Galantamine	CYP2D6	✓	✓
Naloxone	Multi-gene algorithm		✓
Naltrexone	Multi-gene algorithm		✓
Nicotine	Multi-gene algorithm		✓
Rasagiline	Multi-gene algorithm		✓
Ropinirole	Multi-gene algorithm		✓
Rotigotine	Multi-gene algorithm		✓
Selegiline	Multi-gene algorithm		✓

NON-PSYCHOTROPICS

ANTIARRHYTHMICS

Flecainide	CYP2D6	✓	✓
Propafenone	CYP2D6	✓	✓

ANTICOAGULANTS

Acenocoumarol	CYP2C9, VKORC1	✓	✓
Warfarin	CYP2C9, VKORC1	✓	✓

ANTIDIABETIC

Nateglinide	CYP2C9	✓	✓
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ANTIFUNGALS

Flucytosine	DPYD		✓
Voriconazole	CYP2C19	✓	✓

ANTI-NAUSEA

Dronabinol	CYP2C9	✓	✓
Metoclopramide	CYP2D6	✓	✓
Ondansetron	CYP2D6	✓	✓
Tropisetron	CYP2D6	✓	✓

ANTIPLATELET

Clopidogrel	CYP2C19	✓	✓
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ANTIVIRALS

Atazanavir	UGT1A1		✓
Dolutegravir	UGT1A1		✓
Efavirenz	CYP2B6		✓
Raltegravir	UGT1A1		✓

BETA BLOCKERS

Carvedilol	CYP2D6	✓	✓
Metoprolol	CYP2D6	✓	✓
Nebivolol	CYP2D6	✓	✓

IMMUNOSUPPRESSANTS

Azathioprine	TPMT, NUDT15		✓
Tacrolimus	CYP3A5	✓	✓

NSAIDS

Celecoxib	CYP2C9	✓	✓
Flurbiprofen	CYP2C9	✓	✓
Ibuprofen	CYP2C9	✓	✓
Lornoxicam	CYP2C9	✓	✓
Meloxicam	CYP2C9	✓	✓
Piroxicam	CYP2C9	✓	✓
Tenoxicam	CYP2C9	✓	✓

ONCOLOGY/ANTINEOPLASTIC

Belinostat	UGT1A1		✓
Belzutifan	CYP2C19	✓	✓
Capecitabine	DPYD		✓
Erdafitinib	CYP2C9	✓	✓

MEDICATION	GENE(S) INVOLVED		
Fluorouracil	DPYD		✓
Gefitinib	CYP2D6	✓	✓
Irinotecan	UGT1A1		✓
Mercaptopurine	TPMT, NUDT15		✓
Nilotinib	UGT1A1		✓
Sacituzumab Govitecan	UGT1A1		✓
Tamoxifen	CYP2D6	✓	✓
Tegafur	DPYD		✓
Thioguanine	TPMT, NUDT15		✓

OPIOID ANALGESIC

Codeine	CYP2D6	✓	✓
Hydrocodone	CYP2D6	✓	✓
Oliceridine	CYP2D6	✓	✓
Tramadol	CYP2D6	✓	✓

PROTON PUMP INHIBITORS

Dexlansoprazole	CYP2C19	✓	✓
Esomeprazole	CYP2C19	✓	✓
Lansoprazole	CYP2C19	✓	✓
Omeprazole	CYP2C19	✓	✓
Pantoprazole	CYP2C19	✓	✓
Rabeprazole	CYP2C19	✓	✓

STATINS

Atorvastatin	SLCO1B1	✓	✓
Fluvastatin	CYP2C9, SLCO1B1	✓	✓
Lovastatin	SLCO1B1	✓	✓
Pitavastatin	SLCO1B1	✓	✓
Pravastatin	SLCO1B1	✓	✓
Rosuvastatin	SLCO1B1, ABCG2	✓	✓
Simvastatin	SLCO1B1	✓	✓

OTHERS

Abrocitinib	CYP2C19	✓	✓
Allopurinol	ABCG2		✓
Avatrombopag	CYP2C9	✓	✓
Carisoprodol	CYP2C19	✓	✓
Cevimeline	CYP2D6	✓	✓
Elagolix	SLCO1B1	✓	✓
Eliglustat	CYP2D6	✓	✓
Fesoterodine	CYP2D6	✓	✓
Flibanserin	CYP2C19	✓	✓
Lofexidine	CYP2D6	✓	✓
Mavacamten	CYP2C19	✓	✓
Meclizine	CYP2D6	✓	✓
Mirabegron	CYP2D6	✓	✓
Pazopanib	UGT1A1		✓
Pitolisant	CYP2D6	✓	✓
Siponimod	CYP2C9	✓	✓
Tamsulosin	CYP2D6	✓	✓
Tetrabenazine	CYP2D6	✓	✓
Tolterodine	CYP2D6	✓	✓
Valbenazine	CYP2D6	✓	✓