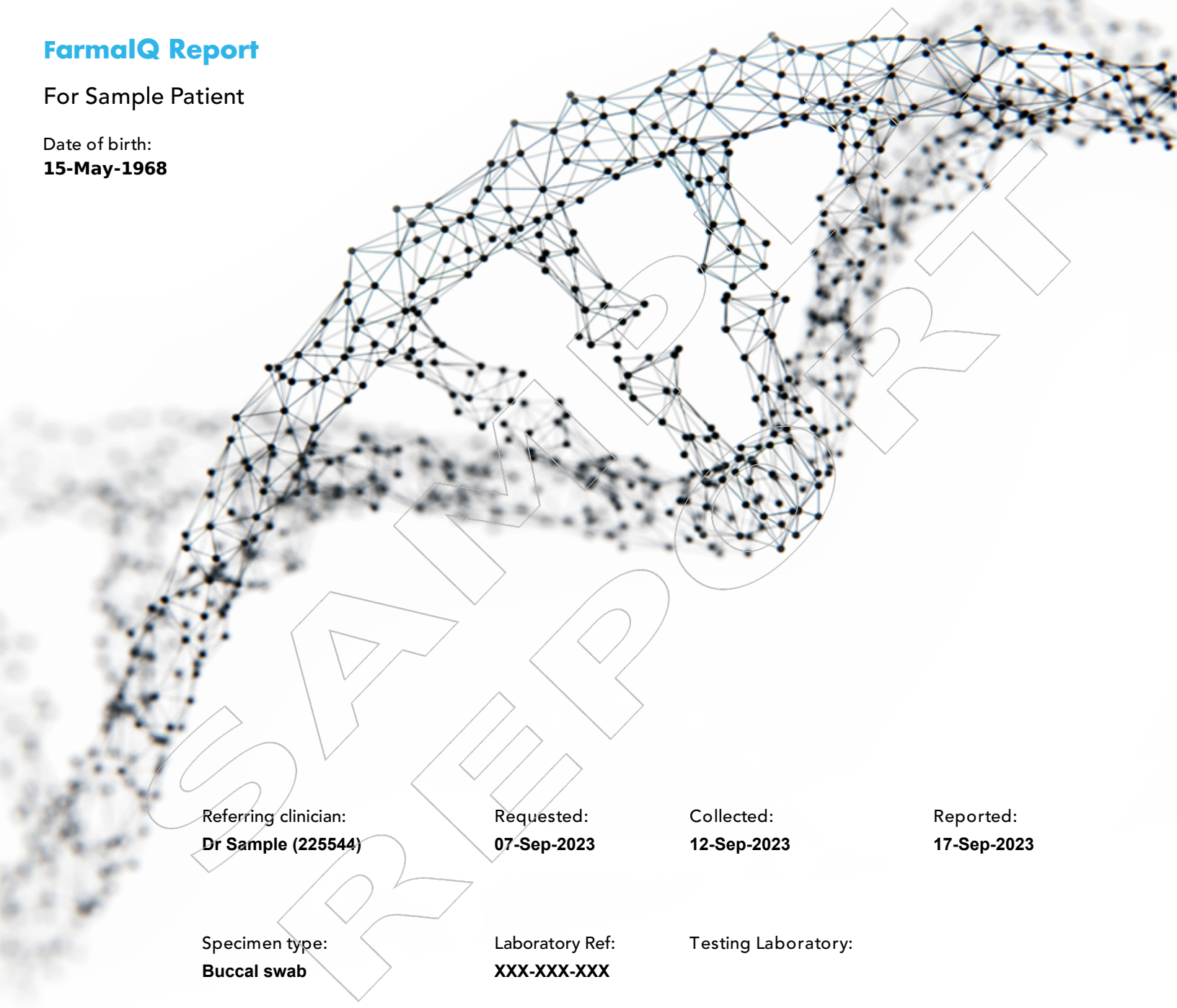
4U Health

PERSONALIZED MEDICATION

FarmaIQ Report

For Sample Patient

Date of birth:
15-May-1968



Referring clinician:	Requested:	Collected:	Reported:
Dr Sample (225544)	**07-Sep-2023**	**12-Sep-2023**	**17-Sep-2023**

Specimen type:	Laboratory Ref:	Testing Laboratory:
Buccal swab	**XXX-XXX-XXX**	

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 personalized 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. Personalized Medication Guide - provides a list of all medications covered by the test categorized 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.

MEDICATIONS OF INTEREST

MEDICATION	INTERPRETATION	RECOMMENDATION
ATORVASTATIN	**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.[1] 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 guidelines[1] 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)[1] 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.
CODEINE PHOSPHATE	**CYP2D6 - Poor metabolizer** **OPRM1 - Lower opioid sensitivity:** 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.[2] 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. Codeine is contraindicated in children under 12 years of age.[2]	Based on the CYP2D6 genotype CPIC and DPWG guidelines[3],[4]provide a strong recommendation to avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid. There is no additional genotype-guided dosing recommendation based on the OPRM1 result.
ESOMEPRAZOLE	**CYP2C19 - Rapid metabolizer:** This genotype predicts slightly increased metabolism of esomeprazole by CYP2C19, which may lead to reduced plasma concentrations and thus a possible reduction in clinical response in conditions such as oesophagitis and H. pylori. However, there is insufficient evidence to support a significant effect on therapeutic effectiveness or side effects. Note this genotype affects esomeprazole and rabeprazole less than other PPIs.	Standard dosing and prescribing measures apply. If response is inadequate, consider a trial of rabeprazole as an alternative.

MEDICATION	INTERPRETATION	RECOMMENDATION
PRASUGREL	**CYP2C19 - Rapid metabolizer:** DPWG[5] 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.

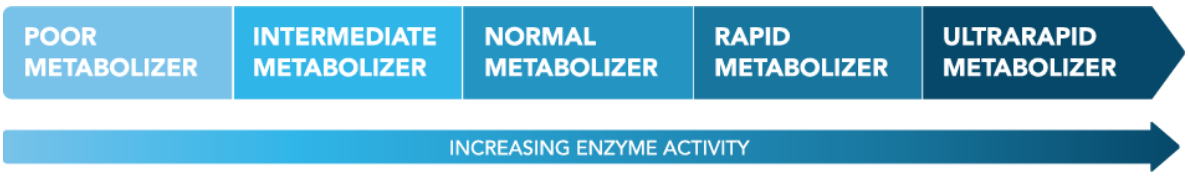
MEDICATIONS WITH NO PRESCRIBING CONSIDERATIONS

CANDESARTAN CILEXETIL, METFORMIN HYDROCHLORIDE, PARACETAMOL

PHARMACOGENOMIC TEST RESULTS SUMMARY

GENE	GENOTYPE	PREDICTED PHENOTYPE
ABCG2 (rs2231142)	CC	**Normal transporter function**
COMT	AA	**Significantly reduced COMT enzyme activity**
CYP1A2	*1F/*1F	**Ultrarapid metabolizer (with inducer present)**
CYP2B6	*1/*6	**Intermediate metabolizer**
CYP2C19	*1/*17	**Rapid metabolizer**
CYP2C9	*1/*3	**Intermediate metabolizer**
CYP2D6	*4/*4	**Poor metabolizer**
CYP3A4	*1/*1	**Normal metabolizer**
CYP3A5	*3/*3	**Poor metabolizer**
F2 (rs1799963)	GG	**No prothrombin G20210A variant detected**
F5 (rs6025)	GG	**No Factor V Leiden variant detected**
HLA-A*31:01 (rs1061235)	AA	**Lower risk of certain hypersensitivity reactions**
HLA-B*15:02 (rs144012689)	TT	**Lower risk of certain hypersensitivity reactions**
MTHFR (rs1801133)	CC	**Normal MTHFR enzyme activity**
OPRM1	GG	**Lower opioid sensitivity**
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. 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
ESOMEPRAZOLE	CYP2C19		

PERSONALIZED 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	Viloxazine	Methylphenidate
Angiotensin receptor blockers		Irbesartan Losartan	
Antianginals	Perhexiline		
Antiarrhythmics	Flecainide Propafenone		
Anticholinergics (genitourinary)	Tolterodine	Darifenacin Fesoterodine	
Anticholinesterases		Donepezil Galantamine	
Anticoagulants	Acenocoumarol Warfarin		Prasugrel Ticagrelor
Antidepressants - other	Vortioxetine ⚠	Bupropion Mirtazapine	
Antidepressants - SNRIs	Venlafaxine ⚠	Duloxetine	
Antidepressants - SSRIs	Fluoxetine Fluvoxamine ⚠ Paroxetine	Citalopram Escitalopram	Sertraline
Antidepressants - TCAs	Amitriptyline ⚠ Clomipramine ⚠ Desipramine ⚠ Doxepin ⚠ Imipramine ⚠ Nortriptyline ⚠ Trimipramine ⚠	Amoxapine Protriptyline	
Antidiabetics		Glimepiride Glipizide Glyburide Nateglinide	Tolbutamide

CLASS	MAJOR	MINOR	USUAL
Antiemetics	Metoclopramide Ondansetron		
Antiepileptics	Fosphenytoin Phenytoin	Brivaracetam	Lacosamide Lamotrigine
Antifungals - Azoles	Voriconazole ⚠		
Antihistamines		Chlorpheniramine Dexchlorpheniramine Promethazine	
Antineoplastics		Cyclophosphamide	
Antiplatelet drugs			Clopidogrel
Antipsychotics	Aripiprazole Aripiprazole Lauroxil Brexpiprazole Haloperidol Iloperidone Pimozide Risperidone Thioridazine ⚠	Chlorpromazine Clozapine Olanzapine Perphenazine	Flupenthixol Quetiapine
Antitussives	Dextromethorphan		
Antivirals	Efavirenz	Nevirapine	Atazanavir
Benzodiazepines		Clobazam Diazepam	
Beta blockers	Metoprolol Timolol	Carvedilol Propranolol	Nebivolol
Calcineurin inhibitors			Tacrolimus
Drugs for alcohol dependence			Naltrexone
Drugs for anxiety and sleep disorders	Pitolisant		
Drugs for gout			Allopurinol
Endocrine drugs		Elagolix	
Haemostatic agents		Avatrombopag	Eltrombopag Lusutrombopag
Hypnotics			Melatonin

CLASS	MAJOR	MINOR	USUAL
Immunomodulators and antineoplastics	Tamoxifen ⚠	Abrocitinib Belzutifan Gefitinib	Erdafitinib Methotrexate
Miscellaneous	Eliglustat Tamsulosin	Cevimeline Dronabinol Flibanserin Lofexidine Meclizine Proguanil	Mirabegron
Mood stabilisers			Carbamazepine Oxcarbazepine
Neurological drugs	Deutetrabenazine Siponimod Tetrabenazine Valbenazine	Carisoprodol	
NSAIDs	Celecoxib Flurbiprofen Ibuprofen Lornoxicam Meloxicam Piroxicam ⚠	Mefenamic Acid	Diclofenac Indomethacin
Oestrogen containing contraceptives			Estetrol Estradiol Ethinylestradiol
Opioid Analgesics	Codeine ⚠ Tramadol ⚠	Hydrocodone Methadone Oliceridine Oxycodone	Alfentanil Buprenorphine Fentanyl Hydromorphone Morphine Sufentanil
Proton pump inhibitors		Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	
Psychostimulants	Amphetamine ⚠	Dextroamphetamine Lisdexamfetamine	
Statins	Atorvastatin Fluvastatin Lovastatin ⚠ Pitavastatin Simvastatin ⚠	Pravastatin Rosuvastatin	

PERSONALIZED PRESCRIBING CONSIDERATIONS

The following tables outline personalized 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 metabolizer:** 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 metabolizers in those who tolerate treatment. This genotype is associated with lower final dose requirements.	CPIC[6] 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 label[7] 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 metabolizers or patients on strong CYP2D6 inhibitors, FDA approved labelling[7] 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 metabolizer:** 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 AMH[8] notes that poor metabolizers may require doses as low as 50 mg once a week.
FLECAINIDE Antiarrhythmics	**CYP2D6 - Poor metabolizer:** Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The DPWG guidelines[9] suggest reducing the dose to 50% of the standard dose, recording an ECG and monitoring the plasma concentration.
PROPAFENONE Antiarrhythmics	**CYP2D6 - Poor metabolizer:** Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The DPWG[10] suggest reducing the dose to 30% of the standard dose, recording an ECG and monitoring plasma concentrations. The FDA-approved drug label advises avoidance of use of propafenone in CP2D6 poor metabolizers who are also taking a CYP3A4 inhibitor.[11]

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
TOLTERODINE Anticholinergics (genitourinary)	**CYP2D6 - Poor metabolizer:** 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 FDA[12] has cautioned regarding this genotype and increased risk for QT prolongation with tolterodine.
ACENOCOUMAROL Anticoagulants	**VKORC1 - Normal VKORC1 enzyme level** **CYP2C9 - Intermediate metabolizer:** Reduced metabolism of acenocoumarol by CYP2C9 is predicted. Normal amount of VKORC1 present (the enzyme inhibited by acenocoumarol). Overall increased sensitivity to acenocoumarol, an increased risk of both supratherapeutic INR and bleeding, and a lower dose requirement are predicted.	Based on the CYP2C9 genotype, DPWG[13] states that no specific action is required for dosing of acenocoumarol. Genetic variation may lead to a decrease in the required maintenance dose, however there is insufficient evidence that this causes problems when therapy is initiated as usual, i.e. with frequent INR monitoring.
WARFARIN Anticoagulants	**VKORC1 - Normal VKORC1 enzyme level** **CYP2C9 - Intermediate metabolizer:** 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 CPIC[14] recommendations to reach the therapeutic dose. The summary of CPIC recommendations include consideration of the use of validated published pharmacogenetic algorithms[15],[16] 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 metabolizer:** Greatly reduced metabolism by CYP2D6 and increased drug exposure is predicted. This may be associated with an increased risk of concentration-dependent adverse effects.[17]	CPIC guidelines[17] 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 metabolized by CYP2D6. The TGA approved Product Information[18] states that a dose adjustment is not required. The FDA[19] approved labelling states that the recommended maximum dose is 10mg for CYP2D6 poor metabolizers. Regardless of which dosing advice is followed, be alert for adverse effects.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
VENLAFAXINE Antidepressants - SNRIs	**CYP2D6 - Poor metabolizer:** 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 guidelines[17] provide an optional recommendation to consider an appropriate alternative not predominantly metabolized by CYP2D6. The DPWG[20] 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 metabolizer** **CYP2C9 - Intermediate metabolizer:** 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, CPIC[17] and DPWG[21] recommend that no specific action on fluoxetine dosing is required for this genotype. The FDA[22] 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.
FLUVOXAMINE Antidepressants - SSRIs	**CYP2D6 - Poor metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Fluvoxamine is metabolized 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, CPIC[17] 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 metabolized by CYP2D6. DPWG[23] suggests no specific action on fluvoxamine dosing is required based on this CYP2D6 genotype.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
PAROXETINE Antidepressants - SSRIs	**CYP2D6 - Poor metabolizer:** Greatly reduced metabolism by CYP2D6 and greatly increased drug exposure are predicted. There may be an increased risk of adverse effects.	CPIC[17] 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 metabolizers. It would also be reasonable to monitor for adverse effects. DPWG[23] recommends that no specific action is required on paroxetine dosing based on this genotype.
AMITRIPTYLINE Antidepressants - TCAs ⚠	**CYP2D6 - Poor metabolizer** **CYP2C19 - Rapid metabolizer:** Amitriptyline is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of amitriptyline are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	For use at higher doses such as in the treatment of depression, CPIC[24] provides an optional recommendation to avoid amitriptyline. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise therapeutic drug monitoring to guide dose adjustments. For use at lower doses such as in treatment of neuropathic pain, caution is advised if using any tricyclic.
CLOMIPRAMINE Antidepressants - TCAs ⚠	**CYP2D6 - Poor metabolizer** **CYP2C19 - Rapid metabolizer:** Clomipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of clomipramine are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[24] provides an optional recommendation to avoid clomipramine. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise 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.
DESIPRAMINE Antidepressants - TCAs ⚠	**CYP2D6 - Poor metabolizer:** Greatly reduced desipramine metabolism and increased drug exposure are predicted. An increased risk of adverse effects is expected.	CPIC guidelines[24] provide an optional recommendation to avoid desipramine and consider an alternative antidepressant not metabolized by CYP2D6. If prescribing desipramine, CPIC guidelines recommend a 50% reduction of the recommended steady-state starting dose, as well as using 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.
DOXEPIN Antidepressants - TCAs ⚠	**CYP2D6 - Poor metabolizer** **CYP2C19 - Rapid metabolizer:** Doxepin is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of doxepin are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[24] provides an optional recommendation to avoid doxepin. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise 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
IMIPRAMINE Antidepressants - TCAs	**CYP2D6 - Poor metabolizer** **CYP2C19 - Rapid metabolizer:** Imipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of imipramine are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[24] provides an optional recommendation to avoid imipramine. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise 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 metabolizer:** 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 guidelines[24] provide a strong recommendation to avoid nortriptyline and consider an alternative antidepressant not metabolized 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.
TRIMIPRAMINE Antidepressants - TCAs	**CYP2D6 - Poor metabolizer** **CYP2C19 - Rapid metabolizer:** Trimipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of trimipramine are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[24] provides an optional recommendation to avoid trimipramine. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise 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.
METOCLOPRAMIDE Antiemetics	**CYP2D6 - Poor metabolizer:** 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 label[25] suggests a dose reduction in poor metabolizers. 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 metabolizer:** 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.	CPIC[26] 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
FOSPHENYTOIN Antiepileptics	**HLA-B*15:02 (rs144012689) - Lower risk of certain hypersensitivity reactions** **CYP2C9 - Intermediate metabolizer:** Fosphenytoin is a prodrug of phenytoin. The rs144012689 TT result provides a high prediction of the absence of HLA-B*15:02 allele. Reduced phenytoin metabolism by CYP2C9 and increased drug exposure are predicted. This CYP2C9 genotype has been associated with an increased risk of concentration-dependent adverse effects.	Where HLA-B*15:02 is absent, based on this CYP2C9 genotype, CPIC guidelines[27] 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. Be aware that this rs144012689 is a screening test only, and furthermore an HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN; if the patient develops any rash or hypersensitivity reactions on fosphenytoin, then discontinuation should be considered in accordance with standard prescribing guidelines.[28,27] Consider avoiding fosphenytoin as an alternative to carbamazepine in patients who are CYP2C9*3 carriers. [29]
PHENYTOIN Antiepileptics	**HLA-B*15:02 (rs144012689) - Lower risk of certain hypersensitivity reactions** **CYP2C9 - Intermediate metabolizer:** The rs144012689 TT result provides a high prediction of the absence of HLA-B*15:02 allele. Reduced phenytoin metabolism by CYP2C9 and increased drug exposure are predicted. This CYP2C9 genotype has been associated with an increased risk of concentration-dependent adverse effects.	Where HLA-B*15:02 is absent, based on this CYP2C9 genotype, CPIC guidelines[27] 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. Be aware that this rs144012689 is a screening test only, and furthermore an HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN; if the patient develops any rash or hypersensitivity reactions on phenytoin, then discontinuation should be considered in accordance with standard prescribing guidelines.[30,27] Consider avoiding phenytoin as an alternative to carbamazepine in patients who are CYP2C9*3 carriers. [29]
VORICONAZOLE Antifungals - Azoles ⚠	**CYP2C19 - Rapid metabolizer:** Increased voriconazole metabolism and reduced plasma concentrations are predicted. Using standard dosing, there is an increased risk of subtherapeutic drug concentrations.	For adult patients, CPIC guidelines[31] provide a moderate recommendation to choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B and posaconazole, as clinically appropriate. For paediatric patients with this genotype, CPIC provides a moderate recommendation to initiate therapy with the recommended standard of care dosing, with meticulous use of therapeutic drug monitoring to titrate dose to therapeutic trough concentrations. CPIC also notes that achieving voriconazole therapeutic concentrations in the paediatric population with rapid metabolizer phenotypes in a timely manner is difficult, thus an alternative antifungal agent is recommended for effective antifungal therapy to be achieved as soon as possible.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ARIPIPRAZOLE Antipsychotics	**CYP2D6 - Poor metabolizer:** Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	FDA-approved labelling [32] 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 information [33] recommends for CYP2D6 poor metabolizers to use a starting and maintenance dose of 300 mg and for CYP2D6 poor metabolizers taking CYP3A4 inhibitors, a 200 mg dose is advised. Note the DPWG[34] recommends administering no more than 10mg/day or 300 mg/month (68-75% of the standard maximum dose), for CYP2D6 poor metabolizers.
ARIPIPRAZOLE LAUROXIL Antipsychotics	**CYP2D6 - Poor metabolizer:** Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	Aristada Initio®: The FDA-approved drug label[35] advises avoiding use of Aristada Initio in CYP2D6 poor metabolizers. Aristada®: For patients known to be CYP2D6 poor metabolizers and are on concomitant strong CYP3A4 inhibitors for more than 2 weeks, the FDA-approved drug label[36] advises reducing the dose to 441 mg from 662 mg, 882 mg or 1064 mg for poor metabolizers. No dosage adjustment is required in patients tolerating 441 mg of Aristada. For patients known to be CYP2D6 poor metabolizers and on concomitant strong CYP2D6 inhibitors, no dose adjustment is required.
BREXPIPRAZOLE Antipsychotics	**CYP2D6 - Poor metabolizer:** 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[37], [38] 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.[38]
HALOPERIDOL Antipsychotics	**CYP2D6 - Poor metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The DPWG[39] recommends using 60% of the normal dose.
ILOPERIDONE Antipsychotics	**CYP2D6 - Poor metabolizer:** Significantly reduced metabolism of iloperidone by CYP2D6 is predicted and therefore increased drug exposure is possible, leading to an increased risk of adverse effects. The FDA-approved drug label notes that poor metabolizers are expected to have higher drug exposures than extensive metabolizers. [40]	The FDA-approved drug label advises that poor metabolizers should have their dose reduced by one-half.[40]

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
PIMOZIDE Antipsychotics	**CYP2D6 - Poor metabolizer:** Negligible metabolism by CYP2D6 and significantly increased drug exposure are predicted. This may increase the risk of concentration dependent adverse effects.	FDA-approved[41] labelling advises: 1) in children, not exceeding a dose of 0.05mg/kg/day and not increasing the dose earlier than 14 days; 2) in adults, not exceeding a dose of 4mg/day and not increasing the dose earlier than 14 days. The DWPG[42] recommends using no more than 50% of the standard maximum dose.
RISPERIDONE Antipsychotics	**CYP2D6 - Poor metabolizer:** 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 DPWG[43] 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.
THIORIDAZINE Antipsychotics ⚠	**CYP2D6 - Poor metabolizer:** Negligible metabolism by CYP2D6 and significantly increased drug exposure are predicted, with the increased risk of adverse effects. The reduction in clearance of thioridazine is associated with increased risk of Torsades de pointes and/or sudden death. Other factors contributing to this increased risk include: bradycardia, hypokalaemia, concomitant use of other drugs that prolong QT interval, and presence of congenital prolongation of the QT interval.	The FDA-approved drug label states that thioridazine is contraindicated in patients with reduced activity of CYP2D6.[44]
DEXTROMETHORPHAN Antitussives	**CYP2D6 - Poor metabolizer:** 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 - Intermediate metabolizer:** Reduced metabolism of efavirenz and higher dose-adjusted trough concentrations compared with normal metabolizers is predicted. This has been associated with an increased risk of concentration-dependent adverse effects, including CNS adverse events.	CPIC and DPWG[45, 46] provide a moderate recommendation to consider initiating efavirenz with decreased dose of 400 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.
METOPROLOL Beta blockers	**CYP2D6 - Poor metabolizer:** 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, DPWG[47] 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.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
TIMOLOL Beta blockers	**CYP2D6 - Poor metabolizer:** Negligible metabolism by CYP2D6 and increased drug exposure are predicted. The poor metabolizer 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.
PITOLISANT Drugs for anxiety and sleep disorders	**CYP2D6 - Poor metabolizer:** Negligible metabolism by CYP2D6 and increased drug exposure are predicted. Higher systemic concentrations have been observed in this genotype than in normal metabolizers, thus a dosage reduction is recommended.[29],[48]	The FDA-approved drug label states that in patients known to be poor CYP2D6 metabolizers, pitolisant should be initiated at 8.9mg once daily and titrated to a maximum dose of 17.8mg once daily after 7 days.[48] Monitor for adverse effects.
TAMOXIFEN Immunomodulators and antineoplastics ⚠	**CYP2D6 - Poor metabolizer:** 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 guidelines[49] 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.
ELIGLUSTAT Miscellaneous	**CYP2D6 - Poor metabolizer:** 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.[50]	The recommended dose of eliglustat depends on whether CYP3A4 and/or CYP2D6 inhibiting medications are co-prescribed. Refer to DPWG guidelines,[50] FDA-approved drug label[51] or TGA-approved product information[52] for prescribing details.
TAMSULOSIN Miscellaneous	**CYP2D6 - Poor metabolizer:** 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 FDA[53] 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 metabolizers, particularly at a dose higher than 0.4mg.
DEUTETRABENAZINE Neurological drugs	**CYP2D6 - Poor metabolizer:** Reduced metabolism by CYP2D6 and significantly increased drug exposure are predicted as compared with extensive. metabolizers,[54] This could lead to increased adverse effects including QT prolongation.	The FDA-approved drug label advises that the in poor metabolizers: 1. Total daily dose should not exceed 36 mg (maximum single dose of 18 mg) 2. A clinically relevant QT prolongation may occur in some patients treated with deutetrabenazine. [54] As such, monitoring for adverse effects is recommended.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
SIPONIMOD Neurological drugs	**CYP2C9 - Intermediate metabolizer:** 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.	DPWG[55] and the FDA-approved drug label[56] 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 metabolizer:** Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA[57] approved drug label advises a maximum daily dose of 50mg, with a maximum recommended single dose of 25mg.
VALBENAZINE Neurological drugs	**CYP2D6 - Poor metabolizer:** Reduced metabolism by CYP2D6 and significantly increased drug exposure are predicted as compared with extensive metabolizers.[58] This could lead to increased adverse effects including QT prolongation.	The FDA-approved drug label advises consideration of a dose reduction in poor metabolizers as drug concentrations may be higher and QT prolongation may be clinically significant.[58] Monitor closely for adverse effects.
CELECOXIB NSAIDs	**CYP2C9 - Intermediate metabolizer:** Moderately reduced metabolism and increased celecoxib exposure are predicted[59]. This may increase the risk of concentration-dependent adverse effects such as gastrointestinal bleeding[60].	CPIC guidelines[61] 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.
FLURBIPROFEN NSAIDs	**CYP2C9 - Intermediate metabolizer:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted[62]. This may increase the risk of adverse effects.	CPIC guidelines[61] 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.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
IBUPROFEN NSAIDs	**CYP2C9 - Intermediate metabolizer:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted[63]. This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding[63].	CPIC guidelines[61] 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.
LORNOXICAM NSAIDs	**CYP2C9 - Intermediate metabolizer:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted. This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding.	CPIC guidelines[61] 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.
MELOXICAM NSAIDs	**CYP2C9 - Intermediate metabolizer:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted.[64] This may be associated with an increased risk of adverse effects, including gastrointestinal bleeding.[60]	CPIC guidelines[61] 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 metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo (such as aspirin, ketorolac, naproxen or sulindac), or choose an NSAID metabolized 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 metabolizer:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted.[63] This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding[60].	CPIC guidelines[61] have a moderate recommendation to choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 variants in vivo (such as aspirin, ketorolac, naproxen or sulindac), or choose an NSAID metabolized by CYP2C9 but with a shorter half-life (such as celecoxib, flurbiprofen, ibuprofen or lornoxicam).

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CODEINE Opioid Analgesics	**CYP2D6 - Poor metabolizer** **OPRM1 - Lower opioid sensitivity:** 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.[2] 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. Codeine is contraindicated in children under 12 years of age.[2]	Based on the CYP2D6 genotype CPIC and DPWG guidelines[3],[4]provide a strong recommendation to avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid. There is no additional genotype-guided dosing recommendation based on the OPRM1 result.
TRAMADOL Opioid Analgesics	**CYP2D6 - Poor metabolizer:** 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.	CPIC guidelines[3] 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 guidelines[4] 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.
AMPHETAMINE Psychostimulants	**CYP2D6 - Poor metabolizer:** Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is involved in the formation of an active metabolite 4-hydroxy-amphetamine. Reduced metabolism by CYP2D6 is predicted which could lead to variations in amphetamine metabolism.[65] The increased levels of amphetamine may lead to an increased risk of adverse effects.[29]	The FDA advises consideration of use of a lower starting dosage, or use of an alternative agent.[29] Monitor for adverse effects.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
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.[1] 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 guidelines[1] 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)[1] 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 metabolizer:** 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.[1] This CYP2C9 genotype predicts increased fluvastatin exposure as compared with normal metabolizers, which may translate to increased myopathy risk.[1] 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 guidelines[1] 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).

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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.[1] 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 guidelines[1] 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)[1] 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.[1] 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 guidelines[1] 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)[1] 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.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
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.[1] 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 guidelines[1] 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)[1] 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
VILOXAZINE ADHD - miscellaneous agents	**CYP2D6 - Poor metabolizer:** Negligible metabolism by CYP2D6 is predicted and this may result in higher systemic concentrations.[29]	No genotype-guided dosing recommendation available. Monitor for adverse effects.
IRBESARTAN Angiotensin receptor blockers	**CYP2C9 - Intermediate metabolizer:** 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 metabolizer:** 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 metabolizer:** Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of adverse effects.[66] 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.
FESOTERODINE Anticholinergics (genitourinary)	**CYP2D6 - Poor metabolizer:** Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of adverse effects. The FDA-approved drug label notes that CYP2D6 poor metabolizers may have increased maximum plasma concentrations of the active metabolite of fesoterodine, as compared to CYP2D6 extensive metabolizers. [67]	No genotype-guided dosing recommendation available. Monitor for adverse effects.
DONEPEZIL Anticholinesterases	**CYP2D6 - Poor metabolizer:** Negligible metabolism via CYP2D6 and increased drug exposure are predicted.[68] 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 metabolizer:** Negligible metabolism via CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA-approved drug label[69] states that dosage adjustment of galantamine is not necessary in patients identified as CYP2D6 poor metabolizers 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.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
BUPROPION Antidepressants - other	**CYP2B6 - Intermediate metabolizer:** Individuals with this genotype may have reduced bupropion metabolism and formation of the active metabolite hydroxybupropion (based on studies mainly involving the *6 and *18 alleles), as compared with individuals carrying only normal and/or increased function alleles.[70] 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.	Be alert to adverse effects and monitor for adequate clinical response. No genotype-guided dosing recommendation available. Usual prescribing considerations apply.
MIRTAZAPINE Antidepressants - other	**CYP2D6 - Poor metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Mirtazapine is metabolized 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.[71]
DULOXETINE Antidepressants - SNRIs	**CYP2D6 - Poor metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Duloxetine is metabolized 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 label[72] notes that concomitant administration of duloxetine and a potent CYP1A2 inhibitor to CYP2D6 poor metabolizers resulted in significant increase in drug exposure. Note that CPIC[17] 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.
CITALOPRAM Antidepressants - SSRIs	**CYP2C19 - Rapid metabolizer:** Increased metabolism of citalopram by CYP2C19 and reduced drug exposure are predicted. This may increase the likelihood of therapeutic failure.	CPIC guidelines[17] provide an optional recommendation to initiate therapy with the recommended starting dose. If patient does not adequately respond, consider titrating to a higher maintenance dose or switching to an alternative antidepressant not predominantly metabolized by CYP2C19.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ESCITALOPRAM Antidepressants - SSRIs	**CYP2C19 - Rapid metabolizer:** Increased metabolism of escitalopram by CYP2C19 and reduced drug exposure are predicted. This may increase the likelihood of therapeutic failure.	CPIC guidelines[17] provide an optional recommendation to initiate therapy with the recommended starting dose. If patient does not adequately respond, consider titrating to a higher maintenance dose or switching to an alternative antidepressant not predominantly metabolized by CYP2C19.
AMOXAPINE Antidepressants - TCAs	**CYP2D6 - Poor metabolizer:** Reduced metabolism of amoxapine by CYP2D6 is predicted and therefore increased drug exposure is possible.[73] The clinical significance of this is not known. The FDA notes that systemic concentrations may be altered with this genotype.[29]	No genotype-guided dosing recommendation available. Monitor for adverse effects.
PROTRIPTYLINE Antidepressants - TCAs	**CYP2D6 - Poor metabolizer:** Reduced metabolism of protriptyline by CYP2D6 is predicted and therefore increased drug exposure is possible.[74] The clinical significance of this is not known.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
GLIMEPIRIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** 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.[75] It would be reasonable to consider a lower starting dose with close monitoring for adverse effects.
GLIPIZIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** 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.[76]	No genotype guided dosing recommendation available. It may be reasonable to consider a lower starting dose with close monitoring for adverse effects.
GLYBURIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** 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 glyburide dosing is required with this genotype.[77] It would be reasonable to consider a lower starting dose with close monitoring for adverse effects.
NATEGLINIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** Reduced nateglinide metabolism and increased drug exposure are predicted.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
BRIVARACETAM Antiepileptics	**CYP2C19 - Rapid metabolizer:** Increased metabolism by CYP2C19 and reduced plasma concentrations are predicted. The clinical significance of this is not known, though reduced effects could be anticipated.	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response. The FDA-approved drug label for brivaracetam states that those using inhibitors of CYP2C19 may require dose reduction.[78]

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CHLORPHENIRAMINE Antihistamines	**CYP2D6 - Poor metabolizer:** 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 metabolizer:** 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 metabolizer:** 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.
CYCLOPHOSPHAMIDE Antineoplastics	**CYP2C19 - Rapid metabolizer:** Increased formation of cyclophosphamide's active metabolite by CYP2C19 is predicted. This may be associated with increased clinical effects (therapeutic and/or adverse).	No genotype-guided dosing recommendation available.
CHLORPROMAZINE Antipsychotics	**CYP2D6 - Poor metabolizer:** 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 metabolizer** **CYP1A2 - Ultrarapid metabolizer (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 chargrilled 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.[79] The DPWG guidelines [39] state that there is no gene-drug interaction for CYP1A2 and clozapine. The FDA-approved drug label[80] states that in CYP2D6 poor metabolizers, plasma concentrations of clozapine may be increased.	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.[81] Based on the CYP2D6 genotype, the FDA-approved drug label[80] states that it may be necessary to reduce the dose in CYP2D6 poor metabolizers, as they may develop higher than expected plasma concentrations when given usual doses. The DPWG guidelines [39] state that no action is required for this CYP2D6 genotype and clozapine.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
OLANZAPINE Antipsychotics	**CYP1A2 - Ultrarapid metabolizer (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 metabolized to a lesser extent by CYP2D6, the DPWG guidelines[39] state that there is no gene-drug interaction for either CYP1A2 or CYP2D6 and olanzapine.	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.[81]
PERPHENAZINE Antipsychotics	**CYP2D6 - Poor metabolizer:** Significantly reduced metabolism of perphenazine by CYP2D6 is predicted and therefore increased drug exposure is possible, leading to an increased risk of adverse effects. The FDA-approved drug label notes that poor metabolizers are expected to have higher drug concentrations than extensive metabolizers, and that one study has demonstrated an increased risk of adverse effects in poor metabolizers than in extensive metabolizers.[82]	No genotype-guided dosing recommendation available. Monitor closely for adverse effects.
NEVIRAPINE Antivirals	**CYP2B6 - Intermediate metabolizer:** Reduced metabolism by CYP2B6 and increased nevirapine exposure are predicted. This is more likely to be significant with high dosages or if drug-drug interactions occur. 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.
CLOBAZAM Benzodiazepines	**CYP2C19 - Rapid metabolizer:** Clobazam is metabolized by CYP3A4 into an active metabolite, N-desmethylclobazam, which is responsible for most of the therapeutic effect. N-desmethylclobazam is further metabolized by CYP2C19 into an inactive metabolite. The CYP2C19 genotype predicts increased metabolism of clobazam's active metabolite and a possible reduction in clinical effects. (Note that the effect of variations in CYP3A4 has not been described).	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
DIAZEPAM Benzodiazepines	**CYP2C19 - Rapid metabolizer:** Diazepam is metabolized by CYP3A4 and CYP2C19 into active metabolites, including desmethyldiazepam, which has a long half-life. The CYP2C19 genotype predicts increased metabolism of both diazepam and desmethyldiazepam, reduced plasma concentrations and possibly reduced clinical effects. (Note that the effect of variations in the CYP3A4 gene on diazepam metabolism have not been described).	Monitor for reduced clinical response. If an alternative benzodiazepine is required, consider agents not extensively metabolized by CYP2C19, such as oxazepam and lorazepam.
CARVEDILOL Beta blockers	**CYP2D6 - Poor metabolizer:** 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 metabolizers had a higher rate of dizziness during up-titration.[83]	DPWG[84] suggests that no specific action on carvedilol dosing is required based on this genotype. Monitor for adverse effects.
PROPRANOLOL Beta blockers	**CYP2D6 - Poor metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Propranolol is metabolized 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 FDA[29] notes that systemic concentrations may be affected in CYP2D6 poor metabolizers.	No genotype-guided dosing guideline available. Monitor for altered clinical effect.
ELAGOLIX Endocrine drugs	**SLCO1B1 - Decreased transporter function:** One SLCO1B1*5 variant allele is present. The FDA-approved drug label notes that individuals with two SLCO1B1*5 variant alleles have higher plasma concentrations of elagolix. The clinical significance of the presence of this single *5 variant allele is uncertain.	No genotype-guided dosing recommendation available. Standard dosing and prescribing measures apply. Monitor for adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
AVATROMBOPAG Haemostatic agents	**CYP2C9 - Intermediate metabolizer** **F5 (rs6025) - No Factor V Leiden variant detected** **F2 (rs1799963) - No prothrombin G20210A variant detected:** A reduced metabolism by CYP2C9 of avatrombopag and higher plasma concentration is predicted.[29] This individual is a non-carrier of Factor V Leiden and non-carrier of the prothrombin G20210A variant, and based on these genotypes, is not at increased risk of thrombosis. This risk may also be influenced by other genetic and clinical factors.	CYP2C9 - For treatment of chronic immune thrombocytopenia, the FDA-approved drug label[85] 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. F5 and F2 - The FDA-approved drug label states that the risk for thrombosis should be considered in patients with risk factors for thromboembolism, including genetic prothrombotic conditions (e.g. Factor V Leiden, prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency).[85]
ABROCITINIB Immunomodulators and antineoplastics	**CYP2C19 - Rapid metabolizer:** Increased metabolism by CYP2C19 is predicted which may lead to reduced plasma concentrations. The clinical significance of this is not known.	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.
BELZUTIFAN Immunomodulators and antineoplastics	**CYP2C19 - Rapid metabolizer:** Increased metabolism by CYP2C19 is predicted which may lead to reduced plasma concentrations. The clinical significance of this is not known.	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.
GEFITINIB Immunomodulators and antineoplastics	**CYP2D6 - Poor metabolizer:** Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA-approved drug label[86] advises that there is no dose adjustment recommendations for gefitinib in individuals with a known CYP2D6 poor metabolizer genotype, but they should be closely monitored for adverse reactions. The DPWG[87] suggests that no specific action on gefitinib dosing is required with this genetic result.
CEVIMELINE Miscellaneous	**CYP2D6 - Poor metabolizer:** Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA-approved drug label[88] advises that cevimeline should be used with caution in individuals known to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events.
DRONABINOL Miscellaneous	**CYP2C9 - Intermediate metabolizer:** Reduced dronabinol metabolism and increased drug exposure are predicted.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
FLIBANSERIN Miscellaneous	**CYP2C19 - Rapid metabolizer:** Increased metabolism by CYP2C19 is predicted such that there may be reduced plasma concentrations. The clinical significance of this is not known.	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
LOFEXIDINE Miscellaneous	**CYP2D6 - Poor metabolizer:** Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA-approved drug label[89] advises monitoring for adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers.
MECLIZINE Miscellaneous	**CYP2D6 - Poor metabolizer:** Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	No genotype-guided dosing recommendation available. The FDA-approved drug label[90] suggests monitoring for adverse effects and clinical effects, as the genetic polymorphism of CYP2D6 could contribute to large variability in meclizine exposure.
PROGUANIL Miscellaneous	**CYP2C19 - Rapid metabolizer:** Increased metabolism of proguanil to the active metabolite cycloguanil is predicted. The clinical significance of this is not clear.	No genotype-guided dosing recommendation available. It would be reasonable to monitor for adverse effects.
CARISOPRODOL Neurological drugs	**CYP2C19 - Rapid metabolizer:** Increased metabolism by CYP2C19 is predicted which may lead to reduced plasma concentrations. The clinical significance of this is not known.	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.
MEFENAMIC ACID NSAIDs	**CYP2C9 - Intermediate metabolizer:** Mefenamic acid is metabolized by CYP2C9.[91] This genotype predicts an increase in mefenamic acid exposure which may potentially increase the risk of adverse effects[92], especially with high dosages or if drug-drug interactions occur.	Standard dosing and prescribing measures apply. Monitor for adverse effects.
HYDROCODONE Opioid Analgesics	**CYP2D6 - Poor metabolizer:** An increase in hydrocodone exposure and a reduction in exposure to the active metabolite hydromorphone are predicted. There is insufficient evidence to determine whether these effects on pharmacokinetics translate into decreased analgesia or side effects.	CPIC[3] provides an optional recommendation to use the hydrocodone label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider a non-codeine or non-tramadol opioid.
METHADONE Opioid Analgesics	**CYP2B6 - Intermediate metabolizer:** Slightly reduced metabolism by CYP2B6 and increased methadone exposure are predicted in most instances. However if a *4 allele is present, there is limited evidence suggesting there may be increased methadone metabolism, leading to reduced drug exposure.	No genotype-guided dosing recommendation available. Monitor for an altered clinical effect, including adverse effects, arising from methadone concentrations out of the expected range.
OLICERIDINE Opioid Analgesics	**CYP2D6 - Poor metabolizer:** Negligible metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of adverse effects such as respiratory depression and sedation.[29]	The FDA[29] and FDA-approved drug label[93] notes that individuals with this genotype may have increased plasma concentrations of oliceridine and require less frequent dosing. Monitor for adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
OXYCODONE Opioid Analgesics	**CYP2D6 - Poor metabolizer:** 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 guidelines[3] have no recommendations to support oxycodone dosing. DPWG[4] also suggest that no specific action on oxycodone dosing is required. Be alert to a reduced response.
DEXLANSOPRAZOLE Proton pump inhibitors	**CYP2C19 - Rapid metabolizer:** This genotype predicts increased metabolism of dexlansoprazole compared to normal metabolizers, which may be linked to an incomplete clinical response in conditions such as oesophagitis and H. pylori.	CPIC guidelines have an optional 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.[94] If response is inadequate, consider the use of esomeprazole or rabeprazole.
ESOMEPRAZOLE Proton pump inhibitors	**CYP2C19 - Rapid metabolizer:** This genotype predicts slightly increased metabolism of esomeprazole by CYP2C19, which may lead to reduced plasma concentrations and thus a possible reduction in clinical response in conditions such as oesophagitis and H. pylori. However, there is insufficient evidence to support a significant effect on therapeutic effectiveness or side effects. Note this genotype affects esomeprazole and rabeprazole less than other PPIs.	Standard dosing and prescribing measures apply. If response is inadequate, consider a trial of rabeprazole as an alternative.
LANSOPRAZOLE Proton pump inhibitors	**CYP2C19 - Rapid metabolizer:** This genotype predicts slightly increased metabolism and reduced plasma concentrations of lansoprazole compared to normal metabolizers, which may be linked to an incomplete clinical response in conditions such as oesophagitis and H. pylori.	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.[94] If response is inadequate, consider the use of esomeprazole or rabeprazole.
OMEPRAZOLE Proton pump inhibitors	**CYP2C19 - Rapid metabolizer:** This genotype predicts slightly increased metabolism and reduced plasma concentrations of omeprazole compared to normal metabolizers, which may be linked to an incomplete clinical response in conditions such as oesophagitis and H. pylori.	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.[94] If response is inadequate, consider use of esomeprazole or rabeprazole.
PANTOPRAZOLE Proton pump inhibitors	**CYP2C19 - Rapid metabolizer:** This genotype predicts slightly increased metabolism and reduced plasma concentrations of pantoprazole compared to normal metabolizers, which may be linked to an incomplete clinical response in conditions such as oesophagitis and H. pylori.	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.[94] If response is inadequate, consider the use of esomeprazole or rabeprazole.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
RABEPRAZOLE Proton pump inhibitors	**CYP2C19 - Rapid metabolizer:** This genotype predicts slightly increased metabolism of rabeprazole by CYP2C19, which may lead to reduced plasma concentrations and thus a possible reduction in clinical response with conditions such as oesophagitis and H. pylori. However, there is insufficient evidence to support a significant effect on therapeutic effectiveness or side effects. Note this genotype affects rabeprazole and esomeprazole less than other PPIs.	Standard dosing and prescribing measures apply. If the response to rabeprazole is inadequate, consider a trial of esomeprazole as an alternative agent.
DEXTROAMPHETAMINE Psychostimulants	**CYP2D6 - Poor metabolizer:** 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.[95]
LISDEXAMFETAMINE Psychostimulants	**CYP2D6 - Poor metabolizer:** 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.[96]
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.[1] 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 guidelines[1] 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)[1] 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ROSUVASTATIN Statins	**ABCG2 (rs2231142) - Normal 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.[1] This ABCG2 genotype is associated with a typical rosuvastatin exposure and myopathy risk.[1] 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 guidelines[1] provide a strong recommendation to prescribe the desired starting dose and adjust doses according to disease-specific and specific population guidelines. Be aware of possible increased risk for myopathy especially for doses over 20 mg.< br/> Based on this SLCO1B1 genotype, the risk of statin-associated musculoskeletal symptoms (SAMS)[1] is as follows: Rosuvastatin 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. Rosuvastatin 5-20mg - Low SAMS risk.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
METHYLPHENIDATE ADHD - miscellaneous agents	**CYP2D6 - Poor metabolizer** **COMT - Significantly reduced COMT enzyme activity:** DPWG guidelines[97], [98] state that there is no gene-drug interaction for methylphenidate with CYP2D6 and COMT.	No dosage recommendation is currently available based on the genetic findings.
PRASUGREL Anticoagulants	**CYP2C19 - Rapid metabolizer:** DPWG[5] 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 - Rapid metabolizer:** DPWG[99] 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.
SERTRALINE Antidepressants - SSRIs	**CYP2B6 - Intermediate metabolizer** **CYP2C19 - Rapid metabolizer:** Sertraline is metabolized by both CYP2C19 and CYP2B6 into less active compounds. A small increase in metabolism by CYP2C19 and reduced metabolism by CYP2B6 is predicted.[17]	CPIC[17] guidelines provide a moderate recommendation to initiate therapy with the recommended starting dose.
TOLBUTAMIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** Reduced metabolism of tolbutamide by CYP2C9 is predicted. This has been associated with a reduction in glucose concentration in some studies[100].	DPWG[101] states that there is no action needed for this gene-drug interaction.
LACOSAMIDE Antiepileptics	**CYP2C19 - Rapid metabolizer:** Increased metabolism by CYP2C19 is predicted which could theoretically lead to reduced lacosamide exposure, although direct evidence is lacking.	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.
LAMOTRIGINE Antiepileptics	**HLA-B*15:02 (rs144012689) - Lower risk of certain hypersensitivity reactions:** The rs144012689 TT result provides a high prediction of the absence of HLA-B*15:02 allele.	No genotype-guided dosing recommendations are available where the HLA-B*15:02 is absent. Be aware that this rs144012689 is a screening test only, and furthermore a HLA-B*15:02 negative test does not eliminate the risk of lamotrigine-induced SJS/TEN; if the patient develops any rash or hypersensitivity reactions on lamotrigine, then discontinuation should be considered in accordance with standard prescribing guidelines.[102]
CLOPIDOGREL Antiplatelet drugs	**CYP2C19 - Rapid metabolizer:** Normal or increased formation of clopidogrel's active metabolite and a normal or enhanced antiplatelet effect are predicted. There is no association with increased bleeding risk.[103]	CPIC guidelines[103] provide a strong recommendation to use the label-recommended dosage if clopidogrel is being prescribed for acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI).
FLUPENTHIXOL Antipsychotics	**CYP2D6 - Poor metabolizer:** DPWG guidelines[104] state that there is no gene-drug interaction for flupenthixol and CYP2D6.	No dosage recommendation is currently available based on the genetic findings.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
QUETIAPINE Antipsychotics	**CYP3A4 - Normal metabolizer:** Normal metabolism of quetiapine by CYP3A4 is predicted. Although quetiapine is also metabolized to a lesser extent by CYP2D6, the DPWG guidelines[39] state that there is no gene-drug interaction for CYP2D6 and quetiapine.	Standard dosing and prescribing measures apply.
ATAZANAVIR Antivirals	**CYP3A5 - Poor metabolizer:** Poor metabolism of atazanavir via CYP3A5 is predicted. However, target drug exposure is expected to be in the normal range because this is a common CYP3A5 phenotype amongst Caucasians, for whom dosing was developed, and there are other enzymes involved in the metabolism of atazanavir. 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 - Usual prescribing considerations apply.
NEBIVOLOL Beta blockers	**CYP2D6 - Poor metabolizer:** Negligible nebivolol 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 label[105] states that no dose adjustments are necessary for CYP2D6 poor metabolizers, as the clinical effect and safety profile were similar between poor and extensive metabolizers. Be alert for excessive beta blockade.
TACROLIMUS Calcineurin inhibitors	**CYP3A5 - Poor metabolizer:** Poor metabolism of tacrolimus is predicted. Higher dose-adjusted trough concentrations and increased chance of achieving concentration targets are also predicted. This phenotype is the most common in Caucasian populations and tacrolimus dosing procedures were developed for these patients.	For use in transplant recipients, other than in liver transplant where donor and recipient livers are of different genotypes, CPIC guidelines[106] recommend using the standard recommended starting dose. Therapeutic drug monitoring should guide ongoing dose adjustments . 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.[106]
NALTREXONE Drugs for alcohol dependence	**OPRM1 - Lower opioid sensitivity:** 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.[107]	CPIC guidelines[3] state that there is insufficient evidence to provide a recommendation for naltrexone dosing based on OPRM1 genotype. Usual prescribing considerations apply.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ALLOPURINOL Drugs for gout	**ABCG2 (rs2231142) - Normal transporter function:** This genotype is associated with typical excretion of uric acid by the kidneys and intestine.	Standard dosing and prescribing measures apply.
ELTROMBOPAG Haemostatic agents	**F5 (rs6025) - No Factor V Leiden variant detected:** This individual is a non-carrier of Factor V Leiden and based on this genotype, is not at increased risk of thrombosis. This risk may also be influenced by other genetic and clinical factors.	The FDA-approved drug label states that the risk for thromboembolism should be considered in patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease).[108]
LUSUTROMBOPAG Haemostatic agents	**F5 (rs6025) - No Factor V Leiden variant detected** **F2 (rs1799963) - No prothrombin G20210A variant detected:** This individual is a non-carrier of Factor V Leiden and non-carrier of the prothrombin G20210A variant, and based on these genotypes, is not at increased risk of thrombosis. This risk may also be influenced by other genetic and clinical factors.	The FDA-approved drug label states that the risk for thrombosis should be considered in patients with risk factors for thromboembolism, including genetic prothrombotic conditions (e.g. Factor V Leiden, prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency).[109]
MELATONIN Hypnotics	**CYP1A2 - Ultrarapid metabolizer (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).[110] 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.
ERDAFITINIB Immunomodulators and antineoplastics	**CYP2C9 - Intermediate metabolizer:** Reduced metabolism by CYP2C9 of erdafitinib is predicted, however no increase in drug exposure was observed compared with the normal genotype.[111]	No genotype-guided dosing recommendation available. Standard dosing and prescribing measures apply.
METHOTREXATE Immunomodulators and antineoplastics	**MTHFR (rs1801133) - Normal MTHFR enzyme activity:** Although there has been some association with this MTHFR genotype and a decreased risk of methotrexate adverse effects compared to the TT or TC genotypes, there is also conflicting evidence. The DPWG guidelines[112] has stated that there is no gene-drug interaction therefore it is determined not to be clinically actionable.	No dosage recommendation is currently available based on the genetic findings.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
MIRABEGRON Miscellaneous	**CYP2D6 - Poor metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted, but only a slight increase in drug exposure was observed in poor metabolizers as compared with extensive metabolizers,[113] which is unlikely to cause clinically significant effects.	No genotype-guided dosing recommendation available. Note that the European Medicines Agency suggests no dose adjustment when used in CYP2D6 poor metabolizers or when used with concurrent CYP2D6 inhibitors.[114] Monitor for adverse effects.
CARBAMAZEPINE Mood stabilisers	**HLA-A*31:01 (rs1061235) - Lower risk of certain hypersensitivity reactions** **HLA-B*15:02 (rs144012689) - Lower risk of certain hypersensitivity reactions:** The rs1061235 AA result provides a high prediction of the absence of the HLA-A*31:01 allele. The rs144012689 TT result provides a high prediction of the absence of the HLA-B*15:02 allele. This result is associated with a normal or reduced risk of cutaneous hypersensitivity reactions to carbamazepine (such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)), drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE).	It would be reasonable to cautiously consider the use of carbamazepine as per standard prescribing guidelines.[115] Be aware that this is a screening test only, if the patient develops any rash or hypersensitivity reactions during treatment with carbamazepine, then discontinuation should be considered in accordance with standard prescribing guidelines.[116]
OXCARBAZEPINE Mood stabilisers	**HLA-B*15:02 (rs144012689) - Lower risk of certain hypersensitivity reactions:** The rs144012689 TT result provides a high prediction of the absence of the HLA-B*15:02 allele. This result is associated with a normal or reduced risk of cutaneous hypersensitivity reactions to oxcarbazepine (such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)).	It would be reasonable to cautiously consider the use of oxcarbazepine as per standard prescribing guidelines.[115] Be aware that this is a screening test only, if the patient develops any rash or hypersensitivity reactions on oxcarbazepine, then discontinuation should be considered in accordance with standard prescribing guidelines.[117]
DICLOFENAC NSAIDs	**CYP2C9 - Intermediate metabolizer:** Diclofenac is only partially metabolized by CYP2C9. This genotype predicts a reduction in diclofenac metabolism by CYP2C9. Whilst this could lead to a small increase in diclofenac exposure,[118] the clinical significance has not been demonstrated.	CPIC guidelines[61] 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 metabolizer:** Indomethacin is only partially metabolized by CYP2C9. This genotype predicts a reduction in indomethacin metabolism by CYP2C9. Whilst this could lead to a small increase in indomethacin exposure,[119] the clinical significance has not been demonstrated.	CPIC guidelines[61] 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
ESTETROL Oestrogen containing contraceptives	**F5 (rs6025) - No Factor V Leiden variant detected** **F2 (rs1799963) - No prothrombin G20210A variant detected:** The GG genotype (non-carrier of Factor V Leiden) is not associated with increased risk of thrombosis. This risk may also be influenced by other genetic and clinical factors. The GG genotype (non-carrier of the prothrombin G20210A variant) is not associated with increased risk of thrombosis. Other genetic and clinical factors may also influence the risk of thrombosis in patients taking oral contraceptives. The use of oestrogen containing contraceptives has been associated with increased risk of thrombosis, regardless of genotype.	No genotype-guided dosing recommendations available. Consider standard dosing and monitoring.
ESTRADIOL Oestrogen containing contraceptives	**F5 (rs6025) - No Factor V Leiden variant detected** **F2 (rs1799963) - No prothrombin G20210A variant detected:** The GG genotype (non-carrier of Factor V Leiden) is not associated with increased risk of thrombosis. This risk may also be influenced by other genetic and clinical factors. The GG genotype (non-carrier of the prothrombin G20210A variant) is not associated with increased risk of thrombosis. Other genetic and clinical factors may also influence the risk of thrombosis in patients taking oral contraceptives. The use of oestrogen containing contraceptives has been associated with increased risk of thrombosis, regardless of genotype.	No genotype-guided dosing recommendations available. Consider standard dosing and monitoring.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ETHINYLESTRADIOL Oestrogen containing contraceptives	**F5 (rs6025) - No Factor V Leiden variant detected** **F2 (rs1799963) - No prothrombin G20210A variant detected:** The GG genotype (non-carrier of Factor V Leiden) is not associated with increased risk of thrombosis. This risk may also be influenced by other genetic and clinical factors. The GG genotype (non-carrier of the prothrombin G20210A variant) is not associated with increased risk of thrombosis. Other genetic and clinical factors may also influence the risk of thrombosis in patients taking oral contraceptives. The use of oestrogen containing contraceptives has been associated with increased risk of thrombosis, regardless of genotype.	No genotype-guided dosing recommendations available. Consider standard dosing and monitoring.
ALFENTANIL Opioid Analgesics	**OPRM1 - Lower opioid sensitivity** **COMT - Significantly reduced COMT enzyme activity:** OPRM1 - Whilst the GG genotype has been associated with reduced sensitivity to some opioid analgesics, there is no effect or insufficient evidence for adverse events, opioid dose requirements, analgesia, or change in opioid dependence/withdrawal therapy for alfentanil. COMT - No effect for opioid adverse events. Insufficient evidence for an association between COMT rs4680 genotype, analgesia and opioid dose requirements.	CPIC[3] states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.
BUPRENORPHINE Opioid Analgesics	**OPRM1 - Lower opioid sensitivity** **COMT - Significantly reduced COMT enzyme activity:** OPRM1 - Whilst the GG genotype has been associated with reduced sensitivity to some opioid analgesics, there is no effect or insufficient evidence for adverse events, opioid dose requirements, analgesia, or change in opioid dependence/withdrawal therapy for buprenorphine. COMT - No effect for opioid adverse events. Insufficient evidence for an association between COMT rs4680 genotype, analgesia and opioid dose requirements.	CPIC[3] states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
FENTANYL Opioid Analgesics	**OPRM1 - Lower opioid sensitivity** **COMT - Significantly reduced COMT enzyme activity:** OPRM1 - Whilst the GG genotype has been associated with reduced sensitivity to some opioid analgesics, there is no effect for fentanyl adverse events and analgesia. There has also been mixed evidence for an association between OPRM1 rs1799971 and fentanyl dose requirements. COMT - No effect for opioid adverse events. Insufficient evidence for an association between COMT rs4680 genotype, analgesia and opioid dose requirements.	CPIC[3] states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.
HYDROMORPHONE Opioid Analgesics	**OPRM1 - Lower opioid sensitivity** **COMT - Significantly reduced COMT enzyme activity:** OPRM1 - Whilst the GG genotype has been associated with reduced sensitivity to some opioid analgesics, there is no effect or insufficient evidence for adverse events, opioid dose requirements, analgesia, or change in opioid dependence/withdrawal therapy for hydromorphone. COMT - No effect for opioid adverse events. Insufficient evidence for an association between COMT rs4680 genotype, analgesia and opioid dose requirements.	CPIC[3] states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.
MORPHINE Opioid Analgesics	**OPRM1 - Lower opioid sensitivity** **COMT - Significantly reduced COMT enzyme activity:** OPRM1 - Whilst the GG 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. COMT - Although the AA genotype has been associated with lower consumption of morphine in some studies, there are conflicting results in other studies.	CPIC[3] states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
SUFENTANIL Opioid Analgesics	**OPRM1 - Lower opioid sensitivity** **COMT - Significantly reduced COMT enzyme activity:** OPRM1 - Whilst the GG genotype has been associated with reduced sensitivity to some opioid analgesics, there is no effect or insufficient evidence for adverse events, opioid dose requirements, analgesia, or change in opioid dependence/withdrawal therapy for sufentanil. COMT - No effect for opioid adverse events. Insufficient evidence for an association between COMT rs4680 genotype, analgesia and opioid dose requirements.	CPIC[3] states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.

DETAILED PHARMACOGENOMIC TEST RESULTS

GENE	GENOTYPE	PREDICTED PHENOTYPE
ABCG2 (rs2231142)	CC	**Normal transporter function:** This individual has two copies of the normal allele which predicts normal function of the ABCG2 encoded transporter. This transporter is relevant for the clearance of certain medications such as rosuvastatin.
COMT	AA	**Significantly reduced COMT enzyme activity:** The COMT enzyme is involved in the metabolism of catecholamine. The AA genotype contains two variant alleles for the COMT gene predicting a three to four-fold reduction in the activity of the COMT enzyme. The AA genotype predicts a lower COMT enzyme activity compared to the AG and GG genotypes.
CYP1A2	*1F/*1F	**Ultrarapid metabolizer (with inducer present):** Due to the presence of two *1F alleles, this individual is predicted to have an ultrarapid metabolizer 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 metabolized by CYP1A2, drug exposure and clinical effects may either be reduced (for an active drug) or increased (for a prodrug).
CYP2B6	*1/*6	**Intermediate metabolizer:** This individual is predicted to have an intermediate metabolizer phenotype due to the presence of one normal function allele and one decreased function allele. Due to technical difficulties in unambiguously determining this genotype, the individual's other possible genotype is *4/*9 which also predicts an intermediate metabolizer phenotype. For a drug extensively metabolized 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/*17	**Rapid metabolizer:** Due to the presence of one normal function allele and one increased function allele, this individual is predicted to have a rapid metabolizer phenotype. For a drug extensively metabolized by CYP2C19, drug exposure and clinical effects may either be slightly decreased (for an active drug) or slightly increased (for a prodrug). This individual is at risk of therapeutic failure (active drug) or adverse effects (prodrug).
CYP2C9	*1/*3	**Intermediate metabolizer:** Due to the presence of one normal function allele and one null allele, this individual is predicted to have an intermediate metabolizer phenotype. For a drug extensively metabolized 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 metabolizer:** Due to the presence of two copies of no function alleles, this individual is predicted to have a poor metabolizer phenotype. For a drug extensively metabolized 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/*1	**Normal metabolizer:** The *22 allele is not present and this individual is expected to have a normal metabolizer phenotype. Whilst many drugs are known to be metabolized by CYP3A4, relatively few genetic variations have been found that affect metabolism of a limited number of these drugs.

GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP3A5	*3/*3	**Poor metabolizer:** Due to the presence of two no function alleles, this individual is predicted to have a poor metabolizer phenotype (CYP3A5 non-expresser). CYP3A5 is known to metabolize certain drugs, including tacrolimus. Note that this individual's phenotype is the most common one amongst Caucasians.
F2 (rs1799963)	GG	**No prothrombin G20210A variant detected:** This individual has the GG genotype for F2 rs1799963, i.e. the prothrombin G20210A variant was not detected. Based on this genotype, the patient does not have an increased risk of venous thrombosis and embolism. The presence of other genetic variants may contribute to an increased risk of thrombosis, such as Factor V Leiden (F5 in this test), antithrombin deficiency or Protein C or S deficiency.[120], [121] Note that other genetic and clinical factors influence the risk of thrombosis in any individual.
F5 (rs6025)	GG	**No Factor V Leiden variant detected:** This individual has the GG genotype for F5 rs6025, i.e., Factor V Leiden was not detected. Based on this genotype, the patient does not have an increased risk of venous thrombosis and embolism. The presence of other genetic variants may contribute to an increased risk of thrombosis, such as the prothrombin G20210A variant (F2 in this test), antithrombin deficiency or Protein C or S deficiency.[120], [121] Note that other genetic and clinical factors influence the risk of thrombosis in any individual.
HLA-A*31:01 (rs1061235)	AA	**Lower risk of certain hypersensitivity reactions:** Testing for a specific rs1061235 variant may be utilized as a screening test for the presence of HLA-A*31:01. HLA-A*31:01 is an allele which, if present, has been associated with hypersensitivity reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, maculopapular eruptions, and drug reaction with eosinophilia and systemic symptoms (DRESS) with carbamazepine. This AA result provides a high prediction of the absence of the HLA-A*31:01 allele. The negative predictive value for this test has been shown to be 100%.[122] The clinical utility for testing for this variant appears to be particularly relevant for carbamazepine, with the FDA-approved drug label noting that the risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for HLA-A*31:01.[116]
HLA-B*15:02 (rs144012689)	TT	**Lower risk of certain hypersensitivity reactions:** Testing for a specific rs144012689 variant may be utilized as a screening test for the presence of HLA-B*15:02. HLA-B*15:02 is an allele which, if present, is associated with serious cutaneous hypersensitivity reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) for certain medications. This TT result provides a high prediction of the absence of the HLA-B*15:02 allele. The negative predictive value for this test has been shown to be 100%.[123] The clinical utility of testing for this variant appears to be particularly relevant for carbamazepine and oxcarbazepine, as there is more limited evidence for other medications. The FDA-approved drug label notes that HLA-B*15:02 is found almost exclusively in patients with Asian ancestry across broad areas of Asia and that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*15:02 prior to initiating treatment with carbamazepine.[116] It is noted that this should also be considered prior to initiating treatment with oxcarbazepine.
MTHFR (rs1801133)	CC	**Normal MTHFR enzyme activity:** Due to the presence of two normal C alleles of the C677T polymorphism, normal MTHFR enzyme activity is predicted. The risk of low folate and high homocysteine are unlikely to be influenced by the genetic result.

GENE	GENOTYPE	PREDICTED PHENOTYPE
OPRM1	GG	**Lower opioid sensitivity:** 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[124],[125] 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%).
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 *SLCO1B1* 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 *CYP2C9* genotype should also be considered together with the *VKORC1* genotype for calculating the initial warfarin dose.

ADDITIONAL GENES WITH EMERGING EVIDENCE

This section contains genes that have limited evidence for clinical implementation and are not utilized in how medications are classified under major, minor, usual or no pharmacogenomic prescribing considerations. The data has been included for informational purposes only and there are currently no recommendations to alter prescribing based on genotype.

GENE	GENOTYPE	COMMENTS
ABCB1	CT	ABCB1 encodes p-glycoprotein, an efflux transporter that transports many agents out of cells. The CT genotype is associated with higher expression and activity of ABCB1 compared to the TT genotype. This finding has been associated with lower treatment efficacy of some antiemetic medications (such as granisetron and ondansetron). Individuals with this genetic result may to have a better control rate of nausea and vomiting compared to individuals with TT genotypes. There are currently no recommendations to alter prescribing.
ADRA2A	GC	This genetic result may be associated with some improvement in response to methylphenidate compared to CC carriers,[126] however, study results are conflicting. There are currently no recommendations to alter prescribing.
APOE (rs7412)	CC	The ApoE gene encodes a protein which is used to form lipoproteins. The ApoE lipoprotein is involved in cholesterol metabolism. This ApoE genotype is associated with lower plasma concentration of APOE. This finding has been shown to result in reduced LDL-C lowering response to atorvastatin treatment compared to CT and TT individuals. There are currently no recommendations to alter prescribing.
CES1A1	GG	Individuals with this genetic result may have increased metabolism of methylphenidate[127] compared to AA or AG carriers. There are currently no recommendations to alter prescribing.
DRD2	GG	This genotype may be associated with a potential reduced risk of adverse effects to some antipsychotics, such as tardive dyskinesia or hyperprolactinaemia compared to the AA or AG genotypes. There are currently no recommendations to alter prescribing.
HTR2A	AG	This genetic result may be associated with a lower risk of side effects for certain SSRIs compared to GG carriers,[128] however, this has not been shown in all studies and there are currently no recommendations to alter prescribing.
SLC6A4	L/S	This genetic result (one long allele and one short allele of the 5HTTLPR) has been associated with improved SSRI response in individuals of Caucasian ancestry compared to SS carriers.[129] However, there are conflicting studies, particularly in other populations. There are currently no recommendations to alter prescribing.
UGT1A4	*3/*3	Individuals with this genetic result may have reduced drug exposure of lamotrigine[130] and olanzapine[131] compared to *1/*1 carriers. However, there is conflicting evidence in relation to this effect and there are currently no recommendations to alter prescribing.
UGT2B15	*1/*2	Individuals with this genetic result may have reduced clearance of certain benzodiazepines, such as lorazepam[132] and oxazepam[133] compared to *1/*1 carriers. However there is limited evidence for this effect and there are currently no recommendations to alter prescribing.

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DISCLAIMER

The current list of reported haplotypes are below. Unless otherwise indicated, the *1 allele denotes the absence of any variant and is designated as the wild type: ABCG2 - rs2231142 (NC_000004.11:g.89052323G>T); COMT – rs4680 (LRG_1010:g.27009G>A); CYP1A2 *1C (LRG_1274:g.2035G>A), *1F (LRG_1274:g.5732C>A), *1K (LRG_1274:g.[5166C>T; 5732C>A]), *1L (LRG_1274:g.[2035G>A; 5732C>A]), *7 (LRG_1274:g.9427G>A), *11 (LRG_1274:g.6452C>A); CYP2B6 *6 (LRG_1267:g.20638G>T), *18 (LRG_1267:g.26018T>C); CYP2C19 *2 (NG_008384.3:g.24179G>A), *3 (NG_008384.3:g.22973G>A), *4A (NG_008384.3:g.5026A>G), *4B (NG_008384.3:g.[4220C>T; 5026A>G), *5 (NG_008384.3:g. 95058C>T), *6 (NG_008384.3:g.17773G>A), *7 (NG_008384.3:g.24319T>A), *8 (NG_008384.3:g.17736T>C), *17 (NG_008384.3:g.4220C>T); CYP2C9 *2 (LRG_1195:g.9133C>T), *3(LRG_1195:g.48139A>C),*4 (LRG_1195:g.48140T>C), *5 (LRG_1195:g.48144C>G), *6 (LRG_1195:g.16126del), *8 (LRG_1195:g. 9152G>A), *11 (LRG_1195:g. 48067C>T), *12 (LRG_1195:g.55863C>T), *13 (LRG_1195:g.8801T>C), *15 (LRG_1195:g.14625C>A), *25 (LRG_1195:g.9056_9065del), *27 (LRG_1195:g. 9152G>T); CYP2D6 *2 (LRG_303:g.7870C>T; 9200G>C), *3 (LRG_303:g.7569del), *4 (LRG_303:g.[5119C>T; 6866G>A; 9200G>C]), *5 (del(CYP2D6)), *6 (LRG_303:g.6727del), *7 (LRG_303:g.7955A>C), *8 (LRG_303:g.[6778G>T; 7870C>T; 9200G>C), *9 (LRG_303:g. 7635_7637del), *10 (LRG_303:g.[5119C>T; 9200G>C]), *11 (LRG_303:g.[9200G>C ;590G>C]), *12 (LRG_303:g.[5143G>A; 7870C>T; 9200G>C]), *114 (LRG_303:g.[5119C>T; 6778G>A ; 7870C>T; 9200G>C]), *14 (LRG_303:g.[6778G>A ;7870C>T; 9200G>C]),*15 (LRG_303:g.5156dup), *17 (LRG_303:g.[6041C>T; 7870C>T; 9200G>C], *18 (NC_000022.11:g.42126666_42126667insAGTGGGCAC), *19 (LRG_303:g.[7559_7562del; 9200G>C;]), *20 (LRG_303:g.[6996dup; 9200G>C]), *29 (LRG_303:g.[7870C>T;8203G>A;9200G>C], *36 (NC_000022.10:g.[42526694G>A ;42522624_42522669con42536337_42536382]), *41(LRG_303:g.[7870C>T; 8008G>A; 9200G>C]), *69 (LRG_303:g.[5119C>T; 8008G>A; 9200G>C]); CYP3A4 *2 (NG_008421.1:g.20826T>C), *17 (NG_008421.1:g.20728T>C), *22 (NG_008421.1:g.20493C>T); CYP3A5 *1A(NG_007938.1:g.12083G>A) *2(NG_007938.1:g.[12083G>A; 32386C>A]), *3 (NG_007938.1:g), *6 (NG_007938.1:g.[12083G>A; 19787G>A]), *7 (NG_007938.1:g.[12083G>A;32228dup]); F2 - rs1799963 (NG_008953.1:g.25313G>A); F5 - rs6025 (NG_011806.1:g.41721G>A); HLA-A*31:01 - rs1061235 (NG_029217.2:g.8057A>T); HLA-B*15:02 - rs144012689 (NG_023187.1:g.7210A>T); MTHFR - rs1801133 (NG_013351.1:g.14783C>T); OPRM1 - rs1799971 NM_000914.4:c.118A>G; SLCO1B1 - rs4149056 NM_006446.4:c.521T>C; VKORC1 - rs9923231 NM_024006.5:c.-1639G>A; ABCB1 -rs1045642 (NG_011513.1:g.208920T>C); ADRA2A - rs1800544 (LRG_545:g.4714G>A); APOE - rs7412 (NG_007084.2:g.8041C>T); CES1A1 - rs71647871 (NG_012057.1:g.14506G>A); DRD2 - rs1800497 (NG_012976.1:g.17316G>A); HTR2A - rs6311 (LRG_1008:g.4692G>T); SLC6A4 - NG_011747.2:g.3628_3670del; UGT1A4 - rs2011425 (NG_002601.2:g.134219T>A or NG_002601.2:g.134219T>G) and UGT2B15 - rs1902023 (NG_052676.1:g.5411T>G).