

PERSONALISED MEDICATION

Pharmacogenomic Report

For PVTsample2 PHCmulti2

Date of birth:
15-Jul-1960

Referring clinician:
testdoc0810 uhpvt

Requested:
09-Jul-2024

Collected:
09-Jul-2024

Reported:
15-Jul-2024

Specimen type:
Blood

Laboratory Ref:
16070002

Testing Laboratory:
GenSeq Labs

Interpreted by:
myDNA Life Pty Ltd.

SAMPLE REPORT

ABOUT THIS REPORT

This report provides clinically relevant information on what the patient's genetic results predict about their response to a number of medications covered by this report.

The information concerns drug metabolism and plasma concentrations (drug exposure), as well as the potential for altered clinical effects.

Based on the available information found in the published literature, each medication has been assigned a category according to the likely clinical significance of each gene-drug interaction.

The three categories are:

MAJOR PRESCRIBING CONSIDERATIONS

A potentially significant effect on drug response is predicted. There may be guidelines or a drug label recommending consideration be given to a change in the dose, the medication type, or further monitoring in order to minimize the risk of the potential clinical issue noted.

Of note, "Major" prescribing considerations do not always preclude the use of a specific medication or necessitate a dosage change if the drug is currently effective and well tolerated, this will be dependent on the individual gene-drug interaction and the clinical circumstances.

MINOR PRESCRIBING CONSIDERATIONS

Altered drug response is possible, but either the clinical significance is thought to be minor or there is currently limited evidence available. Consider monitoring for any potential clinical effects annotated in this report. There are generally no specific recommendations to alter dosage or medication according to current guidelines.

USUAL PRESCRIBING CONSIDERATIONS

Genetic results are not predicted to have a significant effect on drug response, based on the literature currently available, and there are no additional prescribing considerations. Other factors may still influence drug response and therefore usual monitoring for adverse effects and efficacy still applies.

Medications which have a prescribing consideration to use an alternative medication will be annotated with this symbol . Consult the personalised prescribing considerations section of the report for the detailed recommendations.

PHARMACOGENOMIC GUIDELINES

For many medications covered in this report, evidence-based guidelines and drug label information are available and where relevant are referenced in this report.

Key practice guidelines include:

1. Clinical Pharmacogenetics Implementation Consortium (CPIC)
2. The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group (DPWG).
3. The FDA Table of Pharmacogenetic Associations and drug label information

REPORT BREAKDOWN

The report consists of the following 6 sections:

1. Medications of Interest (if provided)- presents summarized and detailed prescribing considerations for medications of interest based on the pharmacogenomic test results.
2. Personalised Medication Guide - provides a list of all medications covered by the test categorised as having major, minor or usual prescribing considerations.
3. Genetic test results summary - presents the patients genotypes for the genes relevant to the medications covered by this report.
4. Medication tables arranged according to the three categories of MAJOR, MINOR or USUAL prescribing considerations.
5. Details of genetic test results - provides an explanation of genotype results and the predicted effect on drug exposure and drug response.
6. References - list of key peer-reviewed literature that has been used to produce the report.

Healius Pathology Companies

MEDICATIONS OF INTEREST

MEDICATION

INTERPRETATION

RECOMMENDATION

PAROXETINE

CYP2D6 - Poor metaboliser:

Greatly reduced metabolism by CYP2D6 and greatly increased drug exposure are predicted. There may be an increased risk of adverse effects.

CPIC¹ guidelines provide a moderate recommendation to consider a 50% reduction of the recommended starting dose with a slower titration schedule and a 50% lower maintenance dose as compared to normal metabolisers. It would also be reasonable to monitor for adverse effects.

DPWG² recommends that no specific action is required on paroxetine dosing based on this genotype.

CARVEDILOL

CYP2D6 - Poor metaboliser:

Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This could potentially lead to increased clinical effects, although the evidence for this with carvedilol is weak. The FDA-approved drug label notes that poor metabolisers had a higher rate of dizziness during up-titration.³

DPWG⁴ suggests that no specific action on carvedilol dosing is required based on this genotype. Monitor for adverse effects.

CLOPIDOGREL

CYP2C19 - Normal metaboliser:

Normal formation of clopidogrel's active metabolite by CYP2C19 is predicted.

CPIC guidelines⁵ provide a strong recommendation to use the label-recommended dosage if clopidogrel is being prescribed for cardiovascular or neurovascular indications.

MEDICATIONS WITH NO PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST

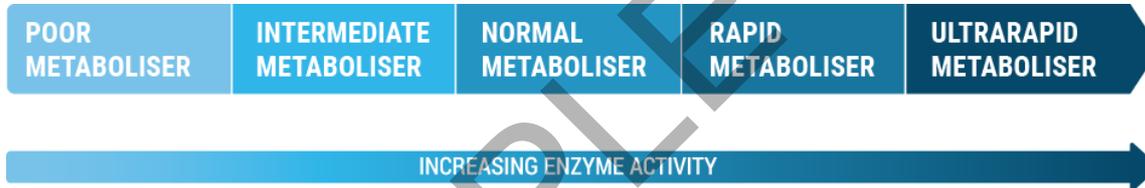
PARACETAMOL

SAMPLE REPORT

PHARMACOGENOMIC TEST RESULTS SUMMARY

GENE	GENOTYPE	PREDICTED PHENOTYPE
ABCG2 (rs2231142)	AA	Poor transporter function
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present)
CYP2B6	*6/*6	Poor metaboliser
CYP2C19	*1/*1	Normal metaboliser
CYP2C9	*1/*3	Intermediate metaboliser
CYP2D6	*4/*4	Poor metaboliser
CYP3A4	*1/*22	Intermediate metaboliser
CYP3A5	*1/*3	Intermediate metaboliser
OPRM1	GG	Reduced mu opioid receptor expression
SLCO1B1	*1/*5	Decreased transporter function
VKORC1	GG	Normal VKORC1 enzyme level

Detailed interpretations of genetic test results are provided at the end of this report.



POTENTIAL DRUG INTERACTIONS

The effect of drug-drug interactions can be additive to the effect of genotype on drug metabolism. Inhibitors can decrease and inducers can increase metabolism, leading to changes in drug concentration and clinical effects.

Comments in the medications of interest and future medications sections only consider the effects of the patient's genotype, not those due to interacting drugs. For the health professional's consideration, the table below identifies which of the patient's current drugs may inhibit or induce those enzymes tested by myDNA. The extent of the inhibition or induction depends on the dose and duration of the therapy. The overall effect on metabolism by a specific enzyme may be estimated by considering both the genetic finding and the potential interacting drug. and future medications sections only consider the effects of the patient's genotype, not those due to interacting drugs. For the health professional's consideration, the table below identifies which of the patient's current drugs may inhibit or induce those enzymes tested by myDNA. The extent of the inhibition or induction depends on the dose and duration of the therapy. The overall effect on metabolism by a specific enzyme may be estimated by considering both the genetic finding and the potential interacting drug.

MEDICATION	INHIBITOR - MODERATE	INHIBITOR - STRONG	INDUCER
PAROXETINE		CYP2D6	

SAMPLE REPORT

PERSONALISED MEDICATION GUIDE

Each medication below has been categorized as having major, minor or usual prescribing considerations based on the pharmacogenomic test results. NOTE: These classifications and recommendations do not account for the effect of any inhibitors or inducers. The table is not an all-inclusive list of medications but includes many commonly prescribed medications.

Legend

Consider alternative medication 

Major prescribing consideration 

Minor prescribing consideration 

Usual prescribing consideration 

CLASS	MAJOR	MINOR	USUAL
ADHD - miscellaneous agents	Atomoxetine		
Angiotensin receptor blockers		Irbesartan Losartan	
Antianginals	Perhexiline		
Antiarrhythmics	Flecainide		
Anticholinergics (genitourinary)	Tolterodine	Darifenacin	
Anticholinesterases		Donepezil Galantamine	
Anticoagulants	Warfarin		Prasugrel Ticagrelor
Antidepressants - other	Vortioxetine 	Agomelatine Bupropion Mianserin Mirtazapine	Moclobemide
Antidepressants - SNRIs	Venlafaxine 	Duloxetine	
Antidepressants - SSRIs	Fluoxetine  Fluvoxamine  Paroxetine  Sertraline		Citalopram Escitalopram
Antidepressants - TCAs	Amitriptyline  Clomipramine  Dosulepin  Doxepin  Imipramine  Nortriptyline 		
Antidiabetics		Glibenclamide Gliclazide Glimepiride Glipizide	Tolbutamide
Antiemetics	Metoclopramide Ondansetron Tropisetron		

CLASS	MAJOR	MINOR	USUAL
Antiepileptics	Fosphenytoin Phenytoin		
Antifungals - Azoles			Voriconazole
Antihistamines		Chlorpheniramine Dexchlorpheniramine Promethazine	
Antineoplastics			Cyclophosphamide
Antiplatelet drugs			Clopidogrel
Antipsychotics	Aripiprazole Brexpiprazole Haloperidol Risperidone Zuclophenthixol	Chlorpromazine Clozapine Olanzapine Quetiapine	Flupenthixol
Antitussives	Dextromethorphan		
Antivirals	Efavirenz	Atazanavir Nevirapine	
Benzodiazepines			Clobazam Diazepam
Beta blockers	Metoprolol Timolol	Carvedilol Propranolol	Nebivolol
Calcineurin inhibitors	Tacrolimus		
Drugs for alcohol dependence			Naltrexone
Drugs for gout	Allopurinol		
Drugs for sexual dysfunction	Dapoxetine ⚠️		
Haemostatic agents		Avatrombopag	
Hypnotics			Melatonin
Immunomodulators and antineoplastics	Tamoxifen ⚠️	Gefitinib	
Miscellaneous	Eliglustat Tamsulosin		Proguanil
Neurological drugs	Siponimod Tetrabenazine		
NSAIDs	Celecoxib Ibuprofen Meloxicam Piroxicam ⚠️	Mefenamic Acid	Diclofenac Indomethacin

CLASS	MAJOR	MINOR	USUAL
Opioid Analgesics	Codeine ⚠️ Methadone Tramadol ⚠️	Oxycodone	Morphine
Proton pump inhibitors		Lansoprazole Omeprazole Pantoprazole	Esomeprazole Rabeprazole
Psychostimulants		Dexamphetamine Lisdexamfetamine	
Statins	Atorvastatin Fluvastatin Lovastatin ⚠️ Pitavastatin Rosuvastatin Simvastatin ⚠️	Pravastatin	

SAMPLE REPORT

PERSONALISED PRESCRIBING CONSIDERATIONS

The following tables outline personalised recommendations for future medications.

These tables do not account for the effect of any inhibitors or inducers. The table is not an all-inclusive list of medications but includes many commonly prescribed medications

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

ATOMOXETINE

ADHD - miscellaneous agents

CYP2D6 - Poor metaboliser:

Greatly reduced metabolism by CYP2D6 and greatly increased drug exposure is predicted. An increased risk of some side effects has been shown for this genotype (e.g. increased blood pressure and heart rate, QT interval prolongation, dry mouth, erectile dysfunction and insomnia) but also greater improvement of ADHD symptoms as compared to non-poor metabolisers in those who tolerate treatment. This genotype is associated with lower final dose requirements.

CPIC⁶ provides a strong recommendation for children and moderate recommendation for adults for dosing of atomoxetine. Refer to CPIC guidelines for details. In summary, Adults: initiate at 40 mg/day. If no clinical response and no adverse events after 2 weeks, increase dose to 80 mg/day. If inadequate response after 2 weeks, consider use of plasma concentrations 2-4 hours after dosing to guide titration. Children: initiate at 0.5mg/kg/day. If no clinical response and no adverse events after 2 weeks, consider use of plasma concentrations 4 hours after dosing to guide titration.

Note: FDA-approved drug label⁷ recommends maximum doses of 1.4mg/kg/day in children up to 70kg and 100 mg daily in adults or children over 70kg.

Note: dosing recommendations should be considered with other clinical factors by the treating clinician(s).

For CYP2D6 poor metabolisers or patients on strong CYP2D6 inhibitors, FDA approved labelling⁷ advises using a reduced dosing strategy (starting dose 0.5mg/kg/day, and only increasing to 1.2mg/kg/day after 4 weeks if required) in children and adolescent patients with body weight <70kg. For children and adolescents >70kg, and for adults, atomoxetine should be initiated at 40mg/day and only increased to 80mg/day after four weeks if necessary.

PERHEXILINE

Antianginals

CYP2D6 - Poor metaboliser:

Greatly reduced metabolism and increased perhexiline exposure are predicted. There is an increased risk of concentration-dependent adverse effects (hepatotoxicity and peripheral neuropathy), especially if appropriate dose reduction and therapeutic drug monitoring do not occur.

Expect a prolonged time to reach steady-state. Early therapeutic drug monitoring is required when perhexiline is used. A greatly reduced maintenance dose requirement is expected. In addition to adjusting dose according to concentration, the AMH⁸ notes that poor metabolisers may require doses as low as 50 mg once a week.

FLECAINIDE

Antiarrhythmics

CYP2D6 - Poor metaboliser:

Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.

The DPWG guidelines⁹ suggest reducing the dose to 50% of the standard dose, recording an ECG and monitoring the plasma concentration.

TOLTERODINE

Anticholinergics (genitourinary)

CYP2D6 - Poor metaboliser:

Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects. Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase tolterodine exposure and the risk of adverse effects.

No genotype-guided dosing recommendation available. Monitor for adverse effects. The FDA¹⁰ has cautioned regarding this genotype and increased risk for QT prolongation with tolterodine.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

WARFARIN

Anticoagulants

VKORC1 - Normal VKORC1 enzyme level CYP2C9 - Intermediate metaboliser:

Reduced metabolism of warfarin by CYP2C9 is predicted. Normal amount of VKORC1 (the enzyme warfarin inhibits). The combined CYP2C9 and VKORC1 results predict increased warfarin sensitivity and increased risk of supratherapeutic INR.

CYP2C9 and VKORC1 - For patients already taking warfarin (e.g. more than 5 doses), dose adjustment is guided by INR.

For patients initiating warfarin, there are CPIC¹¹ recommendations to reach the therapeutic dose. The summary of CPIC recommendations include consideration of the use of validated published pharmacogenetic algorithms^{12,13} available at warfarindosing.org that take into account clinical details as well as genetic findings. See CPIC guidelines for further details. If the patient identifies to be of African ancestry, CPIC provides recommendations for special dosing requirements for warfarin.

VORTIOXETINE

Antidepressants - other



CYP2D6 - Poor metaboliser:

Greatly reduced metabolism by CYP2D6 and increased drug exposure is predicted. This may be associated with an increased risk of concentration-dependent adverse effects.¹

CPIC guidelines¹ provide a moderate recommendation to initiate therapy with 50% of the starting dose and titrate to the maximum recommended dose of 10mg, or to consider an appropriate alternative not predominantly metabolised by CYP2D6.

The TGA approved Product Information¹⁴ states that a dose adjustment is not required. The FDA¹⁵ approved labelling states that the recommended maximum dose is 10mg for CYP2D6 poor metabolisers. Regardless of which dosing advice is followed, be alert for adverse effects.

VENLAFAXINE

Antidepressants - SNRIs



CYP2D6 - Poor metaboliser:

Greatly reduced metabolism of venlafaxine into O-desvenlafaxine (also an active drug) is predicted. This will result in increased venlafaxine exposure and reduced O-desvenlafaxine exposure. The clinical impact of this is unclear, however there may be an increased risk of adverse effects, such as gastrointestinal discomfort. There are indications that the effectiveness of venlafaxine is reduced when used for management of depression in patients with this genotype.

CPIC guidelines¹ provide an optional recommendation to consider an appropriate alternative not predominantly metabolised by CYP2D6.

The DPWG¹⁶ recommends:

It is not possible to offer adequately substantiated advice for dose reduction based on the literature.

1. Choose an alternative.

2. If an alternative is not an option and side effects occur: a) Reduce the dose b) Check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine (this is not routinely available for venlafaxine).

It is not known whether it is possible to reduce the dose to such an extent that effectiveness is maintained without side effects. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.

FLUOXETINE

Antidepressants - SSRIs

CYP2D6 - Poor metaboliser

CYP2C9 - Intermediate metaboliser:

The metabolism of fluoxetine is complex due to the involvement of several CYP enzymes (especially CYP2D6 and CYP2C9), the formation of active metabolites and the enzyme-inhibiting effect of the parent drug and metabolites (especially on CYP2D6). The CYP2D6 genotype predicts increased fluoxetine exposure and reduced formation of the active S-norfluoxetine metabolite. The CYP2C9 genotype predicts reduced metabolism via this pathway. There may be an increased risk of adverse effects.

Based on the CYP2D6 genotype, CPIC¹ and DPWG¹⁷ recommend that no specific action on fluoxetine dosing is required for this genotype.

The FDA¹⁸ has cautioned regarding this genotype and increased risk for QT prolongation with fluoxetine.

Monitor for altered clinical effect, including adverse effects. If adverse effects are a concern, consider an alternative antidepressant for which normal metabolism is predicted.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

FLUVOXAMINE

Antidepressants - SSRIs



CYP2D6 - Poor metaboliser

CYP1A2 - Ultrarapid metaboliser (with inducer present):

Fluvoxamine is metabolised by both CYP2D6 (predominant pathway) and CYP1A2. Negligible metabolism by CYP2D6 and increased metabolism by CYP1A2 in the presence of enzyme inducers such as cigarette smoke are predicted. Note that fluvoxamine itself will inhibit CYP1A2, which could negate the effect of enzyme induction, especially with increasing dose. Fluvoxamine exposure is likely to be increased. There is some evidence that increased drug exposure is associated with adverse effects, such as gastrointestinal upset.

Based on the CYP2D6 genotype, CPIC¹ provides an optional recommendation to consider a 25-50% reduction of the starting dose and a slower titration schedule, or to consider an appropriate alternative not predominantly metabolised by CYP2D6. DPWG² suggests no specific action on fluvoxamine dosing is required based on this CYP2D6 genotype.

PAROXETINE

Antidepressants - SSRIs

CYP2D6 - Poor metaboliser:

Greatly reduced metabolism by CYP2D6 and greatly increased drug exposure are predicted. There may be an increased risk of adverse effects.

CPIC¹ guidelines provide a moderate recommendation to consider a 50% reduction of the recommended starting dose with a slower titration schedule and a 50% lower maintenance dose as compared to normal metabolisers. It would also be reasonable to monitor for adverse effects.

DPWG² recommends that no specific action is required on paroxetine dosing based on this genotype.

SERTRALINE

Antidepressants - SSRIs

CYP2B6 - Poor metaboliser

CYP2C19 - Normal metaboliser:

Sertraline is metabolised by both CYP2C19 and CYP2B6 into less active compounds. Normal metabolism by CYP2C19 and greatly reduced metabolism by CYP2B6 is predicted.¹

CPIC¹ guidelines provide an optional recommendation to consider a lower starting dose, slower titration schedule and a 25% reduction of the standard maintenance dose. Otherwise, switch to an appropriate alternative not predominantly metabolised by CYP2B6.

AMITRIPTYLINE

Antidepressants - TCAs



CYP2D6 - Poor metaboliser

CYP2C19 - Normal metaboliser:

Amitriptyline is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of amitriptyline and negligible metabolism (via CYP2D6) of the active metabolite are predicted. Higher plasma concentrations of the active metabolite may increase the risk of adverse effects.

For use at higher doses such as in the treatment of depression, CPIC¹⁹ provides a strong recommendation to avoid amitriptyline use and consider use of an alternative not metabolised by CYP2D6. If a tricyclic is required, consider 50% reduction of the recommended steady-state starting dose. Consider therapeutic drug monitoring to guide dose adjustments.

For use at lower doses such as in treatment of neuropathic pain, initial dose adjustments are not recommended but close monitoring for adverse effects is advisable.

CLOMIPRAMINE

Antidepressants - TCAs



CYP2D6 - Poor metaboliser

CYP2C19 - Normal metaboliser:

Clomipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of clomipramine and negligible metabolism (via CYP2D6) of the active metabolite are predicted. Higher plasma concentrations of the active metabolite may increase the risk of adverse effects.

CPIC¹⁹ provides an optional recommendation to avoid clomipramine use and consider use of an alternative not metabolised by CYP2D6. If a tricyclic is required, consider 50% reduction of the recommended steady-state starting dose. Consider therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

DOSULEPIN

Antidepressants - TCAs



CYP2D6 - Poor metaboliser

CYP2C19 - Normal metaboliser:

Dosulepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of Dosulepin and negligible metabolism (via CYP2D6) of the active metabolite are predicted. Higher plasma concentrations of the active metabolite may increase the risk of adverse effects.

CPIC¹⁹ provides an optional recommendation to avoid dosulepin use and consider use of an alternative not metabolised by CYP2D6. If a tricyclic is required, consider 50% reduction of the recommended steady-state starting dose. Consider therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.

DOXEPIIN

Antidepressants - TCAs



CYP2D6 - Poor metaboliser

CYP2C19 - Normal metaboliser:

Doxepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of doxepin and negligible metabolism (via CYP2D6) of the active metabolite are predicted. Higher plasma concentrations of the active metabolite may increase the risk of adverse effects.

CPIC¹⁹ provides an optional recommendation to avoid doxepin use and consider use of an alternative not metabolised by CYP2D6. If a tricyclic is required, consider 50% reduction of the recommended steady-state starting dose. Consider therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.

IMIPRAMINE

Antidepressants - TCAs



CYP2D6 - Poor metaboliser

CYP2C19 - Normal metaboliser:

Imipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of imipramine and negligible metabolism (via CYP2D6) of the active metabolite are predicted. Higher plasma concentrations of the active metabolite may increase the risk of adverse effects.

CPIC¹⁹ provides an optional recommendation to avoid imipramine use and consider use of an alternative not metabolised by CYP2D6. If a tricyclic is required, consider 50% reduction of the recommended steady-state starting dose. Consider therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.

NORTRIPTYLINE

Antidepressants - TCAs



CYP2D6 - Poor metaboliser:

Greatly reduced nortriptyline metabolism and increased drug exposure are predicted. An increased risk of adverse effects is expected.

For use at higher doses such as in the treatment of depression, CPIC guidelines¹⁹ provide a strong recommendation to avoid nortriptyline and consider an alternative antidepressant not metabolised by CYP2D6. If prescribing nortriptyline, CPIC guidelines recommend a 50% reduction of the recommended steady-state starting dose, as well as using therapeutic drug monitoring to guide dose adjustments.

For use at lower doses such as in treatment of neuropathic pain, initial dose adjustments are not recommended but close monitoring for adverse effects is advisable.

METOCLOPRAMIDE

Antiemetics

CYP2D6 - Poor metaboliser:

Reduced metabolism of metoclopramide by CYP2D6 is predicted. There may be an increased risk of extrapyramidal adverse effects, particularly at higher doses.

The FDA-approved drug label²⁰ suggests a dose reduction in poor metabolisers. The suggested dose for use in gastrointestinal reflux is 5 mg four times daily or 10 mg three times daily; the suggested dose for use in diabetic gastroparesis is 5 mg four times daily. Monitor for adverse effects.

ONDANSETRON

Antiemetics

CYP2D6 - Poor metaboliser:

Negligible metabolism via CYP2D6 and increased drug exposure are predicted. This has been associated with an improved antiemetic response. It may also increase the risk of concentration-dependent adverse effects.

CPIC²¹ notes that there is insufficient evidence for the clinical impact based on this CYP2D6 genotype. The usual starting dose is suggested. It would be advisable to monitor for adverse effects, especially with the use of higher doses.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

TROPISETRON Antiemetics

CYP2D6 - Poor metaboliser:
Significantly reduced metabolism via CYP2D6 and increased drug exposure are predicted. This has been associated with an improved antiemetic response. It may also increase the risk of concentration-dependent adverse effects.

CPIC²¹ notes that there is insufficient evidence for the clinical impact based on this CYP2D6 genotype. The usual starting dose is suggested. It would be advisable to monitor for adverse effects, especially with the use of higher doses.

FOSPHENYTOIN Antiepileptics

CYP2C9 - Intermediate metaboliser:
Fosphenytoin is a prodrug of phenytoin. Reduced phenytoin metabolism and increased drug exposure are predicted. This genotype has been associated with an increased risk of concentration-dependent adverse effects.

Based on the CYP2C9 genotype, CPIC guidelines²² provide a moderate recommendation to use the typical initial or loading dose and for subsequent doses to use approximately 25% less than the typical maintenance dose. Subsequent dose adjustments should be guided by therapeutic drug monitoring and clinical response.

CPIC guidelines also address genetic testing for the presence of the HLA-B*15:02 allele (not currently tested by myDNA, but which may be requested through a local service if required) which is known to increase the risk of phenytoin-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. The guidelines state that if both HLA-B*15:02 and CYP2C9 genotypes are known, consider the HLA-B*15:02 genotype first, then CYP2C9 genotype. In the instance of an HLA-B*15:02 positive result, CPIC guidelines provide a strong recommendation to not use phenytoin/fosphenytoin in patients who have never had phenytoin before, and to also avoid carbamazepine and oxcarbazepine. Phenytoin may be used cautiously in patients who have tolerated the drug previously for longer than three months without occurrence of adverse skin reactions.

PHENYTOIN Antiepileptics

CYP2C9 - Intermediate metaboliser:
Reduced phenytoin metabolism and increased drug exposure are predicted. This genotype has been associated with an increased risk of concentration-dependent adverse effects.

Based on the CYP2C9 genotype, CPIC guidelines²² provide a moderate recommendation to use the typical initial or loading dose and for subsequent doses to use approximately 25% less than the typical maintenance dose. Subsequent dose adjustments should be guided by therapeutic drug monitoring and clinical response.

CPIC also addresses genetic testing for the presence of the HLA-B*15:02 allele (not currently tested by myDNA, but which may be requested through a local service if required) which is known to increase the risk of phenytoin-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. The guidelines state that if both HLA-B*15:02 and CYP2C9 genotypes are known, consider the HLA-B*15:02 genotype first, then CYP2C9 genotype. In the instance of an HLA-B*15:02 positive result, CPIC provide a strong recommendation to not use phenytoin in patients who have never had phenytoin before, and to also avoid carbamazepine and oxcarbazepine. Phenytoin may be used cautiously in patients who have tolerated the drug previously for longer than three months without occurrence of adverse skin reactions.

SAMPLE REPORT

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

ARIPIPRAZOLE
Antipsychotics

CYP2D6 - Poor metaboliser:
Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.

FDA-approved labelling²³ advises use of 50% of the usual dose. Additionally, if aripiprazole is prescribed together with a strong CYP3A4 inhibiting drug, the dose should be reduced to 25% of the usual dose.
For the injectable depot (Abilify Maintena®), the FDA- approved label and TGA-approved product information²⁴ recommends for CYP2D6 poor metabolisers to use a starting and maintenance dose of 300 mg and for CYP2D6 poor metabolisers taking CYP3A4 inhibitors, a 200 mg dose is advised.
Note the DPWG²⁵ recommends administering no more than 10mg/day or 300 mg/month (68-75% of the standard maximum dose), for CYP2D6 poor metabolisers.

BREXPIPIRAZOLE
Antipsychotics

CYP2D6 - Poor metaboliser:
Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.

DPWG guidelines and FDA-approved labelling^{26, 27} advise initial treatment with 50% of the usual dose and adjusting according to clinical response. Additionally, if brexpiprazole is prescribed together with a strong CYP3A4 inhibiting drug, the dose should be reduced to 25% of the usual dose.²⁷

HALOPERIDOL
Antipsychotics

CYP2D6 - Poor metaboliser:
Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.

The DPWG²⁸ recommends using 60% of the normal dose.

RISPERIDONE
Antipsychotics

CYP2D6 - Poor metaboliser:
Poor metabolism and increased drug exposure to risperidone is predicted. This has been associated with both an increased risk of certain adverse effects and a stronger decrease in symptoms when used in schizophrenia. An increased proportion of therapeutic failure has been observed with this genotype.

The DPWG²⁹ suggests using 67% of the standard dose. If problematic side effects originating from the central nervous system occur despite this reduced dose, a further reduction in dose to 50% of the standard dose is advised.

ZUCLOPENTHIXOL
Antipsychotics

CYP2D6 - Poor metaboliser:
Poor metabolism and increased drug exposure are predicted. This has been associated with an increased risk of adverse effects.

The DPWG²⁸ recommends using 50% of the normal dose.

DEXTROMETHORPHAN
Antitussives

CYP2D6 - Poor metaboliser:
Greatly reduced metabolism and increased drug exposure are predicted. This may increase the risk of adverse effects.

No genotype-guided dosing recommendation available. Monitor for adverse effects.

EFAVIRENZ
Antivirals

CYP2B6 - Poor metaboliser:
Greatly reduced metabolism of efavirenz and higher dose-adjusted trough concentrations compared with normal metabolisers is predicted. This has been associated with a significantly increased risk of concentration-dependent adverse effects (including CNS adverse events, hepatic injury and QTc prolongation) and treatment discontinuation.

CPIC³⁰ provides a moderate recommendation to consider initiating efavirenz with decreased dose of 400 or 200 mg/day. If therapeutic drug monitoring is available and a decreased dose of efavirenz is prescribed, consider obtaining steady-state plasma efavirenz concentrations to ensure they are in the suggested therapeutic range. The potential benefits and risks of the reduced dose and pill number should be considered.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

METOPROLOL Beta blockers

CYP2D6 - Poor metaboliser:
Negligible metabolism by CYP2D6 and greatly increased metoprolol exposure are predicted. Clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Be alert to adverse effects such as bradycardia. Where a more gradual reduction in heart rate is desired, or where there are greater concerns for symptomatic bradycardia, DPWG³¹ has recommendations to increase the dose in smaller steps and/or prescribe no more than 25% of the standard dose. If currently well tolerated and clinical response has been adequate, a change to therapy may not be required.

TIMOLOL Beta blockers

CYP2D6 - Poor metaboliser:
Negligible metabolism by CYP2D6 and increased drug exposure are predicted. The poor metaboliser phenotype has been associated with increased clinical effects, including systemic beta-blocking adverse effects, observed with ophthalmic timolol aqueous (but not gel) preparations.

Monitor for systemic beta blocker adverse effects such as bradycardia and bronchospasm.

TACROLIMUS Calcineurin inhibitors

CYP3A5 - Intermediate metaboliser:
Intermediate metabolism of tacrolimus is predicted. Lower dose-adjusted plasma concentrations of tacrolimus are also predicted when usual prescribing procedures are followed (note that the majority of Caucasians are poor metabolisers of tacrolimus who tend to have higher drug concentrations and prescribing procedures were developed for them). This is associated with a reduction in time that the tacrolimus concentration is in the therapeutic range and potentially with increased risk for transplant rejection.

For use in transplant recipients, other than in liver transplant where donor and recipient livers are of different genotypes, CPIC guidelines³² recommend using an increased starting dose 1.5-2 times the recommended starting dose. Starting oral dose should not exceed 0.3mg/kg/day. Therapeutic drug monitoring should guide ongoing dose adjustments. DPWG guideline³³ recommendations are to use 1.5 times the initial dose and adjust based on therapeutic drug monitoring.

In liver transplants where the transplanted liver has a different genotype from the recipient's genotype, there is insufficient evidence to support a dose recommendation.^{32, 33}

ALLOPURINOL Drugs for gout

ABCG2 (rs2231142) - Poor transporter function:
This genotype is associated with a reduced excretion of uric acid by the kidneys and intestine, meaning that a stronger inhibition of the uric acid production by allopurinol is required to achieve the desired uric acid concentration. The effectiveness of allopurinol is reduced, so that a higher dose is required.

The DPWG guideline³⁴ recommends using 1.4 times the standard dose. This equates to a dose titration schedule of 100, 300, 400, 600 and 700 mg/day instead of the usual schedule of 100, 200, 300, 400 and 500 mg/day.

DAPOXETINE Drugs for sexual dysfunction



CYP2D6 - Poor metaboliser:
Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of adverse effects. Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase dapoxetine exposure and the risk of adverse effects.

The TGA³⁵ approved product information recommends caution with prescribing, given the increased predicted drug exposure. Consider alternative therapy. If using dapoxetine, monitor closely for adverse effects.

TAMOXIFEN Immunomodulators and antineoplastics



CYP2D6 - Poor metaboliser:
Reduced formation of tamoxifen's active metabolite endoxifen by CYP2D6 is predicted. There is conflicting evidence on the effect of this genotype on cancer outcomes. Some studies have shown an increased risk of disease recurrence and higher mortality, whilst others have not shown such effects.

For the adjuvant treatment of ER+ breast cancer, CPIC guidelines³⁶ provides a strong recommendation to use alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women.

Note that higher dose tamoxifen (40mg/d) increases but does not normalize endoxifen concentrations, and can be considered if there are contraindications to aromatase inhibitor therapy.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

ELIGLUSTAT

Miscellaneous

CYP2D6 - Poor metaboliser:

Negligible metabolism of eliglustat by CYP2D6 and greatly increased drug exposure are predicted. Increased risk of adverse effects such as a small, dose dependent elongation of the QT interval, especially if appropriate dose adjustments are not made. CYP3A4 inhibitors increase this risk further.³⁷

The recommended dose of eliglustat depends on whether CYP3A4 and/or CYP2D6 inhibiting medications are co-prescribed. Refer to DPWG guidelines,³⁷ FDA-approved drug label³⁸ or TGA-approved product information³⁹ for prescribing details.

TAMSULOSIN

Miscellaneous

CYP2D6 - Poor metaboliser:

Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects. Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase tamsulosin exposure and the risk of adverse effects.

Monitor for adverse effects. The FDA⁴⁰ has cautioned regarding this genotype and recommends the 0.4mg dose should not be used with strong inhibitors of CYP3A4 and should be used with caution in combination with strong or moderate inhibitors of CYP2D6 or in patients known to be CYP2D6 poor metabolisers, particularly at a dose higher than 0.4mg.

SIPONIMOD

Neurological drugs

CYP2C9 - Intermediate metaboliser:

A reduced metabolism of siponimod and higher plasma concentration is predicted with the *1/*3 genotype, and by extension, other genotypes with comparable genetic variations to *1/*3.

DPWG⁴¹ and the FDA-approved drug label⁴² recommend the use of 50% of the normal maintenance dose in patients with the CYP2C9 *1/*3 genotype. The FDA-approved drug label states that in patients with the CYP2C9 *1/*3 genotype, treatment initiation should be with a 4-day titration, starting at 0.25 mg daily and gradually increasing until the maintenance dose of 1 mg on Day 5 of treatment.

They also advise reconsideration or recommend against concomitant use of siponimod with moderate or strong CYP3A4 inducers in such patients due to a decrease in siponimod exposure.

It would be reasonable to apply this recommendation to patients with a comparable genetic variation.

TETRABENAZINE

Neurological drugs

CYP2D6 - Poor metaboliser:

Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.

The FDA⁴³ approved drug label advises a maximum daily dose of 50mg, with a maximum recommended single dose of 25mg.

CELECOXIB

NSAIDs

CYP2C9 - Intermediate metaboliser:

Moderately reduced metabolism and increased celecoxib exposure are predicted⁴⁴. This may increase the risk of concentration-dependent adverse effects such as gastrointestinal bleeding⁴⁵.

CPIC guidelines⁴⁶ have a moderate recommendation to initiate therapy with the lowest recommended starting dose. Titrate upward to clinical effect or maximum recommended dose with caution. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Carefully monitor for adverse effects such as blood pressure and kidney function. Consider general measures to manage the risk of toxicity such as considering alternative treatments, using the lowest effective dose and gastroprotective agents as clinically appropriate.

IBUPROFEN

NSAIDs

CYP2C9 - Intermediate metaboliser:

Reduced metabolism by CYP2C9 and increased drug exposure are predicted⁴⁷. This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding⁴⁷.

CPIC guidelines⁴⁶ have a moderate recommendation to initiate therapy with the lowest recommended starting dose. Titrate upward to clinical effect or maximum recommended dose with caution. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Carefully monitor for adverse effects such as blood pressure and kidney function. Consider general measures to manage the risk of toxicity such as considering alternative treatments, using the lowest effective dose and gastroprotective agents as clinically appropriate.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

MELOXICAM

NSAIDs

CYP2C9 - Intermediate metaboliser:

Reduced metabolism by CYP2C9 and increased drug exposure are predicted.⁴⁸ This may be associated with an increased risk of adverse effects, including gastrointestinal bleeding.⁴⁵

CPIC guidelines⁴⁶ have a moderate recommendation to initiate therapy with 50% of the lowest recommended starting dose. Titrate upward to the clinical effect or 50% of the maximum recommended dose with caution. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Upward dose titration should not occur until after steady state is reached (at least 7 days). Carefully monitor adverse events such as blood pressure and kidney function. Alternatively, consider an alternative therapy not metabolised by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo (such as aspirin, ketorolac, naproxen or sulindac), or choose an NSAID metabolised by CYP2C9 but with a shorter half life (such as celecoxib, flurbiprofen, ibuprofen or lornoxicam). Consider general measures to manage the risk of toxicity such as considering alternative treatments, using the lowest effective dose and gastroprotective agents as clinically appropriate.

PIROXICAM

NSAIDs



CYP2C9 - Intermediate metaboliser:

Reduced metabolism by CYP2C9 and increased drug exposure are predicted.⁴⁷ This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding.⁴⁵

CPIC guidelines⁴⁶ have a moderate recommendation to choose an alternative therapy not metabolised by CYP2C9 or not significantly impacted by CYP2C9 variants in vivo (such as aspirin, ketorolac, naproxen or sulindac), or choose an NSAID metabolised by CYP2C9 but with a shorter half-life (such as celecoxib, flurbiprofen, ibuprofen or lornoxicam).

CODEINE

Opioid Analgesics



CYP2D6 - Poor metaboliser

OPRM1 - Reduced mu opioid receptor expression:

Greatly reduced metabolism of codeine by CYP2D6 into its active metabolite morphine is predicted. There is a high likelihood of an inadequate analgesic response to codeine.⁴⁹

Based on the CYP2D6 genotype CPIC and DPWG guidelines^{50,51} provide a strong recommendation to avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid.

Whilst this OPRM1 genotype has been associated with reduced sensitivity to morphine and by extrapolation, to codeine as well, there is insufficient evidence for its clinical significance.

There is no additional genotype-guided dosing recommendation based on the OPRM1 result.

Codeine is contraindicated in children under 12 years of age.⁴⁹

METHADONE

Opioid Analgesics

CYP2B6 - Poor metaboliser:

Reduced metabolism by CYP2B6 and increased methadone exposure are predicted (note that S-methadone, which leads to QT prolongation and cardiac arrhythmia, is more affected by this genotype, than R-methadone, which is responsible for the typical opioid effects of the drug). This may lead to increased adverse effects, including QT prolongation and cardiac arrhythmia, as well as sedation and respiratory depression. This genotype has been associated with lower methadone dose requirements when used as methadone maintenance therapy in some, but not all studies. Note that the majority of published pharmacogenetic data for methadone examined the *6 and *9 alleles.

No genotype-guided dosing recommendation available. Monitor for adverse effects, which may include ECG measurement of the QT interval. Consider a more cautious dosing strategy, such as using lower doses and increasing the interval between dose adjustments. Alternative pharmacotherapies could also be considered.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

TRAMADOL

Opioid Analgesics



INTERPRETATION

CYP2D6 - Poor metaboliser:

Negligible formation of tramadol's active metabolite is predicted. This could lead to a reduction in analgesic response.

Note that tramadol is a serotonergic drug. There is an increased risk of serotonin toxicity when used together with other serotonergic drugs.

RECOMMENDATION

CPIC guidelines⁵⁰ provide a strong recommendation to avoid tramadol use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-codeine opioid.

DPWG guidelines⁵¹ provide a recommendation to be alert to possible reduced analgesic effects. In the case of reduced effectiveness, increase the dose or choose a non-codeine alternative.

ATORVASTATIN

Statins

SLCO1B1 - Decreased transporter function:

This SLCO1B1 genotype is associated with increased atorvastatin exposure compared with a normal function genotype, which may translate to increased risk of atorvastatin related myopathy.⁵²

Other factors that may further increase this myopathy risk include: higher doses, certain co-administered drugs, female sex, patient frailty, renal failure, hypothyroidism, advanced age, low BMI, intense physical exercise and Asian or African ancestry.

Based on this SLCO1B1 genotype, CPIC guidelines⁵² provide a moderate recommendation to prescribe less than or equal to 40 mg as a starting dose and adjust doses based on disease-specific guidelines. Be aware of possible increased risk for myopathy especially for the 40 mg dose. If doses >40mg are needed for desired efficacy, consider combination therapy (i.e. atorvastatin plus non-statin guideline directed medical therapy).

Based on this SLCO1B1 genotype, the risk of statin-associated musculoskeletal symptoms (SAMS)⁵² is as follows:

Atorvastatin 80mg - High SAMS risk

If used < 1 year: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 1 year without SAMS: it is reasonable to continue.

Atorvastatin 40mg - Moderate SAMS risk

If used < 4 weeks: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 4 weeks without SAMS: it is reasonable to continue.

Atorvastatin 10-20mg - Low SAMS risk.

FLUVASTATIN

Statins

SLCO1B1 - Decreased transporter function

CYP2C9 - Intermediate metaboliser:

This SLCO1B1 genotype is associated with an increased exposure to fluvastatin as compared with the normal function genotype; there is typical myopathy risk with doses of less than or equal to 40mg.⁵²

This CYP2C9 genotype predicts increased fluvastatin exposure as compared with normal metabolisers, which may translate to increased myopathy risk.⁵²

Other factors that may further increase this myopathy risk include: higher doses, certain co-administered drugs, female sex, patient frailty, renal failure, hypothyroidism, advanced age, low BMI, intense physical exercise and Asian or African ancestry.

CPIC guidelines⁵² provide an optional recommendation to prescribe less than or equal to 20mg daily as a starting dose and adjust doses based on disease-specific guidelines. If doses >20mg are required for desired efficacy, consider an alternative statin or combination therapy (i.e. fluvastatin plus non-statin guideline directed medical therapy).

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

LOVASTATIN

Statins



SLCO1B1 - Decreased transporter function:

This SLCO1B1 genotype is associated with an increased lovastatin exposure compared with a normal function genotype, which may translate to increased myopathy risk.⁵²

Other factors that may further increase this myopathy risk: higher doses, certain co-administered drugs, female sex, patient frailty, renal failure, hypothyroidism, advanced age, low BMI, intense physical exercise and Asian or African ancestry.

CPIC guidelines⁵² provide a moderate recommendation to prescribe an alternative statin depending on the desired potency. If lovastatin therapy is warranted, limit dose to less than or equal to 20mg daily.

Based on this SLCO1B1 genotype, the risk of statin-associated musculoskeletal symptoms (SAMS)⁵² is as follows:

Lovastatin 40-80mg - High SAMS risk

If used < 1 year: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 1 year without SAMS: it is reasonable to continue.

Lovastatin 20mg - Moderate SAMS risk

If used < 4 weeks: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 4 weeks without SAMS: it is reasonable to continue.

PITAVASTATIN

Statins

SLCO1B1 - Decreased transporter function:

This SLCO1B1 genotype is associated with an increased pitavastatin exposure compared with a normal function genotype, which may translate to increased myopathy risk.⁵²

Other factors that may further increase this myopathy risk include: higher doses, certain co-administered drugs, female sex, patient frailty, renal failure, hypothyroidism, advanced age, low BMI, intense physical exercise and Asian or African ancestry.

CPIC guidelines⁵² provide a moderate recommendation to prescribe a less than or equal to 2 mg starting dose and adjust doses based on disease-specific guidelines. Be aware of possible increased risk for myopathy, especially for doses >1 mg. If a dose >2 mg is required for desired efficacy, consider an alternative statin or combination therapy (i.e. pitavastatin plus non-statin guideline directed medical therapy).

Based on this SLCO1B1 genotype, the risk of statin-associated musculoskeletal symptoms (SAMS)⁵² is as follows:

Pitavastatin 4mg - High SAMS risk

If used < 1 year: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 1 year without SAMS: it is reasonable to continue.

Pitavastatin 2mg - Moderate SAMS risk

If used < 4 weeks: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 4 weeks without SAMS: it is reasonable to continue.

Pitavastatin 1mg - Low SAMS risk.

SAMPLER

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

ROSUVASTATIN Statins

ABCG2 (rs2231142) - Poor transporter function

SLCO1B1 - Decreased transporter function:
This SLCO1B1 genotype is associated with an increased rosuvastatin exposure compared with a normal function genotype, however is associated with a typical myopathy risk with doses of rosuvastatin up to 20 mg.⁵² This ABCG2 genotype predicts increased rosuvastatin exposure and increased lipid-lowering effects compared with the normal or decreased function genotype, however the effect on myopathy risk is unknown.⁵²

Other factors that may further increase this myopathy risk include: higher doses, certain co-administered drugs, female sex, patient frailty, renal failure, hypothyroidism, advanced age, low BMI, intense physical exercise and Asian or African ancestry.

CPIC guidelines⁵² provide an optional recommendation to use a starting dose of up to 10 mg and adjust dose based on disease-specific and specific population guidelines. If doses over 10 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e. rosuvastatin plus non-statin guideline directed medical therapy).

SIMVASTATIN Statins



SLCO1B1 - Decreased transporter function:

This SLCO1B1 genotype is associated with increased simvastatin exposure and increased myopathy risk compared with the normal function genotype.⁵²

Other factors that may further increase this myopathy risk include: higher doses, certain co-administered drugs, female sex, patient frailty, renal failure, hypothyroidism, advanced age, low BMI, intense physical exercise and Asian or African ancestry.

Based on this SLCO1B1 genotype, CPIC guidelines⁵² provide a strong recommendation to prescribe an alternative statin depending on desired potency. If simvastatin therapy is warranted, limit dose to <20 mg daily.

Based on this SLCO1B1 genotype, the risk of statin-associated musculoskeletal symptoms (SAMS)⁵² is as follows:

Simvastatin 20-40mg - High SAMS risk

If used < 1 year: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 1 year without SAMS: it is reasonable to continue.

Simvastatin 10mg - Moderate SAMS risk

If used < 4 weeks: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 4 weeks without SAMS: it is reasonable to continue.

SAMPLE REPORT

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

IRBESARTAN

Angiotensin receptor blockers

CYP2C9 - Intermediate metaboliser:

Reduced irbesartan metabolism and increased drug exposure are predicted. This may be associated with a greater blood pressure lowering effect as well as concentration-dependent adverse effect.

No genotype-guided dosing recommendation available. Monitor for adverse effects.

LOSARTAN

Angiotensin receptor blockers

CYP2C9 - Intermediate metaboliser:

A reduction in the formation of losartan's active metabolite is predicted. This may be exacerbated by the co-administration of CYP2C9 inhibiting medications. This may lead to reduced clinical effects.

No genotype-guided dosing recommendation available. Monitor for a reduced clinical response and consider alternative therapy as required.

DARIFENACIN

Anticholinergics (genitourinary)

CYP2D6 - Poor metaboliser:

Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of adverse effects.⁵³ Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase darifenacin exposure and the risk of adverse effects.

No genotype-guided dosing recommendation available. Caution with co-administered CYP3A4 inhibiting drugs. Monitor for adverse effects.

DONEPEZIL

Anticholinesterases

CYP2D6 - Poor metaboliser:

Negligible metabolism via CYP2D6 and increased drug exposure are predicted.⁵⁴ This may increase the risk of concentration-dependent adverse effects and a poorer response to therapy.

No genotype-guided dosing recommendation available. Monitor for adverse effects or a poor response to therapy. Note that the CYP2D6 genotype is not expected to affect the metabolism of an alternate cholinesterase inhibitor, rivastigmine.

GALANTAMINE

Anticholinesterases

CYP2D6 - Poor metaboliser:

Negligible metabolism via CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.

The FDA-approved drug label⁵⁵ states that dosage adjustment of galantamine is not necessary in patients identified as CYP2D6 poor metabolisers as the dose is individually titrated to tolerability. Monitor for adverse effects or a poor response to therapy. Note that the CYP2D6 genotype is not expected to affect the metabolism of an alternate cholinesterase inhibitor, rivastigmine.

AGOMELATINE

Antidepressants - other

CYP1A2 - Ultrarapid metaboliser (with inducer present):

Increased agomelatine metabolism and reduced plasma concentrations are predicted^{56, 57}. This effect is expected to be enhanced with exposure to enzyme inducers such as tobacco smoking, daily consumption of cruciferous vegetables or chargrilled meat, and certain medications (e.g. omeprazole). The clinical significance of this has not yet been established.

No genotype-guided dosing recommendation available. It would be reasonable to monitor for an adequate clinical response.

BUPROPION

Antidepressants - other

CYP2B6 - Poor metaboliser:

Individuals with this genotype may have reduced bupropion metabolism and formation of the active metabolite hydroxybupropion (this is extrapolated mainly from data involving the *6 reduced function allele), as compared with individuals carrying only normal or increased function alleles.^{58, 59} Reduced CYP2B6 function may result in reduced effect and/or adverse effects, however, direct evidence is lacking. Other genetic and clinical factors may also affect bupropion metabolism.

Monitor for adequate clinical response and/or adverse effects.

No genotype-guided dosing recommendation available. Usual prescribing considerations apply.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

MIANSERIN

Antidepressants - other

CYP2D6 - Poor metaboliser:

Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This could increase the risk of adverse effects.

No genotype guided dosing recommendation is available. Be alert for adverse effects.

MIRTAZAPINE

Antidepressants - other

CYP2D6 - Poor metaboliser

CYP1A2 - Ultrarapid metaboliser (with inducer present):

Mirtazapine is metabolised by a number of enzymes, including CYP2D6 and CYP1A2. Negligible metabolism by CYP2D6 and increased metabolism by CYP1A2 in the presence of enzyme inducers (e.g. cigarette smoking) are predicted. The overall effect on plasma concentrations and clinical effects is difficult to predict.

Monitor for altered clinical effect. Based on the CYP2D6 genotype, DPWG suggests that no specific action on mirtazapine dosing is required.⁶⁰

DULOXETINE

Antidepressants - SNRIs

CYP2D6 - Poor metaboliser

CYP1A2 - Ultrarapid metaboliser (with inducer present):

Duloxetine is metabolised by both CYP1A2 and CYP2D6, with CYP1A2 likely to have the major role. Negligible metabolism of duloxetine by CYP2D6 and increased metabolism by CYP1A2 in patients exposed to enzyme inducers (e.g. cigarette smoke) is predicted. The overall effect on duloxetine plasma concentrations and clinical response is difficult to predict. The FDA-approved drug label⁶¹ notes that concomitant administration of duloxetine and a potent CYP1A2 inhibitor to CYP2D6 poor metabolisers resulted in significant increase in drug exposure. Note that CPIC¹ state that there are currently no recommendations for dosing of duloxetine based on CYP2D6 genotype.

No genotype-guided dosing recommendation available. Be alert to an inadequate response, especially in smokers.

GLIBENCLAMIDE

Antidiabetics

CYP2C9 - Intermediate metaboliser:

Reduced metabolism and increased drug exposure are predicted. This has been associated with a greater reduction in HbA1c as well as increased likelihood of hypoglycaemia.

DPWG suggests that no specific action on glibenclamide dosing is required with this genotype.⁶² It would be reasonable to consider a lower starting dose with close monitoring for adverse effects.

GLICLAZIDE

Antidiabetics

CYP2C9 - Intermediate metaboliser

CYP2C19 - Normal metaboliser:

This CYP2C9 genotype has been associated with increased clinical effects (hypoglycaemia, reduced HbA1c). This CYP2C19 genotype predicts normal metabolism of gliclazide. The overall effect of both genotypes is not known for sure.

Based on the CYP2C9 genotype, DPWG suggests that no specific action on gliclazide dosing is required with this genotype.⁶³

GLIMEPIRIDE

Antidiabetics

CYP2C9 - Intermediate metaboliser:

Reduced metabolism and increased drug exposure are predicted. This has been associated with a greater reduction in HbA1c as well as increased likelihood of hypoglycaemia.

DPWG suggests that no specific action on glimepiride dosing is required with this genotype.⁶⁴ It would be reasonable to consider a lower starting dose with close monitoring for adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

GLIPIZIDE Antidiabetics

CYP2C9 - Intermediate metaboliser:
Reduced metabolism and increased drug exposure are predicted. This may be associated with an increase in insulin response to glipizide and has also been linked to an increased likelihood of hypoglycaemia in patients over 60 years of age.⁶⁵

No genotype guided dosing recommendation available. It may be reasonable to consider a lower starting dose with close monitoring for adverse effects.

CHLORPHENIRAMINE Antihistamines

CYP2D6 - Poor metaboliser:
Reduced metabolism of chlorpheniramine and increased drug exposure are predicted. There may potentially be an increased risk of adverse effects, such as drowsiness, although evidence for this is limited.

No genotype-guided dosing recommendation available. Consider using a lower starting dose. Monitor for adverse effects.

DEXCHLORPHENIRAMINE Antihistamines

CYP2D6 - Poor metaboliser:
Reduced metabolism of dexchlorpheniramine and increased drug exposure are predicted. There may potentially be an increased risk of adverse effects, such as drowsiness, although evidence for this is limited.

No genotype-guided dosing recommendation available. Consider using a lower starting dose. Monitor for adverse effects.

PROMETHAZINE Antihistamines

CYP2D6 - Poor metaboliser:
Reduced metabolism of promethazine and increased drug exposure are predicted. There may potentially be an increased risk of adverse effects, such as drowsiness, although evidence for this is limited.

No genotype-guided dosing recommendation available. Consider using a lower starting dose. Monitor for adverse effects.

CHLORPROMAZINE Antipsychotics

CYP2D6 - Poor metaboliser:
Greatly reduced metabolism of chlorpromazine by CYP2D6 and increased drug exposure are predicted. There may be an increased risk of adverse effects.

No genotype-guided dosing recommendation available. Monitor for adverse effects.

CLOZAPINE Antipsychotics

CYP2D6 - Poor metaboliser
CYP1A2 - Ultrarapid metaboliser (with inducer present):
Based on the CYP1A2 genotype, increased metabolism of clozapine and reduced drug exposure are predicted in the presence of inducers such as tobacco smoking, daily consumption of cruciferous vegetables or char-grilled meat, and certain medications (e.g. omeprazole). This CYP1A2 genotype has also been associated with a reduced clinical response to clozapine, which is more marked in smokers.⁶⁶ The DPWG guidelines²⁸ state that there is no gene-drug interaction for CYP1A2 and clozapine.

Based on the CYP1A2 genotype, no genotype-guided dosing recommendation available. Monitor for reduced clinical effect, especially in a patient exposed to enzyme inducers. If exposure to enzyme inducers stops abruptly (e.g. tobacco smoking cessation) monitor for emergent concentration-dependent adverse effects. Some authorities have recommended a dose reduction at the time of smoking cessation.⁶⁸

The FDA-approved drug label⁶⁷ states that in CYP2D6 poor metabolisers, plasma concentrations of clozapine may be increased.

Based on the CYP2D6 genotype, the FDA-approved drug label⁶⁷ states that it may be necessary to reduce the dose in CYP2D6 poor metabolisers, as they may develop higher than expected plasma concentrations when given usual doses. The DPWG guidelines²⁸ state that no action is required for this CYP2D6 genotype and clozapine.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

OLANZAPINE

Antipsychotics

INTERPRETATION

CYP1A2 - Ultrarapid metaboliser (with inducer present):

Increased metabolism of olanzapine by CYP1A2 and reduced drug exposure are predicted, especially in the presence of inducers such as tobacco smoking, daily consumption of cruciferous vegetables or chargrilled meat and certain medications (e.g. omeprazole). This genotype has been associated with a reduced clinical response to olanzapine independent of smoking, but this has not been confirmed in all studies. Although olanzapine is metabolised to a lesser extent by CYP2D6, the DPWG guidelines²⁸ state that there is no gene-drug interaction for either CYP1A2 or CYP2D6 and olanzapine.

RECOMMENDATION

No genotype-guided dosing recommendation is available. Monitor for reduced clinical effect, especially in a patient exposed to enzyme inducers. If exposure to enzyme inducers stops abruptly (e.g. tobacco smoking cessation) monitor for emergent concentration-dependent adverse effects. Some authorities have recommended a dose reduction at the time of smoking cessation.⁶⁸

QUETIAPINE

Antipsychotics

CYP3A4 - Intermediate metaboliser:

Reduced metabolism of quetiapine to inactive metabolites and an active metabolite with anti-depressant effects. Effect on plasma concentration is limited (20% increase compared with normal metabolisers).^{69,70} This may potentially be associated with increased clinical effects (therapeutic and/or adverse), although direct evidence is lacking. Although quetiapine is also metabolised to a lesser extent by CYP2D6, the DPWG guidelines²⁸ state that there is no gene-drug interaction for CYP2D6 and quetiapine.

The DPWG guidelines state that no action is required based on this genotype.⁶⁹ Be alert for increased clinical effects.

ATAZANAVIR

Antivirals

CYP3A5 - Intermediate metaboliser:

Moderately increased atazanavir metabolism and reduced drug exposure are predicted (metabolism is increased when compared with most Caucasian people who are CYP3A5 poor metabolisers). Co-administration with ritonavir ("ritonavir-boosting") may partly or wholly offset the increased atazanavir metabolism associated with this genotype.⁷¹

Note that a test for a variation in the UGT1A1 gene is available. This test is useful for predicting the risk of atazanavir-induced hyperbilirubinemia, and if results are available, they may be considered in addition to the CYP3A5 results.

CYP3A5 - No genotype-guided dosing recommendation available. Monitor for a reduced clinical effect.

NEVIRAPINE

Antivirals

CYP2B6 - Poor metaboliser:

Greatly reduced metabolism by CYP2B6 and increased nevirapine exposure are predicted. There may be an increased risk for concentration-dependent adverse effects. There may be an increased risk of Stevens-Johnson Syndrome/TEN with nevirapine treatment in individuals with the 516G>T allele (present in *6) and the 983T>C allele (present in *18), compared with those without these alleles. This is only one of a number of risk factors associated with Stevens-Johnson Syndrome.

No genotype-guided dosing recommendation available. Monitor for adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION

DRUG CATEGORY

CARVEDILOL

Beta blockers

INTERPRETATION

CYP2D6 - Poor metaboliser:

Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This could potentially lead to increased clinical effects, although the evidence for this with carvedilol is weak. The FDA-approved drug label notes that poor metabolisers had a higher rate of dizziness during up-titration.³

RECOMMENDATION

DPWG⁴ suggests that no specific action on carvedilol dosing is required based on this genotype. Monitor for adverse effects.

PROPRANOLOL

Beta blockers

CYP2D6 - Poor metaboliser

CYP1A2 - Ultrarapid metaboliser (with inducer present):

Propranolol is metabolised by both CYP2D6 and CYP1A2 and also has an active metabolite. This genotype predicts negligible metabolism by CYP2D6 and increased metabolism by CYP1A2 (the latter mainly in the presence of inducers such as cigarette smoke). The overall effect on drug exposure is not known. The FDA⁷² notes that systemic concentrations may be affected in CYP2D6 poor metabolisers.

No genotype-guided dosing guideline available. Monitor for altered clinical effect.

AVATROMBOPAG

Haemostatic agents

CYP2C9 - Intermediate metaboliser:

A reduced metabolism by CYP2C9 of avatrombopag and higher plasma concentration is predicted.⁷²

CYP2C9 - For treatment of chronic immune thrombocytopenia, the FDA-approved drug label⁷³ and TGA-approved product information⁷⁴ advises a reduced dose with concomitant use of a moderate or strong dual inhibitor of CYP2C9 and CYP3A4 due to the increased risk of toxicity. It advises an increased starting dose with concomitant use of a moderate or strong dual inducer of CYP2C9 and CYP3A4 due to a possible reduction in efficacy.

GEFITINIB

Immunomodulators and antineoplastics

CYP2D6 - Poor metaboliser:

Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.

The FDA-approved drug label⁷⁵ advises that there is no dose adjustment recommendations for gefitinib in individuals with a known CYP2D6 poor metaboliser genotype, but they should be closely monitored for adverse reactions. The DPWG⁷⁶ suggests that no specific action on gefitinib dosing is required with this genetic result.

MEFENAMIC ACID

NSAIDs

CYP2C9 - Intermediate metaboliser:

Mefenamic acid is metabolised by CYP2C9.⁷⁷ This genotype predicts an increase in mefenamic acid exposure which may potentially increase the risk of adverse effects⁷⁸, especially with high dosages or if drug-drug interactions occur.

Standard dosing and prescribing measures apply. Monitor for adverse effects.

OXYCODONE

Opioid Analgesics

CYP2D6 - Poor metaboliser:

Significantly reduced exposure to oxycodone's active metabolite, oxymorphone, is predicted. Although this may potentially lead to reduced analgesia or increased oxycodone consumption, there is limited evidence to suggest that this is clinically significant.

Due to inconsistent evidence for adverse effects and analgesia, CPIC guidelines⁵⁰ have no recommendations to support oxycodone dosing.

DPWG⁵¹ also suggest that no specific action on oxycodone dosing is required. Be alert to a reduced response.

LANSOPRAZOLE

Proton pump inhibitors

CYP2C19 - Normal metaboliser:

This genotype predicts typical metabolism of lansoprazole. However, this rate of metabolism has been associated with a potentially incomplete clinical response in conditions such as oesophagitis and H. pylori, compared to intermediate and poor metabolisers.

CPIC guidelines have a moderate recommendation to initiate a standard starting daily dose. Consider increasing the dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis, and giving the daily dose in divided doses.⁷⁹ If response is inadequate, consider the use of esomeprazole or rabeprazole.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

OMEPRAZOLE

Proton pump inhibitors

CYP2C19 - Normal metaboliser:

This genotype predicts typical metabolism of omeprazole. However, this rate of metabolism has been associated with a potentially incomplete clinical response in conditions such as oesophagitis and H. pylori, compared to intermediate and poor metabolisers.

CPIC guidelines have a moderate recommendation to initiate a standard starting daily dose. Consider increasing the dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis, and giving the daily dose in divided doses.⁷⁹ If response is inadequate, consider use of esomeprazole or rabeprazole.

PANTOPRAZOLE

Proton pump inhibitors

CYP2C19 - Normal metaboliser:

This genotype predicts typical metabolism of pantoprazole. However, this rate of metabolism has been associated with a potentially incomplete clinical response in conditions such as oesophagitis and H. pylori, compared to intermediate and poor metabolisers.

CPIC guidelines have a moderate recommendation to initiate a standard starting daily dose. Consider increasing the dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis, and giving the daily dose in divided doses.⁷⁹ If response is inadequate, consider the use of esomeprazole or rabeprazole.

DEXAMPHETAMINE

Psychostimulants

CYP2D6 - Poor metaboliser:

Dexamphetamine is eliminated by both the kidney (as unchanged drug) and the liver, with CYP2D6 playing a significant role. Negligible metabolism via CYP2D6 and increased dexamphetamine exposure is predicted. Clinical effects may be increased.

The FDA-approved drug label suggests a lower starting dose and monitoring for adverse effects where there is a lack of CYP2D6 function.⁸⁰

LISDEXAMFETAMINE

Psychostimulants

CYP2D6 - Poor metaboliser:

Lisdexamfetamine is a prodrug of dextroamphetamine (also known as dexamfetamine). Dextroamphetamine is eliminated by both the kidney (as unchanged drug) and the liver, with CYP2D6 playing a significant role. Negligible metabolism via CYP2D6 and increased dextroamphetamine exposure is predicted. Clinical effects may be increased.

The FDA-approved drug label suggests a lower starting dose and monitoring for adverse effects where there is a lack of CYP2D6 function.⁸¹

PRAVASTATIN

Statins

SLCO1B1 - Decreased transporter function:

This SLCO1B1 genotype is associated with an increased pravastatin exposure compared with a normal function genotype. There is a typical myopathy risk with doses less than or equal to 40mg.⁵²

Other factors that may further increase this myopathy risk include: higher doses, certain co-administered drugs, female sex, patient frailty, renal failure, hypothyroidism, advanced age, low BMI, intense physical exercise and Asian or African ancestry.

CPIC guidelines⁵² provide a moderate recommendation to prescribe the desired starting dose and adjust doses based on disease specific guidelines. Be aware of possible increased risk for myopathy, especially with doses >40mg daily.

Based on this SLCO1B1 genotype, the risk of statin-associated musculoskeletal symptoms (SAMS)⁵² is as follows:

Pravastatin 80mg - Moderate SAMS risk

If used < 4 weeks: Consider changing to a statin/dose combination with lower SAMS risk.

If used > 4 weeks without SAMS: it is reasonable to continue.

Pravastatin 10-40mg - Low SAMS risk.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
PRASUGREL Anticoagulants	CYP2C19 - Normal metaboliser: DPWG ⁸² states that there is no gene-drug interaction for CYP2C19 and prasugrel.	No genotype-guided dosing recommendation available for this genotype. Standard dosing and prescribing measures apply.
TICAGRELOR Anticoagulants	CYP2C19 - Normal metaboliser: DPWG ⁸³ states that there is no gene-drug interaction for ticagrelor and CYP2C19.	No genotype-guided dosing recommendation available for this genotype. Standard dosing and prescribing measures apply.
MOCLOBEMIDE Antidepressants - other	CYP2C19 - Normal metaboliser: Normal metabolism of moclobemide by CYP2C19 is predicted.	Standard dosing and prescribing measures apply.
CITALOPRAM Antidepressants - SSRIs	CYP2C19 - Normal metaboliser: Normal metabolism of citalopram by CYP2C19 is predicted.	CPIC guidelines ¹ provide a strong recommendation to initiate therapy with the recommended starting dose.
ESCITALOPRAM Antidepressants - SSRIs	CYP2C19 - Normal metaboliser: Normal metabolism of escitalopram by CYP2C19 is predicted.	CPIC guidelines ¹ provide a strong recommendation to initiate therapy with the recommended starting dose.
TOLBUTAMIDE Antidiabetics	CYP2C9 - Intermediate metaboliser: Reduced metabolism of tolbutamide by CYP2C9 is predicted. This has been associated with a reduction in glucose concentration in some studies ⁸⁴ .	DPWG ⁸⁵ states that there is no action needed for this gene-drug interaction.
VORICONAZOLE Antifungals - Azoles	CYP2C19 - Normal metaboliser: Normal voriconazole metabolism by CYP2C19 is predicted.	CPIC guidelines ⁸⁶ provide a strong recommendation to initiate therapy with the recommended standard of care dosing.
CYCLOPHOSPHAMIDE Antineoplastics	CYP2C19 - Normal metaboliser: Normal metabolism of cyclophosphamide by CYP2C19 into its active metabolite is predicted.	No genotype-guided dosing recommendation available.
CLOPIDOGREL Antiplatelet drugs	CYP2C19 - Normal metaboliser: Normal formation of clopidogrel's active metabolite by CYP2C19 is predicted.	CPIC guidelines ⁵ provide a strong recommendation to use the label-recommended dosage if clopidogrel is being prescribed for cardiovascular or neurovascular indications.
FLUPENTHIXOL Antipsychotics	CYP2D6 - Poor metaboliser: DPWG guidelines ⁸⁷ state that there is no gene-drug interaction for flupenthixol and CYP2D6.	No dosage recommendation is currently available based on the genetic findings.
CLOBAZAM Benzodiazepines	CYP2C19 - Normal metaboliser: Clobazam is metabolised by CYP3A4 into an active metabolite, N-desmethylclobazam, which is responsible for most of the therapeutic effect. N-desmethylclobazam is further metabolised by CYP2C19 into an inactive metabolite. Normal metabolism of clobazam's active metabolite is predicted. (Note that the effect of variations in CYP3A4 has not been described).	Standard dosing and prescribing measures apply.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

DIAZEPAM Benzodiazepines

CYP2C19 - Normal metaboliser:
Diazepam is metabolised by CYP3A4 and CYP2C19 into active metabolites, including desmethyldiazepam, which has a long half-life. The CYP2C19 genotype predicts normal CYP2C19-mediated metabolism of both diazepam and desmethyldiazepam. (Note that the effect of variations in the CYP3A4 gene on diazepam metabolism have not been described).

Standard dosing and prescribing measures apply.

NEBIVOLOL Beta blockers

CYP2D6 - Poor metaboliser:
Negligible neбиволол metabolism by CYP2D6 and increased drug exposure are predicted. However, this has not been convincingly linked to increased beta blocking effects.

The FDA-approved drug label⁸⁸ states that no dose adjustments are necessary for CYP2D6 poor metabolisers, as the clinical effect and safety profile were similar between poor and extensive metabolisers. Be alert for excessive beta blockade.

NALTREXONE Drugs for alcohol dependence

OPRM1 - Reduced mu opioid receptor expression:
There is currently insufficient evidence to support an association between the OPRM1 genotype and the response to naltrexone. It has been suggested that the G allele may be associated with a lower relapse rate, longer time to relapse and less heavy drinking days when naltrexone is used in the management of alcohol use disorder in a few studies, however in other studies and a recent meta-analysis, this was not observed.⁸⁹

CPIC guidelines⁵⁰ state that there is insufficient evidence to provide a recommendation for naltrexone dosing based on OPRM1 genotype. Usual prescribing considerations apply.

MELATONIN Hypnotics

CYP1A2 - Ultrarapid metaboliser (with inducer present):
Increased metabolism of melatonin and reduced exposure, especially in the presence of inducers such as tobacco smoking, daily consumption of cruciferous vegetables or chargrilled meat and certain medications (e.g. omeprazole).⁹⁰ The clinical significance of this is not known.

No genotype-guided dosing recommendation available. It would be reasonable to monitor for an adequate clinical response.

PROGUANIL Miscellaneous

CYP2C19 - Normal metaboliser:
Normal metabolism of proguanil by CYP2C19 into its active metabolite cycloguanil is predicted.

No genotype-guided dosing recommendation available.

DICLOFENAC NSAIDs

CYP2C9 - Intermediate metaboliser:
Diclofenac is only partially metabolised by CYP2C9. This genotype predicts a reduction in diclofenac metabolism by CYP2C9. Whilst this could lead to a small increase in diclofenac exposure,⁹¹ the clinical significance has not been demonstrated.

CPIC guidelines⁴⁶ state that there is insufficient evidence to provide a recommendation to guide clinical practice at this time.

Standard dosing and prescribing measures apply. Be alert to adverse effects.

INDOMETHACIN NSAIDs

CYP2C9 - Intermediate metaboliser:
Indomethacin is only partially metabolised by CYP2C9. This genotype predicts a reduction in indomethacin metabolism by CYP2C9. Whilst this could lead to a small increase in indomethacin exposure,⁹² the clinical significance has not been demonstrated.

CPIC guidelines⁴⁶ state that there is insufficient evidence to provide a recommendation to guide clinical practice at this time.

Standard dosing and prescribing measures apply. Be alert to adverse effects.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY

INTERPRETATION

RECOMMENDATION

MORPHINE
Opioid Analgesics

OPRM1 - Reduced mu opioid receptor expression:
Whilst this genotype has been associated with reduced sensitivity to morphine (including slightly increased morphine consumption in post-operative and chronic pain settings), there is insufficient evidence for its clinical significance.

CPIC⁵⁰ states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time.

Standard dosing and prescribing measures apply. It may be reasonable to consider the possibility of reduced clinical response during dose titration.

ESOMEPRAZOLE
Proton pump inhibitors

CYP2C19 - Normal metaboliser:
Typical metabolism of esomeprazole by CYP2C19 is predicted. Note that this genotype has a lesser effect with esomeprazole and rabeprazole compared to other PPIs.

Standard dosing and prescribing measures apply. If response is inadequate, consider a trial of rabeprazole as an alternative.

RABEPRAZOLE
Proton pump inhibitors

CYP2C19 - Normal metaboliser:
Normal metabolism of rabeprazole by CYP2C19 is predicted. Note that this genotype has a lesser effect with rabeprazole and esomeprazole compared to other PPIs.

Standard dosing and prescribing measures apply. If the response to rabeprazole is inadequate, consider a trial of esomeprazole as an alternative agent.

SAMPLE REPORT

DETAILED PHARMACOGENOMIC TEST RESULTS

GENE	GENOTYPE	PREDICTED PHENOTYPE
ABCG2 (rs2231142)	AA	Poor transporter function: Due to the presence of two decreased function alleles, this individual is predicted to have poor function of the ABCG2 encoded transporter. Decreased clearance of certain medications such as rosuvastatin is expected.
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present): Due to the presence of two *1F alleles, this individual is predicted to have an ultrarapid metaboliser phenotype. Enzyme activity is highest in the presence of inducers, such as tobacco smoke, regular consumption of cruciferous vegetables or chargrilled meats, and certain drugs. For a drug extensively metabolised by CYP1A2, drug exposure and clinical effects may either be reduced (for an active drug) or increased (for a prodrug).
CYP2B6	*6/*6	Poor metaboliser: This individual is predicted to have a poor metaboliser phenotype due to the presence of two copies of reduced function alleles. For a drug extensively metabolised by CYP2B6, drug exposure and clinical effects may either be increased (for an active drug) or decreased (for a prodrug). This individual is at risk of experiencing adverse effects (active drug) or therapeutic failure (prodrug).
CYP2C19	*1/*1	Normal metaboliser: Due to the presence of two copies of normal function alleles, this individual is predicted to have a normal metaboliser phenotype. For a drug extensively metabolised by CYP2C19, drug exposure and clinical effects may be expected to lie within the normal range.
CYP2C9	*1/*3	Intermediate metaboliser: Due to the presence of one normal function allele and one null allele, this individual is predicted to have an intermediate metaboliser phenotype. For a drug extensively metabolised by CYP2C9, drug exposure and clinical effects may either be increased (for an active drug) or decreased (for a prodrug). This may increase the likelihood of adverse effects (active drug) or therapeutic failure (prodrug).
CYP2D6	*4/*4	Poor metaboliser: Due to the presence of two copies of no function alleles, this individual is predicted to have a poor metaboliser phenotype. For a drug extensively metabolised by CYP2D6, drug exposure and clinical effects may either be greatly increased (for an active drug) or greatly decreased (for a prodrug). The individual is at risk of experiencing adverse effects (active drug) or therapeutic failure (prodrug).
CYP3A4	*1/*22	Intermediate metaboliser: This individual carries one copy of the decreased function *22 allele and is predicted to have an intermediate metaboliser phenotype. Reduced metabolism of certain CYP3A4 substrate drugs (e.g. quetiapine) is expected. This may result in increased drug exposure and clinical effects. Note that if the *18 allele is present, it seems to have substrate-dependent activity.
CYP3A5	*1/*3	Intermediate metaboliser: This individual carries one normal functioning allele and one non-functioning allele and is predicted to have an intermediate metaboliser phenotype (CYP3A5 expresser). CYP3A5 is known to metabolise certain drugs, including tacrolimus.
OPRM1	GG	Reduced mu opioid receptor expression: The GG genotype contains two variant alleles for the OPRM1 gene which encodes the mu opioid receptor. Whilst the evidence around OPRM1 genetic variation continues to develop, it appears that the G allele is associated with a reduced response to certain opioids (in particular, morphine). These findings are supported by a number of cohort studies and at least two meta-analyses ^{93,94} however, this is not shown in all studies. For naltrexone in the management of alcohol use disorder, some studies have shown an association of the G allele with superior clinical outcomes. Note the frequency of the variant allele (G) is higher in people of Asian ancestry (around 40%) than European ancestry (around 15%).

SAMPLE REPORT

GENE	GENOTYPE	PREDICTED PHENOTYPE
SLCO1B1	*1/*5	Decreased transporter function: This individual carries one copy of the decreased function *5 allele and is predicted to have decreased function of the <i>SLCO1B1</i> encoded transporter. Decreased clearance of certain medications such as simvastatin is expected.
VKORC1	GG	Normal VKORC1 enzyme level: The VKORC1 enzyme is predicted to be present in normal amounts and the response to warfarin will be normal. The <i>CYP2C9</i> genotype should also be considered together with the <i>VKORC1</i> genotype for calculating the initial warfarin dose.

SAMPLE REPORT

REFERENCES

- 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 [published online ahead of print, 2023 Apr 9]. *Clin Pharmacol Ther.* 2023;10.1002/cpt.2903. doi:10.1002/cpt.2903
- Brouwer J, Nijenhuis M, Soree B, Guchelaar HJ, Swen JJ, van Schaik RHN, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2C19 and CYP2D6 and SSRIs. *Eur J Hum Genet.* 2021.
- DailyMed - CARVEDILOL PHOSPHATE capsule, extended release. 2019. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bcfe4b84-500e-4b93-ba20-aa7c4297b0ae> [Accessed 14 October 2020]
- [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA448817/guidelineAnnotation/PA166104974> [accessed 2 March 2020]
- Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clin Pharmacol Ther.* 2022.
- Brown JT, Bishop JR, Sangkuhl K, Nurmi EL, Mueller DJ, Dinh JC, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. *Clin Pharmacol Ther.* 2019;106(1):94-102.
- DailyMed - STRATTERA- atomoxetine hydrochloride capsule. 2020. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=309de576-c318-404a-bc15-660c2b1876fb> [Accessed 21 September 2020]
- Australian Medical Handbook, Perhexiline. 2021. [ONLINE] Available at: <https://amhonline.amh.net.au.acs.hcn.com.au/chapters/cardiovascular-drugs/drugs-angina/other-antianginal-drugs/perhexiline> [Accessed 19 April 2021]
- [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA449646/guidelineAnnotation/PA166104969> [accessed 2 March 2020]
- DailyMed - TOLTERODINE- tolterodine tablet. 2016. [ONLINE] Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=304023e8-57ad-4dd7-9cf0-a4524623aa6c> [Accessed 02 December 2022]
- Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clin Pharmacol Ther.* 2017; 102(3): 397-404.
- Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther.* 2008; 84(3) 326-331.
- International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Eng J Med.* 2009; 360(8): 753-764
- TGA eBS - Product and Consumer Medicine Information Licence. 2016. TGA eBS - Product and Consumer Medicine Information Licence. [ONLINE] Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-01635-1>. [Accessed 11 October 2016].
- DailyMed - BRINTELLIX- vortioxetine tablet, film coated . 2016. DailyMed - BRINTELLIX- vortioxetine tablet, film coated . [ONLINE] Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4b0700c9-b417-4c3a-b36f-de461e125bd3>. [Accessed 02 December 2022].
- [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA451866/guidelineAnnotation/PA166104968> [accessed 10 Sep 2019]
- [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA449673/guidelineAnnotation/PA166182852> [accessed 20 April 2020]
- [ONLINE] Available at <https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c88f33ed-6dfb-4c5e-bc01-d8e36dd97299> [Accessed 02 December 2022]
- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Muller DJ, Shimoda K, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther.* 2016.
- DailyMed - REGLAN- metoclopramide hydrochloride tablet. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=de55c133-eb08-4a35-91a2-5dc093027397> [Accessed 02 December 2022]
- Bell G, Caudle K, Whirl-Carrillo M, Gordon R, Hikino K, Prows C et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clinical Pharmacology & Therapeutics.* 2017 (epub ahead of print).
- Karnes JH, Rettie AE, Somogyi AA, Huddart R, Fohner AE, Formea CM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. *Clin Pharmacol Ther.* 2021;109(2):302-9.
- DailyMed - AIPRIPRAZOLE- aripiprazole tablet. 2019. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac> [Accessed 18 September 2019]
- TGA eBS - Product and Consumer Medicine Information Licence. 2016. TGA eBS - Product and Consumer Medicine Information Licence. [ONLINE] Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-02300-1>. [Accessed 17 October 2016].
- [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA10026/guidelineAnnotation/PA166104937> [accessed 22 Jul 2022]
- [ONLINE] Available at <https://www.pharmgkb.org/guidelineAnnotation/PA166184527> [accessed 14 October 2020]
- DailyMed - REXULTI-brexipiprazole tablet. 2017. [ONLINE] Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2d301358-6291-4ec1-bd87-37b4ad9bd850> [Accessed 29 September 2017]
- Beunk L, Nijenhuis M, Soree B, De Boer-Veger NJ, Buunk AM, Guchelaar HJ, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics. *Eur J Hum Genet [Internet].* Epub 2023 Mar 31 [cited 2023 May 1]; Available from: <https://doi.org/10.1038/s41431-023-01347-3>
- [ONLINE] Available at: <https://www.pharmgkb.org/chemical/PA451257/guidelineAnnotation/PA166104943> [accessed 09 November 2021]
- Desta, Z., Gammal, R.S., Gong, L., Whirl-Carrillo, M., Gaur, A.H., Sukasem et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. *Clinical Pharmacology & Therapeutics.* 2019; 106(4): 726-733
- [ONLINE] Available at: <https://www.pharmgkb.org/chemical/PA450480/guidelineAnnotation/PA166104995> [accessed 10 Sep 2019]
- Birdwell K, Decker B, Barbarino J, Peterson J, Stein C, Sadee W et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. *Clin Pharmacol Ther.* 2015;98(1):19-24.
- [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA451578/guidelineAnnotation/PA166104983> [accessed 15 August 2022]

34. [ONLINE] Available at: <https://www.pharmgkb.org/chemical/PA448320/guidelineAnnotation/PA166264961> [Accessed 18 July 2022]
35. TGA eBS - Product and Consumer Medicine Information Licence. 2016. TGA eBS - Product and Consumer Medicine Information Licence. [ONLINE] Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01477-1&d=2016101016114622483>. [Accessed 10 October 2016].
36. Goetz MP, Sangkuhl K, Guchelaar HJ, Schwab M, Province M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. *Clin Pharmacol Ther.* 2018.
37. [ONLINE] Available at: <https://www.pharmgkb.org/chemical/PA166123486/guidelineAnnotation/PA166182823> [Accessed 23 May 2022]
38. DailyMed - CERDELGA- eliglustat capsule. 2021. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=819f828a-b888-4e46-83fc-94d774a28a83> [Accessed 01 December 2022]
39. TGA eBS - Product and Consumer Medicine Information Licence. 2016. TGA eBS - Product and Consumer Medicine Information Licence. [ONLINE] Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-01196-1>. [Accessed 11 May 2020].
40. DailyMed - FLOMAX- tamsulosin capsule. 2017. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c00d5f7b-dad7-4479-aae2-fea7c0db40ed> [Accessed 02 December 2022]
41. [ONLINE] Available at <https://www.pharmgkb.org/guidelineAnnotation/PA166211021> [Accessed 19 October 2020]
42. DailyMed - MAYZENT- sponimod tablet, film coated. 2020. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=44492772-5aed-4627-bd85-e8e89f308bb3> [Accessed 02 December 2022]
43. DailyMed - TETRABENAZINE- tetrabenazine tablet. 2017. [ONLINE] Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a9c0e69d-adb2-4fca-9410-c9ae9ccf93ee#section-8.7> [Accessed 02 December 2022]
44. Prieto-Pérez R, Ochoa D, Cabaleiro T, Román M, Sánchez-Rojas S, Talegón M et al. Evaluation of the relationship between polymorphisms in CYP2C8 and CYP2C9 and the pharmacokinetics of celecoxib. *The Journal of Clinical Pharmacology.* 2013;53(12):1261-1267.
45. Carbonell N, Verstuyft C, Massard J, Letierce A, Cellier C, Deforges L et al. CYP2C9*3 Loss-of-Function Allele Is Associated With Acute Upper Gastrointestinal Bleeding Related to the Use of NSAIDs Other Than Aspirin. *Clinical Pharmacology & Therapeutics.* 2010;87(6):693-698.
46. Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. *Clin Pharmacol Ther.* Online publication 19 March 2020. doi:10.1002/cpt.1830
47. Wyatt J, Pettit W, Hariforoosh S. Pharmacogenetics of nonsteroidal anti-inflammatory drugs. *The Pharmacogenomics Journal.* 2012;12(6):462-467.
48. Lee H, Bae J, Choi C, Lee Y, Byeon J, Jang C et al. Strongly increased exposure of meloxicam in CYP2C9*3/*3 individuals. *Pharmacogenetics and Genomics.* 2014;24(2):113-117.
49. [ONLINE] Available at <https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations> [Accessed 15 March 2020]
50. Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, OPRM1, and COMT genotype and select opioid therapy. *Clin Pharmacol Ther.* Online publication 2 January 2021. DOI: 10.1002/cpt.2149
51. Matic M, Nijenhuis M, Soree B, de Boer-Veger NJ, Buunk AM, Houwink EJF et al. Correction: Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6 and opioids (codeine, tramadol and oxycodone). *Eur J Hum Genet.* 2022 Oct;30(10):1196. doi: 10.1038/s41431-021-00969-9.
52. Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, et al. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SLCO1B1, ABCG2, and CYP2C9 and statin-associated musculoskeletal symptoms. *Clin Pharmacol Ther.* 2022
53. DailyMed - DARIFENACIN- darifenacin hydrobromide tablet, extended release. 2019. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6e8470d1-c3e6-4644-b70a-aa47ddf79676> [Accessed 14 October 2020]
54. DailyMed - DONEPEZIL- donepezil hydrochloride tablet. 2019 [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=11ac01f4-d26e-47b2-9660-d514ab097fdb> [Accessed 25 November 2022]
55. DailyMed - GALANTAMINE- galantamine hydrobromide tablet, film coated. 2020. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fa3cb01f-85bf-5cc8-7cf3-650d8729078c> [Accessed 02 December 2022]
56. Song L, Du Q, Jiang X, Wang L. Effect of CYP1A2 polymorphism on the pharmacokinetics of agomelatine in Chinese healthy male volunteers. *J Clin Pharm Ther.* 2014 April;39(2):204-9.
57. Saiz-Rodríguez M, Ochoa D, Belmonte C, Román M, Vieira de Lara D, Zubiaur P, et al. Polymorphisms in CYP1A2, CYP2C9 and ABCB1 affect agomelatine pharmacokinetics. *J Psychopharmacol.* 2019 Apr;33(4):522-531.
58. Benowitz NL, Zhu AZX, Tyndale RF, Dempsey D, Jacob P 3rd. Influence of CYP2B6 genetic variants on plasma and urine concentrations of bupropion and metabolites at steady state. *Pharmacogenet Genomics.* 2013; 23(3):135-41.
59. Høiseth G, Haslemo T, Uthus LH, Molden E. Effect of CYP2B6*6 on Steady-State Serum Concentrations of Bupropion and Hydroxybupropion in Psychiatric Patients: A Study Based on Therapeutic Drug Monitoring Data. *Ther Drug Monit.* 2015; 37(5):589-93.
60. [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA450522/guidelineAnnotation/PA166104967> [accessed 13 January 2020]
61. DailyMed - DULOXETINE- duloxetine hydrochloride capsule, delayed release. 2019. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0a541d20-5466-433b-a104-40a7b2296076> [Accessed 25 November 2022]
62. [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA449782/guidelineAnnotation/PA166104953> [accessed 23 March 2020]
63. [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA10892/guidelineAnnotation/PA166104971> [accessed 23 March 2020]
64. [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA449761/guidelineAnnotation/PA166104978> [accessed 23 March 2020]
65. Klen J, Dolžan V, Janež A. CYP2C9, KCNJ11 and ABCC8 polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients. *Eur J Clin Pharmacol.* 2014;70(4):421-8
66. Balibey H, Basoglu C, Lundgren S, Babaoglu M, Yasar U, Herken H et al. CYP1A21F Polymorphism Decreases Clinical Response to Clozapine in Patients with Schizophrenia. *BCP.* 2011;:93.
67. DailyMed - CLOZAPINE tablet. 2020. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=25c0c6d5-f7b0-48e4-e054-00144ff8d46c> [Accessed 26 October 2020]

68. Tsuda Y, Saruwatari J, Yasui-Furukori N. Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. *BMJ Open*. 2014;4(3):e004216.
69. [ONLINE] Available at: <https://www.pharmgkb.org/chemical/PA451201/guidelineAnnotation/PA166265421> [accessed 27 June 2022]
70. van der Weide K, van der Weide J. The influence of the CYP3A4*22 polymorphism on serum concentration of quetiapine in psychiatric patients. *J Clin Psychopharmacol*. 2014;34(2):256-60.
71. Anderson PL, Aquilante CL, Gardner EM, Predhomme J, McDaniel P, Bushman LR, et al. Atazanavir pharmacokinetics in genetically determined CYP3A5 expressors versus non-expressors. *J Antimicrob Chemother*. 2009;64(5):1071-9.
72. [ONLINE] Available at <https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations> [Accessed 4 November 2020]
73. DailyMed - DOPTLET- avatrombopag maleate tablet, film coated. 2020. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e2d5960d-6c18-46cc-86bd-089222b09852> [Accessed 26 October 2020]
74. [ONLINE] Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2023-PI-01082-1&d=20231016172310101> [Accessed 16 Oct 2023]
75. DailyMed - IRESSA- gefitinib tablet, coated. 2019. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=827d60e8-7e07-41b7-c28b-49ef1c4a5a41> [Accessed 02 December 2022]
76. [ONLINE] Available at <https://www.pharmgkb.org/guidelineAnnotation/PA166182809> [Accessed 26 October 2020]
77. Goldstein J. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *British Journal of Clinical Pharmacology*. 2001;52(4):349-355.
78. TGA eBS - Product and Consumer Medicine Information Licence [Internet]. <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03251-3&d=2017020116114622483>
79. Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, Rouby NE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. *Clin Pharmacol Ther*. Online publication 8 August 2020. doi: 10.1002/cpt.2015
80. [ONLINE] Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6b8c97ac-c83c-4a1f-a33c-121239253abf> [Accessed 6 June 2021]
81. [ONLINE] Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=704e4378-ca83-445c-8b45-3cfa51c1ecad> [Accessed 6 June 2021]
82. [ONLINE] Available at: <https://www.pharmgkb.org/guidelineAnnotation/PA166182820> [Accessed 24 October 2022]
83. [ONLINE] Available at: <https://www.pharmgkb.org/guidelineAnnotation/PA166182807/annotation> [Accessed 24 October 2022]
84. [ONLINE] Available at <https://www.g-standaard.nl/risicoanalyse/B0001903.PDF> [Accessed 25 October 2022]
85. [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA451718/guidelineAnnotation/PA166104986> [Accessed 25 October 2022]
86. Moriyama B, Obeng A, Barbarino J, Penzak S, Henning S, Scott S et al. Clinical Pharmacogenetics Implementation Consortium (CPIC®) Guideline for CYP2C19 and Voriconazole Therapy. *Clinical Pharmacology & Therapeutics*. 2016;.
87. [ONLINE] Available at <https://www.pharmgkb.org/chemical/PA10268/guidelineAnnotation/PA166104981> [Accessed 25 October 2022]
88. DailyMed - BYSTOLIC- nebivolol hydrochloride tablet. 2019. [ONLINE] <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8b8ad213-1dc8-454e-a524-075685c0e1a8> [Accessed 14 October 2020]
89. Hartwell EE, Feinn R, Morris PE, Gelernter J, Krystal J, Arias AJ, Hoffman M, Petrakis I, Gueorguieva R, Schacht JP, Oslin D, Anton RF, Kranzler HR. Systematic review and meta-analysis of the moderating effect of rs1799971 in OPRM1, the mu-opioid receptor gene, on response to naltrexone treatment of alcohol use disorder. *Addiction*. 2020 Aug;115(8):1426-1437. doi: 10.1111/add.14975. Epub 2020 Feb 11. PMID: 31961981; PMCID: PMC7340566.
90. Härtter S, Korhonen T, Lundgren S, Rane A, Tolonen A, Turpeinen M et al. Effect of Caffeine Intake 12 or 24 Hours Prior to Melatonin Intake and CYP1A2*1F Polymorphism on CYP1A2 Phenotyping by Melatonin. *Basic Clinical Pharmacology Toxicology*. 2006;99(4):300-304.
91. Morin S, Lorient M, Poirier J, Tenneze L, Beaune P, Funck-Brentano C et al. Is diclofenac a valuable CYP2C9 probe in humans?. *European Journal of Clinical Pharmacology*. 2001;56(11):793-797.
92. Rodrigues A. IMPACT OF CYP2C9 GENOTYPE ON PHARMACOKINETICS: ARE ALL CYCLOOXYGENASE INHIBITORS THE SAME?. *Drug Metabolism and Disposition*. 2005;33(11):1567-1575.
93. Zhen-Yu Ren, Xiao-Qing Xu, Yan-Ping Bao, Jia He, Le Shi et al. The Impact of Genetic Variation on Sensitivity to Opioid Analgesics in Patients with Postoperative Pain: A Systematic Review and Meta-Analysis. *Pain Physician* 2015; 18:131-152.
94. In Cheol Hwang, Ji-Young Park, Seung-Kwon Myung, Hong Yup Ahn, Ken-ichi Fukuda, Qin Liao. OPRM1 A118G Gene Variant and Postoperative Opioid Requirement A Systematic Review and Meta-analysis. *Anesthesiology* 2014; 121:825-34.

SPEAK TO A SPECIALIST

For all health practitioner enquiries please contact customer care on
T: 1800 822 999
E: info@genomicdiagnostics.com.au

Electronic Signature:

Approved pathology practitioner: A/Professor Les Sheffield (23077)

This report has been prepared by the myDNA Clinical Team

Laboratory Results provided by:

GenSeq Labs (NATA 20082)

DISCLAIMER

Response to medications is complex and may also be influenced by other genetic and non-genetic factors which are not tested for (e.g. patient adherence to prescription regimen, concurrent illness, drug-drug interactions). This report is just one clinical factor which is intended to be considered in addition to other clinical information as part of a comprehensive medical evaluation by the treating clinician. It is advised that medications should not be changed solely based on this report and it is the responsibility of the treating clinician to consider all information relating to the patient to determine the most appropriate course of treatment. Unless instructed by their doctor, patients are advised not to alter the dose or stop any medications. This report does not serve as medical advice and myDNA is not liable for medical judgement with regards to diagnosis, prognosis or treatment.

Clinical monitoring should occur for all medications. It is not intended to imply that drugs listed in this report are approved for certain indications or that they have comparable efficacy or safety.

The test only determines response to the medications indicated in this report. Allergic reactions cannot be detected by this test. The test does not detect all known variants in the genes tested. If an individual carries a rare variant not covered by the test, the phenotype may be inaccurately reported.

Genetic counselling is recommended to properly review and explain these results to the tested individual as there may be implications for both the individual in addition to family members. This is not provided by myDNA and responsibility to arrange this is with the ordering physician or patient.

The information provided in the report is believed to be accurate at the time of publishing and is based on the current evidence available in the literature at that time. However, as the scientific literature and prescribing guidelines are updated over time, interpretations and recommendations relating to the prescribing of medications indicated in this report may change.

The pharmacogenomic guidance in this report primarily applies to adult patients over the age of 18 years. Therefore, caution should be exercised if the guidance in this report is to be used for patients under the age of 18 years.

TEST METHODOLOGY AND LIMITATIONS

Pharmacogenomics testing and clinical interpretation was performed by GenSeq Labs (a subsidiary of myDNA) in a NATA accredited laboratory (NATA accredited lab No 20082). DNA is extracted from a blood or cheek swab sample and SNP genotyping is performed using open array technology (Life Technologies QuantStudio 12K). CYP2D6 copy number is established by real time PCR (QuantStudio 6), allowing for quantification of up to 4 copies. 3D PCR (QuantStudio 3D) is used to determine which allele is duplicated. The genomic regions listed in this report were tested using the Life Technologies QuantStudio System; there is a possibility that the tested individual is a carrier for additional, undetected variants that may affect results. Although molecular tests are highly accurate, rare diagnostic errors may occur that interfere with analysis. Sources of these errors include sample mix-up, trace contamination, and other technical errors. The presence of additional variants nearby may interfere with variant detection. Genetic counselling is recommended to properly review and explain these results to the tested individual. Allergic reactions cannot be detected by this genetic test. The test does not detect all known variants in the genes tested. If an individual carries a rare variant not covered by the test, the phenotype may be inaccurately reported. The interpretation and clinical recommendations are based on the above results as reported by GenSeq Labs and also uses information provided to myDNA by the referring healthcare professionals. This report also assumes correct labelling of sample tubes and that the sample is from the indicated patient.

TEST PANEL OF GENES AND VARIANTS

The following clinically actionable variants are tested: ABCG2 - rs2231142 (NC_000004.11:g.89052323G>T); CYP1A2 *1F(LRG_1274:g.5732C>A); CYP2B6 *4 (LRG_1267:g.23060A>T), *6 (LRG_1267:g.[20638G>T;23060A>T]), *9 (LRG_1267:g.20638G>T), *18.001 (LRG_1267:g.26018T>C), *18.002 (LRG_1267:g.[23060A>T;26018T>C]), *22 (LRG_1267:g.4926T>C); CYP2C19 *2(NG_008384.3:g.24179G>A), *3(NG_008384.3:g.22973G>A), *9 (NG_008384.3:g.17809G>A) *17(NG_008384.3:g.4220C>T); CYP2C9 *2(LRG_1195:g.9133C>T), *3(LRG_1195:g.48139A>C), *5 (LRG_1195:g.48144C>G), *6 (LRG_1195:g.16126del), *8 (LRG_1195:g.9152G>A), *11 (LRG_1195:g.48067C>T), *27 (LRG_1195:g.9152G>T); CYP2D6 *2 (LRG_303:g.7870C>T), *3 (LRG_303:g.7569del), *4 (LRG_303:g.[5119C>T;6047G>A]), *5 (del(CYP2D6)), *6 (LRG_303:g.6727del), *7 (LRG_303:g.7955A>C), *8 (LRG_303:g.[6778G>T;7870C>T]), *9 (LRG_303:g.7635_7637del), *10 (LRG_303:g.5119C>T), *12 (LRG_303:g.[5143G>A;7870C>T]), *114 (LRG_303:g.[5119C>T;6778G>A;7870C>T]), *14 (LRG_303:g.[6778G>A;7870C>T]), *17 (LRG_303:g.[6041C>T;7870C>T]), *29 (LRG_303:g.[7870C>T;8203G>A]), *36 (NC_000022.10:g.[42526694G>A;42522624_42522669con42536337_42536382]), *41(LRG_303:g.[7870C>T;8008G>A]); CYP3A4 *22(NG_008421.1:g.20493C>T); CYP3A5 *3 (NG_007938.1:g.12083G>A), *6(NG_007938.1:g.19787G>A), *7(NG_007938.1:g.32228dup); OPRM1 - rs1799971 NM_000914.4:c.118A>G; SLCO1B1 - rs4149056 NM_006446.4:c.521T>C and VKORC1 - rs9923231 NM_024006.5:c.-1639G>A. The *1 allele denotes the absence of any variant and is designated as the wild type. The *1A allele denotes the absence of the *1F variant for CYP1A2. Only a single variant SNP is tested for the CYP1A2, CYP3A4, OPRM1 and SLCO1B1 genes. All variants are named using the HGVS nomenclature.