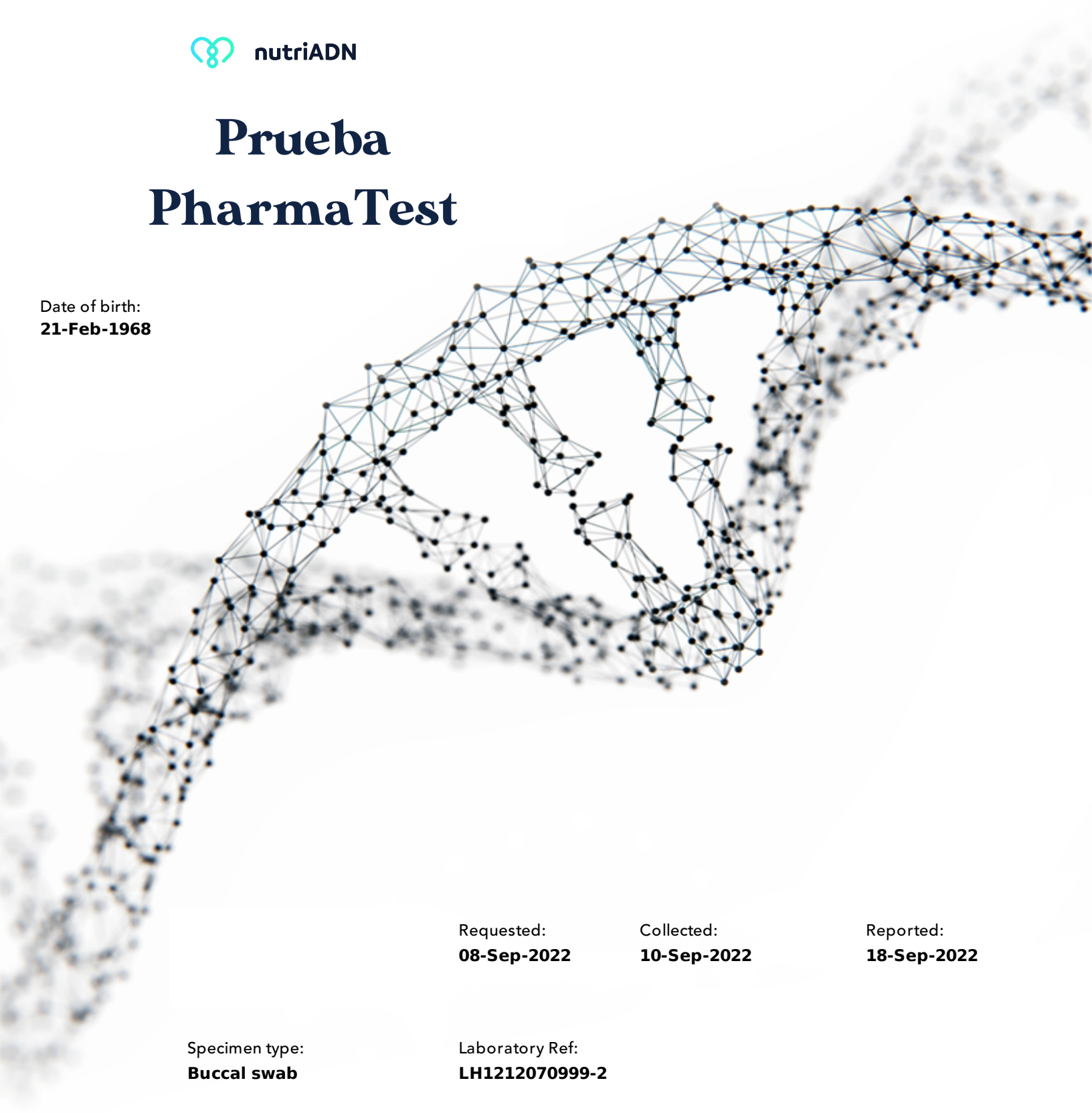
nutriADN

Prueba PharmaTest

Date of birth:
21-Feb-1968



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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 SUMMARY

MEDICATION	GENE(S)	PRESCRIBING CONSIDERATIONS
CLOPIDOGREL	CYP2C19	**Reduced / inadequate response**
SERTRALINE	CYP2C19	**Increased therapeutic and/or adverse effects**
ESOMEPRAZOLE	CYP2C19	**No altered effect predicted by genotype**

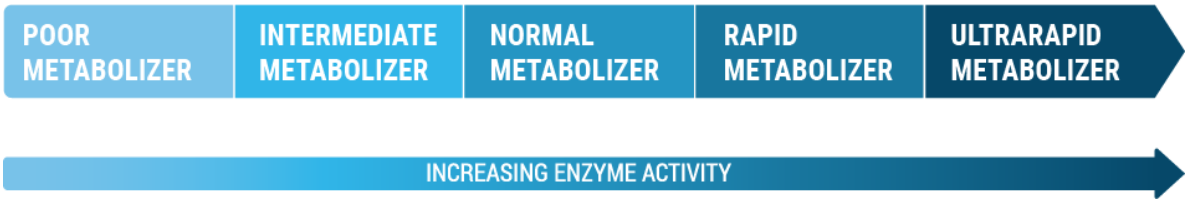
MEDICATIONS WITH NO PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST

CANDESARTAN CILEXETIL, METFORMIN HYDROCHLORIDE, TAPENTADOL

PHARMACOGENOMIC TEST RESULTS SUMMARY

GENE	GENOTYPE	PREDICTED PHENOTYPE
COMT	AA	**Higher opioid sensitivity**
CYP1A2	*1F/*1F	**Ultrarapid metabolizer (with inducer present)**
CYP2B6	*1/*6	**Intermediate metabolizer**
CYP2C19	*1/*2	**Intermediate metabolizer**
CYP2C9	*1/*2	**Intermediate metabolizer**
CYP2D6	*1/*4	**Intermediate metabolizer**
CYP3A4	*1/*1	**Normal metabolizer**
CYP3A5	*3/*3	**Poor metabolizer**
OPRM1	AA	**Higher opioid sensitivity**
SLCO1B1	*1/*1	**Normal transporter function**
VKORC1	AG	**Moderately reduced VKORC1 enzyme level**

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



POTENTIAL DRUG INTERACTIONS

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

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

MEDICATION	INHIBITOR - MODERATE	INHIBITOR - STRONG	INDUCER
ESOMEPRAZOLE	CYP2C19		

MEDICATIONS OF INTEREST EXPANDED

MEDICATION	INTERPRETATION	RECOMMENDATION
CLOPIDOGREL	**CYP2C19 - Intermediate metabolizer:** Reduced formation of clopidogrel's active metabolite and a reduced antiplatelet effect are predicted. This genotype has been associated with an increased risk of cardiac and cerebrovascular events.[1]	For management of acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI), CPIC guidelines[1] provide a strong recommendation to avoid the use of standard dose (75 mg) clopidogrel if possible, and to use prasugrel or ticagrelor at standard dose if there is no contraindication. For management of neurovascular indications, CPIC guidelines[1] provide a moderate recommendation to consider an alternative P2Y12 inhibitor at standard dose if clinically indicated and if there is no contraindication. Alternative P2Y12 inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of TIA or stroke.
SERTRALINE	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism when compared to extensive metabolizers is predicted.[2] However, the DPWG classifies this genetic result as having a minor influence on sertraline plasma concentration and no effect on side effects.[3]	CPIC guidelines[2] provide a strong recommendation to initiate therapy with the recommended starting dose. The DPWG guideline states that there is not enough evidence to recommend adjustment of therapy.[3]
ESOMEPRAZOLE	**CYP2C19 - Intermediate metabolizer:** This genotype predicts reduced metabolism of esomeprazole by CYP2C19, and increased plasma concentrations. However, there is insufficient evidence to support a significant effect on therapeutic effectiveness or side effects.	The DPWG suggests that no specific action on esomeprazole dosing is required with this genotype.[4]

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

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

CLASS	MAJOR	MINOR	USUAL
Miscellaneous		Avatrombopag Cevimeline Cyclophosphamide Dronabinol Eliglustat Flibanserin Lofexidine Meclizine Proguanil Tamsulosin	Atazanavir Mirabegron
Neurological drugs		Carisoprodol Deutetrabenazine Tetrabenazine Valbenazine	Siponimod
NSAIDs		Celecoxib Flurbiprofen Ibuprofen Lornoxicam Meloxicam Piroxicam	Diclofenac Indomethacin Mefenamic Acid
Opioid Analgesics	Codeine Tramadol	Hydrocodone Methadone Oliceridine Oxycodone	Morphine
Proton pump inhibitors		Dexlansoprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	Esomeprazole
Psychostimulants		Amphetamine Dextroamphetamine Lisdexamfetamine	
Statins	Fluvastatin		Atorvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin

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
FLECAINIDE Antiarrhythmics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	For indications other than the diagnosis of Brugada syndrome, the DPWG[5] suggests reducing the dose to 75% of the standard dose, recording an ECG and monitoring the plasma concentration. For provocation testing for diagnosis of Brugada syndrome, no specific dose adjustment for flecainide is recommended.
PROPAFENONE Antiarrhythmics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The DPWG[6] suggests either: 1) adjusting the dose in response to plasma concentration, recording an ECG and being alert to side effects, or 2) selecting an alternative drug (e.g., sotalol, amiodarone).
ACENOCOUMAROL Anticoagulants	**VKORC1 - Moderately reduced VKORC1 enzyme level** **CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism of acenocoumarol by CYP2C9 is predicted. Reduced 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 and VKORC1 genotypes, DPWG[7],[8] 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 - Moderately reduced VKORC1 enzyme level** **CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism of warfarin by CYP2C9 is predicted. Reduced amount of VKORC1 (the enzyme warfarin inhibits). Overall increased warfarin sensitivity and increased risk of supratherapeutic INR.	For patients already taking warfarin (eg more than 5 doses), dose adjustment is guided by INR. For patients initiating warfarin, there are CPIC[9] recommendations to reach the therapeutic dose. The summary of CPIC recommendations include consideration of the use of validated published pharmacogenetic algorithms[10],[11] 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.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
VENLAFAXINE Antidepressants - SNRIs 	**CYP2D6 - Intermediate metabolizer:** 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. There may be an increased risk of adverse effects, such as gastrointestinal discomfort.	The DPWG[12] 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.
CITALOPRAM Antidepressants - SSRIs	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism of citalopram by CYP2C19 and increased drug exposure are predicted. This may increase the likelihood of adverse effects, especially with higher doses or if drug-drug interactions occur.	CPIC guidelines[2] provide a strong recommendation to initiate therapy with the recommended starting dose. Monitor for adverse effects. DPWG guidelines recommend not exceeding the following doses: 30mg as tablets or 22mg as drops for adults up to 65 years; 15mg as tablets or 10mg as drops for adults 65 years and over.[3]
ESCITALOPRAM Antidepressants - SSRIs	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism of escitalopram by CYP2C19 and increased drug exposure are predicted. This may increase the likelihood of adverse effects, especially with higher doses or if drug-drug interactions occur.	CPIC guidelines[2] provide a strong recommendation to initiate therapy with the recommended starting dose. Monitor for adverse effects. DPWG guidelines recommend not exceeding 75% of the standard maximum dose, i.e. a maximum of 15 mg/day for adults up to 65 years and 7.5 mg/day for adults 65 years and over.[3]
AMITRIPTYLINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer** **CYP2C19 - Intermediate metabolizer:** Amitriptyline is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Reduced metabolism of both amitriptyline and its active metabolite are predicted.	For use at higher doses such as in the treatment of depression, CPIC[13] provides an optional recommendation to consider a 25% reduction of the recommended steady-state starting dose and utilisation of therapeutic drug monitoring to guide dose adjustments. Close monitoring for adverse effects is advisable. For use at lower doses such as in treatment of neuropathic pain, standard dosing and prescribing measures apply, with monitoring of adverse effects.
CLOMIPRAMINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer** **CYP2C19 - Intermediate metabolizer:** Clomipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Reduced metabolism of both clomipramine and its active metabolite are predicted.	CPIC[13] provides an optional recommendation to consider a 25% reduction of the recommended steady-state starting dose and utilisation of therapeutic drug monitoring to guide dose adjustments. Close monitoring for adverse effects is advisable. Note that these dosing 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
DESIPRAMINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer:** Reduced desipramine metabolism and increased exposure are predicted. This may increase the risk of adverse effects. Concentration-related adverse effects are less likely to be problematic at the lower doses used for treatment of conditions such as neuropathic pain.	CPIC[13] provides an optional recommendation to consider a 25% reduction of the recommended steady-state starting dose and utilisation of therapeutic drug monitoring to guide dose adjustments. Close monitoring for adverse effects is advisable. Note that these dosing recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
DOXEPIN Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer** **CYP2C19 - Intermediate metabolizer:** Doxepin is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Reduced metabolism of both doxepin and its active metabolite are predicted.	CPIC[13] provides an optional recommendation to consider a 25% reduction of the recommended steady-state starting dose and utilisation of therapeutic drug monitoring to guide dose adjustments. Close monitoring for adverse effects is advisable. Note that these dosing recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
IMIPRAMINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer** **CYP2C19 - Intermediate metabolizer:** Imipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Reduced metabolism of both imipramine and its active metabolite are predicted. This may increase the risk of adverse effects.	CPIC[13] provides an optional recommendation to consider a 25% reduction of the recommended steady-state starting dose and utilisation of therapeutic drug monitoring to guide dose adjustments. Close monitoring for adverse effects is advisable. Note that these dosing recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
NORTRIPTYLINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer:** Reduced nortriptyline metabolism and increased exposure are predicted. This may increase the risk of adverse effects. Concentration-related adverse effects are less likely to be problematic at the lower doses used for treatment of conditions such as neuropathic pain.	For use at higher doses such as in the treatment of depression, CPIC[13] provides a recommendation to consider a 25% reduction of the recommended steady-state starting dose and utilisation of therapeutic drug monitoring to guide dose adjustments. Close monitoring for adverse effects is advisable. For use at lower doses such as in treatment of neuropathic pain, standard dosing and prescribing measures apply, with monitoring for adverse effects.
TRIMIPRAMINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer** **CYP2C19 - Intermediate metabolizer:** Trimipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Reduced metabolism of both trimipramine and its active metabolite are predicted.	CPIC[13] provides an optional recommendation to consider a 25% reduction of the recommended steady-state starting dose and utilisation of therapeutic drug monitoring to guide dose adjustments. Close monitoring for adverse effects is advisable. Note that these dosing 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
CLOPIDOGREL Antiplatelet drugs	**CYP2C19 - Intermediate metabolizer:** Reduced formation of clopidogrel's active metabolite and a reduced antiplatelet effect are predicted. This genotype has been associated with an increased risk of cardiac and cerebrovascular events.[1]	For management of acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI), CPIC guidelines[1] provide a strong recommendation to avoid the use of standard dose (75 mg) clopidogrel if possible, and to use prasugrel or ticagrelor at standard dose if there is no contraindication. For management of neurovascular indications, CPIC guidelines[1] provide a moderate recommendation to consider an alternative P2Y12 inhibitor at standard dose if clinically indicated and if there is no contraindication. Alternative P2Y12 inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of TIA or stroke.
PIMOZIDE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the likelihood of concentration-dependent adverse effects, especially with high doses or if drug-drug interactions occur. There is a theoretically increased risk of QT prolongation (thus torsade de points); the recommendations for a lower dose aim to reduce the risk of excessively high plasma concentration of drug.	DPWG[14] recommends using no more than 80% of the standard maximum dose. Monitor for adverse effects.
THIORIDAZINE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may potentially increase the risk of concentration-dependent adverse effects. The reduction in clearance of thioridazine may be 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.	Note that the FDA-approved drug label states that thioridazine is contraindicated in patients with reduced activity of CYP2D6.[15] This includes patients with genetic variations leading to reduced activity, or patients with concomitant use of CYP2D6 inhibitors. Drugs that reduce clearance of thioridazine through other mechanisms also increase the risk of adverse events.
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[16] provides 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.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
TAMOXIFEN Immunomodulators and antineoplastics 	**CYP2D6 - Intermediate 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, whilst others have not shown such effects.	There is controversy whether any treatment changes are required. For the adjuvant treatment of ER+ breast cancer, CPIC guidelines[17] provides an optional* recommendation to consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but label-approved tamoxifen dose (eg 40 mg/day). Avoid CYP2D6 strong to weak inhibitors. *An optional recommendation means there is still controversy about the recommendation due to weaker evidence.
CODEINE Opioid Analgesics	**CYP2D6 - Intermediate metabolizer** **OPRM1 - Higher opioid sensitivity:** Reduced metabolism of codeine into its active metabolite morphine is predicted. This could lead to a reduction in analgesic response to codeine. Whilst this OPRM1 genotype has been associated with increased sensitivity to morphine and by extrapolation, to codeine as well, there is insufficient evidence for its clinical significance.	CPIC[18] provides a moderate recommendation to prescribe codeine according to usual label recommended age or weight specific dosing. Monitor for a reduced clinical response. If response is inadequate and 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 - Intermediate metabolizer:** Reduced 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[18] provide an optional recommendation to use tramadol according to usual label recommended age or weight specific dosing. If no response and opioid use is warranted, consider non-codeine opioid.
FLUVASTATIN Statins	**SLCO1B1 - Normal transporter function** **CYP2C9 - Intermediate metabolizer:** This SLCO1B1 genotype is associated with typical statin exposure and myopathy risk.[19] This CYP2C9 genotype predicts increased fluvastatin exposure as compared with normal metabolizers, which may translate to increased myopathy risk.[19] 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[19] provide a moderate recommendation to prescribe less than or equal to 40mg daily as a starting dose and adjust doses based on disease-specific guidelines. If doses >40mg are required for desired efficacy, consider an alternative statin or combination therapy (i.e. fluvastatin plus non-statin guideline directed medical therapy).

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ATOMOXETINE ADHD - miscellaneous agents	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure is predicted, although this is of questionable clinical significance. Adequate serum concentrations for the intended effect may not be achieved with standard dosing.	CPIC[20] provides a moderate recommendation for dosing in children and adults. Refer to CPIC guidelines for details. In summary, Adults: initiate at 40mg/day, increase to 80 mg/day after 3 days. After 2 weeks, consider increasing dose to 100 mg/day. If no clinical response after 2 weeks, consider use of peak plasma concentrations to guide titration. Children: initiate at 0.5mg/kg/day, increase to 1.2 mg/kg/day after 3 days. After 2 weeks, consider use of peak plasma concentrations to guide titration. Note: FDA-approved drug label[21] 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).
VILOXAZINE ADHD - miscellaneous agents	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and theoretically increased drug exposure is predicted.	No genotype-guided dosing recommendation available. Be alert to adverse effects.
IRBESARTAN Angiotensin receptor blockers	**CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism of irbesartan by CYP2C9 and slightly increased drug exposure are predicted. There is some evidence for an increased antihypertensive effect.	Standard dosing and prescribing measures apply.
PERHEXILINE Antianginals	**CYP2D6 - Intermediate metabolizer:** 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 reduced maintenance dose requirement is expected. Monitor closely for concentration-dependent adverse effects.
DARIFENACIN Anticholinergics (genitourinary)	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of adverse effects. Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase darifenacin exposure and the risk of adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
FESOTERODINE Anticholinergics (genitourinary)	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and theoretically increased drug exposure is predicted.	No genotype-guided dosing recommendation available. Be alert to adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
TOLTERODINE Anticholinergics (genitourinary)	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	No genotype-guided dosing recommendation is available. Monitor for adverse effects.
DONEPEZIL Anticholinesterases	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism via CYP2D6 and increased drug exposure are predicted. 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 - Intermediate metabolizer:** Reduced metabolism via CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	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.
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.[22] 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 - Intermediate metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Mirtazapine is metabolized by a number of enzymes, including CYP2D6 and CYP1A2. Reduced 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.[23]
VORTIOXETINE Antidepressants - other	**CYP2D6 - Intermediate metabolizer:** Reduced vortioxetine metabolism and increased drug exposure is predicted. This may increase the risk of adverse effects, although direct evidence is lacking.	No genotype-guided dosing recommendation available. Be alert for adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
DULOXETINE Antidepressants - SNRIs	**CYP2D6 - Intermediate metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Duloxetine is metabolized by both CYP1A2 and CYP2D6, with CYP1A2 likely to have the major role. Reduced duloxetine metabolism by CYP2D6 and increased metabolism by CYP1A2 in patients exposed to enzyme inducers (e.g. cigarette smoke) are predicted. The overall effect on duloxetine plasma concentrations and clinical response is difficult to predict.	No genotype-guided dosing recommendation available. Monitor for an altered clinical response.
FLUOXETINE Antidepressants - SSRIs	**CYP2D6 - Intermediate 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 inhibition of CYP2D6 by fluoxetine and its metabolites. 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. However, fluoxetine and its metabolites can strongly inhibit CYP2D6 function, potentially converting the phenotype to a poor metabolizer which can last for up to 9 weeks after cessation of fluoxetine (this is particularly relevant if commencing a drug extensively metabolized by CYP2D6 during this time). This CYP2D6 inhibition is dose and duration of therapy dependent and could potentially lead to late onset adverse effects on a previously tolerated fluoxetine dose.	Based on the CYP2D6 genotype, DPWG[24] recommends that no specific action on fluoxetine dosing is required for this genotype. 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 - Intermediate metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Fluvoxamine is metabolized by both CYP2D6 (predominant pathway) and CYP1A2. Reduced 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. Whilst difficult to predict, the exposure to fluvoxamine may 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[2] provides a moderate recommendation to initiate therapy with the recommended starting dose. DPWG [25] suggests no specific action on fluvoxamine dosing is required based on this CYP2D6 genotype.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
PAROXETINE Antidepressants - SSRIs	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism and increased paroxetine exposure are predicted. As paroxetine is a strong inhibitor of CYP2D6, the CYP2D6 function is expected to decrease further with ongoing therapy (so-called phenocopying). As a result of this, the metabolism of paroxetine (and other CYP2D6 substrate drugs) will be slower than is predicted by the genotype. There may be increased adverse effects.	CPIC[2] guidelines provide a moderate recommendation to initiate therapy with the recommended starting dose. It would also be reasonable to monitor closely for adverse effects.
SERTRALINE Antidepressants - SSRIs	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism when compared to extensive metabolizers is predicted.[2] However, the DPWG classifies this genetic result as having a minor influence on sertraline plasma concentration and no effect on side effects.[3]	CPIC guidelines[2] provide a strong recommendation to initiate therapy with the recommended starting dose. The DPWG guideline states that there is not enough evidence to recommend adjustment of therapy.[3]
AMOXAPINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer:** Slightly reduced metabolism of amoxapine by CYP2D6 is predicted which could theoretically lead to slightly increased amoxapine exposure, although direct evidence is lacking. The FDA notes that systemic concentrations may be altered with this genotype.[26]	No genotype-guided dosing recommendation available. Consider standard dosing. Monitor for adverse effects.
PROTRIPTYLINE Antidepressants - TCAs	**CYP2D6 - Intermediate metabolizer:** Slightly reduced metabolism of protriptyline by CYP2D6 is predicted which could theoretically lead to slightly increased amoxapine exposure, although direct evidence is lacking.	No genotype-guided dosing recommendation available. Consider standard dosing. Monitor for adverse effects.
GLIMEPIRIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism and increased drug exposure are predicted. This is unlikely to be clinically significant except with high dosages or if drug-drug interactions occur.	Standard dosing and prescribing measures apply. DPWG suggests that no specific action on glimepiride dosing is required with this genotype.[27]
GLYBURIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism and increased drug exposure are predicted. This is unlikely to be clinically significant except with high dosages or if drug-drug interactions occur.	Standard dosing and prescribing measures apply. DPWG suggests that no specific action on glyburide dosing is required with this genotype.[28]
METOCLOPRAMIDE Antiemetics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism of metoclopramide by CYP2D6 is predicted. There may be an increased risk of extrapyramidal adverse effects, particularly at higher doses.	No genotype-guided dosing recommendation available. Monitor for adverse effects.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ONDANSETRON Antiemetics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism via CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	CPIC[29] 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.
BRIVARACETAM Antiepileptics	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism by CYP2C19 and increased brivaracetam exposure are predicted. The FDA-approved drug label for brivaracetam note that intermediate metabolizers may have increased levels of brivaracetam.[30] There may be an increased risk of adverse effects.	No genotype-guided dosing recommendation available. The FDA-approved drug label for brivaracetam states that those using inhibitors of CYP2C19 may require dose reduction.[30] Monitor for adverse effects.
FOSPHENYTOIN Antiepileptics	**CYP2C9 - Intermediate metabolizer:** Fosphenytoin is a prodrug of phenytoin. Slightly reduced phenytoin metabolism and increased drug exposure are predicted. This genotype does not appear to be associated with an increased risk of adverse effects. [31]	Based on the CYP2C9 genotype, CPIC guidelines[31] provide a moderate recommendation that no adjustments are needed from typical dosing strategies; subsequent dose adjustments should be guided by therapeutic drug monitoring and clinical response. CPIC guidelines also address genetic testing for the presence of the HLA-B*15:02 allele (not currently tested by myDNA, but which may be requested through a local service if required) which is known to increase the risk of phenytoin-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. The guidelines state that if both HLA-B*15:02 and CYP2C9 genotypes are known, consider the HLA-B*15:02 genotype first, then CYP2C9 genotype. In the instance of an HLA-B*15:02 positive result, CPIC guidelines provide a strong recommendation to not use phenytoin/fosphenytoin in patients who have never had phenytoin before, and to also avoid carbamazepine and oxcarbazepine. Phenytoin may be used cautiously in patients who have tolerated the drug previously for longer than three months without occurrence of adverse skin reactions.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
PHENYTOIN Antiepileptics	**CYP2C9 - Intermediate metabolizer:** Slightly reduced phenytoin metabolism and increased drug exposure are predicted. This genotype does not appear to be associated with an increased risk of adverse effects. [31]	Based on the CYP2C9 genotype, CPIC guidelines[31] provide a moderate recommendation that no adjustments are needed from typical dosing strategies; subsequent dose adjustments should be guided by therapeutic drug monitoring and clinical response. CPIC also addresses genetic testing for the presence of the HLA-B*15:02 allele (not currently tested by myDNA, but which may be requested through a local service if required) which is known to increase the risk of phenytoin-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. The guidelines state that if both HLA-B*15:02 and CYP2C9 genotypes are known, consider the HLA-B*15:02 genotype first, then CYP2C9 genotype. In the instance of an HLA-B*15:02 positive result, CPIC provide a strong recommendation to not use phenytoin in patients who have never had phenytoin before, and to also avoid carbamazepine and oxcarbazepine. Phenytoin may be used cautiously in patients who have tolerated the drug previously for longer than three months without occurrence of adverse skin reactions.
VORICONAZOLE Antifungals - Azoles	**CYP2C19 - Intermediate metabolizer:** Reduced voriconazole metabolism and higher drug concentrations are predicted.	CPIC guidelines[32] provide a moderate recommendation to initiate therapy with the recommended standard of care dosing. DPWG guidelines[33] recommend monitoring of plasma concentrations.
CHLORPHENIRAMINE Antihistamines	**CYP2D6 - Intermediate 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 - Intermediate 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 - Intermediate 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ARIPIPRAZOLE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. Whilst the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole may be increased to a limited degree, there is insufficient evidence that this increases the risk of side effects.	Monitor for adverse effects. The DPWG[34] suggests that no specific action on aripiprazole dosing is required with this genotype.
ARIPIPRAZOLE LAUROXIL Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 is predicted, which could theoretically lead to an increased drug exposure, but there is insufficient evidence that this increases the risk of side effects.	Standard dosing and prescribing measures apply. Monitor for adverse effects. Aristada Initio®: The FDA-approved drug label[35] advises avoiding concomitant use of Aristada Initio with strong CYP3A4 or CYP2D6 inhibitors, or strong CYP3A4 inducers, due to inability for dose modification. Aristada®: If taking concomitant strong CYP3A4 or CYP2D6 inhibitor for more than 2 weeks, the FDA-approved drug label[36] advises reducing the dose of Aristada to the next lower strength; no dosage adjustment is necessary if tolerating 441 mg dose. If taking concomitant strong CYP3A4 and CYP2D6 inhibitors, avoid use of 662mg, 882mg or 1064 mg dose; no dosage adjustment is necessary if tolerating 441 mg dose. If taking concomitant CYP3A4 inducers for more than 2 weeks, increase the 441 mg dose to 662 mg; no dose adjustment for 662 mg, 882 mg or 1062 mg doses.
BREXPIPRAZOLE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	DPWG guidelines[37] suggest that no specific action on brexpiprazole dosing is required based on this genotype. Monitor for adverse effects.
CHLORPROMAZINE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism of chlorpromazine by CYP2D6 and slightly increased drug exposure are predicted. The clinical significance is not known, though an increase in adverse effects is possible.	No genotype-guided dosing recommendation available. Monitor for adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CLOZAPINE Antipsychotics	**CYP2D6 - Intermediate metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Based on the CYP1A2 genotype, increased metabolism of clozapine 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 CYP1A2 genotype has also been associated with a reduced clinical response to clozapine, which is more marked in smokers.[38] Based on the CYP2D6 genotype, reduced metabolism and increased drug exposure are predicted. The clinical significance of this is uncertain.	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.[39]
HALOPERIDOL Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	Monitor for adverse effects. The DPWG[40] suggests that no specific action on haloperidol dosing is required with this genotype.
ILOPERIDONE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism of iloperidone by CYP2D6 is predicted which could lead to increased drug exposure.	No genotype-guided dosing recommendation available. Consider standard dosing. Monitor for adverse effects.
OLANZAPINE Antipsychotics	**CYP1A2 - Ultrarapid metabolizer (with inducer present):** Increased metabolism of olanzapine 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.	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.[39]
PERPHENAZINE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism of perphenazine by CYP2D6 is predicted which could lead to increased perphenazine exposure.	No genotype-guided dosing recommendation available. Consider standard dosing. Monitor for adverse effects.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
RISPERIDONE Antipsychotics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism and increased drug exposure are predicted. This may increase the risk of adverse effects, although there is little evidence to suggest that this is clinically significant. This genetic variation may lead to a decrease in the required maintenance dose.	The DPWG[41] suggests that no specific action on risperidone dosing is required with this genetic result, as the effects on dose may be within the range of normal biological variation. It would be reasonable to be alert to adverse effects and adjust dose according to clinical response.
DEXTROMETHORPHAN Antitussives	**CYP2D6 - Intermediate metabolizer:** 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.
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 - Intermediate 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. Reduced metabolism of clobazam's active metabolite and a possible increase in clinical effects is predicted. (Note that the effect of variations in CYP3A4 has not been described).	No genotype-guided dosing recommendation available. Be alert to increased clinical effects.
DIAZEPAM Benzodiazepines	**CYP2C19 - Intermediate metabolizer:** Diazepam is metabolized by CYP3A4 and CYP2C19 into active metabolites, including desmethyldiazepam, which has a long half-life. The CYP2C19 genotype predicts reduced metabolism of both diazepam and desmethyldiazepam, increased plasma concentrations and possibly increased clinical effects (including prolonged sedation). (Note that the effect of variations in the CYP3A4 gene on diazepam metabolism have not been described).	If excessive clinical effects (e.g. sedation) are problematic, consider reducing the dose or prescribing an alternative benzodiazepine not extensively metabolized by CYP2C19, such as oxazepam or lorazepam.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CARVEDILOL Beta blockers	**CYP2D6 - Intermediate metabolizer:** Reduced 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.	DPWG[42] suggests that no specific action on carvedilol dosing is required based on this genotype. Monitor for adverse effects.
METOPROLOL Beta blockers	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug 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[43] has recommendations to increase the dose in smaller steps and/or prescribe no more than 50% of the standard dose. If currently well tolerated and clinical response has been adequate, a change to therapy may not be required.
PROPRANOLOL Beta blockers	**CYP2D6 - Intermediate metabolizer** **CYP1A2 - Ultrarapid metabolizer (with inducer present):** Propranolol is metabolized by both CYP2D6 and CYP1A2 and also has an active metabolite. This genotype predicts reduced 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.	No genotype-guided dosing guideline available. Monitor for altered clinical effect.
TIMOLOL Beta blockers	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased systemic drug exposure are predicted. This could theoretically lead to increased clinical effects, however evidence for this is lacking.	Monitor for systemic beta blocker adverse effects such as bradycardia and bronchospasm.
PITOLISANT Drugs for anxiety and sleep disorders	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and theoretically increased drug exposure is predicted.	No genotype-guided dosing recommendation available. Be alert to adverse effects.
GEFITINIB Immunomodulators and antineoplastics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 is predicted, which could theoretically lead to increased drug exposure. This could increase the risk of adverse effects.	Standard dosing and prescribing measures apply. Monitor for adverse effects and adjust therapy accordingly. The DPWG[44] suggests that no specific action on gefitinib dosing is required with this genetic result.
AVATROMBOPAG Miscellaneous	**CYP2C9 - Intermediate metabolizer:** There may be slightly reduced metabolism by CYP2C9 and thus slightly increased exposure to avatrombopag.	For treatment of chronic immune thrombocytopenia, the FDA-approved drug label[45] 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CEVIMELINE Miscellaneous	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 is predicted, which could theoretically lead to an increased drug exposure. This could increase the risk of adverse effects.	No genotype-guided dosing recommendation available. Standard dosing and prescribing measures apply. Monitor for adverse effects.
CYCLOPHOSPHAMIDE Miscellaneous	**CYP2C19 - Intermediate metabolizer:** Reduced formation of cyclophosphamide's active metabolite by CYP2C19 is predicted. This may be associated with reduced clinical effects (therapeutic and/or adverse)	No genotype-guided dosing recommendation available.
DRONABINOL Miscellaneous	**CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism of dronabinol by CYP2C9 and slightly increased drug exposure are predicted.	Standard dosing and prescribing measures apply.
ELIGLUSTAT Miscellaneous	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism of eliglustat and increased drug exposure are predicted. This may increase the risk of adverse effects. However, in the absence of CYP2D6 and CYP3A4 inhibitors, this does not result in a clinically significant increased risk of side effects.[46]	The recommended dose of eliglustat depends on whether CYP3A4 and/or CYP2D6 inhibiting medications are co-prescribed. Refer to DPWG guidelines,[46] FDA-approved drug label[47] or TGA-approved product information[48] for prescribing details.
FLIBANSERIN Miscellaneous	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism by CYP2C19 and increased flibanserin exposure is predicted. There may be an increased risk of adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
LOFEXIDINE Miscellaneous	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 is predicted, which could theoretically lead to increased drug exposure. This could increase the risk of adverse effects.	No genotype-guided dosing recommendation available. Standard dosing and prescribing measures apply. Monitor for adverse effects.
MECLIZINE Miscellaneous	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 is predicted, which could theoretically lead to increased drug exposure. This could increase the risk of adverse effects.	No genotype-guided dosing recommendation available. The FDA-approved drug label[49] 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 - Intermediate metabolizer:** Reduced metabolism of proguanil into its active metabolite cycloguanil is predicted. The clinical significance is not known for sure, though a reduced clinical response would be possible.	No genotype-guided dosing recommendation available.
TAMSULOSIN Miscellaneous	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may could potentially increase the risk of concentration-dependent adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CARISOPRODOL Neurological drugs	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism by CYP2C19 and increased carisoprodol exposure is possible. The clinical significance of this is not known, although there may be an increased risk of adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
DEUTETRABENAZINE Neurological drugs	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism of deutetrabenazine by CYP2D6 is predicted which could theoretically lead to increased drug exposure, although direct evidence is lacking.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
TETRABENAZINE Neurological drugs	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA[50] approved drug label advises a maximum daily dose of 100mg, with a maximum recommended single dose of 37.5mg.
VALBENAZINE Neurological drugs	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism of valbenazine by CYP2D6 is predicted which could theoretically lead to increased drug exposure, although direct evidence is lacking.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
CELECOXIB NSAIDs	**CYP2C9 - Intermediate metabolizer:** There may be mildly reduced metabolism and increased celecoxib exposure.[51] This is more likely to be clinically significant if high doses are used or drug-drug interactions occur.	CPIC guidelines[52] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
FLURBIPROFEN NSAIDs	**CYP2C9 - Intermediate metabolizer:** Mildly reduced metabolism by CYP2C9 and increased drug exposure are predicted. This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[52] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
IBUPROFEN NSAIDs	**CYP2C9 - Intermediate metabolizer:** Mildly reduced metabolism by CYP2C9 and increased drug exposure are predicted[53]. This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[52] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
LORNOXICAM NSAIDs	**CYP2C9 - Intermediate metabolizer:** Mildly reduced metabolism by CYP2C9 and increased drug exposure are predicted. This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[52] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.

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MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
MELOXICAM NSAIDs	**CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism by CYP2C9 and increased drug exposure are predicted.[54] This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[52] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
PIROXICAM NSAIDs	**CYP2C9 - Intermediate metabolizer:** Mildly reduced metabolism by CYP2C9 and increased drug exposure are predicted.[53] This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[52] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
HYDROCODONE Opioid Analgesics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 could lead to an increase in hydrocodone exposure and a reduction in exposure to the active metabolite, hydromorphone, thereby potentially reducing the analgesic response. However, there is minimal evidence for this pharmacokinetic or clinical effect.	CPIC [18] 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. This is more likely to be significant with high dosages or if drug-drug interactions occur.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
OLICERIDINE Opioid Analgesics	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and theoretically increased drug exposure is predicted.	No genotype-guided dosing recommendation available. Be alert to adverse effects.
OXYCODONE Opioid Analgesics	**CYP2D6 - Intermediate metabolizer:** Reduced exposure to oxycodone's active metabolite, oxymorphone, is predicted. Although this could potentially lead to reduced analgesia, there is limited evidence to suggest that this is clinically significant.	DPWG[55] suggest that no specific action on oxycodone dosing is required. Be alert to a reduced analgesic response.
DEXLANSOPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metabolizer:** This genotype predicts reduced metabolism and increased plasma concentrations of dexlansoprazole[56]. It may enhance gastric acid suppression and clinical response, as well potentially increased toxicity compared to normal metabolizers.	CPIC guidelines have an optional recommendation to initiate a standard starting daily dose. For chronic therapy (>12 weeks) where efficacy is achieved, consider a 50% reduction in daily dose and monitor for continued efficacy.[57]

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
LANSOPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metabolizer:** This genotype predicts reduced metabolism and increased plasma concentrations of lansoprazole. It also predicts enhanced gastric acid suppression and improved healing of oesophagitis and H. pylori eradication, as well potentially increased toxicity compared to normal metabolizers.	CPIC guidelines have an optional recommendation to initiate a standard starting daily dose. For chronic therapy (>12 weeks) where efficacy is achieved, consider a 50% reduction in daily dose and monitor for continued efficacy.[57]
OMEPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metabolizer:** This genotype predicts reduced metabolism and increased plasma concentrations of omeprazole. It also predicts enhanced gastric acid suppression and improved healing of oesophagitis and H. pylori eradication, as well potentially increased toxicity compared to normal metabolizers.	CPIC guidelines have an optional recommendation to initiate a standard starting daily dose. For chronic therapy (>12 weeks) where efficacy is achieved, consider a 50% reduction in daily dose and monitor for continued efficacy.[57]
PANTOPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metabolizer:** This genotype predicts reduced metabolism and increased plasma concentrations of pantoprazole. It also predicts enhanced gastric acid suppression and improved healing of oesophagitis and H. pylori eradication, as well potentially increased toxicity compared to normal metabolizers.	CPIC guidelines have an optional recommendation to initiate a standard starting daily dose. For chronic therapy (>12 weeks) where efficacy is achieved, consider a 50% reduction in daily dose and monitor for continued efficacy.[57]
RABEPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metabolizer:** This genotype predicts reduced metabolism of rabeprazole by CYP2C19 and increased plasma concentrations. However, there is insufficient evidence to support a significant effect on therapeutic effectiveness or side effects.	The DPWG suggests that no specific action on rabeprazole dosing is required with this genotype.[58]
AMPHETAMINE Psychostimulants	**CYP2D6 - Intermediate 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.[59]. Whilst this could potentially increase drug exposure, the clinical significance of this has not yet been established.	No genotype-guided dosing recommendation available. Consider standard dosing. It would be reasonable to monitor for adverse effects.
DEXTROAMPHETAMINE Psychostimulants	**CYP2D6 - Intermediate metabolizer:** Dextroamphetamine is eliminated by both the kidney (as unchanged drug) and the liver, with CYP2D6 playing a significant role. Reduced metabolism via CYP2D6 and increased dextroamphetamine exposure is predicted, however the clinical significance of this has not yet been established.	No genotype-guided dosing recommendation available. It would be reasonable to monitor for adverse effects.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
LISDEXAMFETAMINE Psychostimulants	**CYP2D6 - Intermediate 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. Reduced metabolism via CYP2D6 and increased dextroamphetamine exposure is predicted, however the clinical significance of this has not yet been established.	No genotype-guided dosing recommendation available. It would be reasonable to monitor for adverse effects.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
GLIPIZIDE Antidiabetics	**CYP2C9 - Intermediate metabolizer:** Slightly reduced metabolism and increased drug exposure are predicted. This is unlikely to be clinically significant except with high dosages or if drug-drug interactions occur.	No genotype guided dosing recommendation available. Standard dosing and prescribing measures apply.
LACOSAMIDE Antiepileptics	**CYP2C19 - Intermediate metabolizer:** Reduced metabolism by CYP2C19 and increased lacosamide exposure is possible. The clinical significance of this is not known, although this could potentially increase the risk of concentration-dependent adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
QUETIAPINE Antipsychotics	**CYP3A4 - Normal metabolizer:** Normal metabolism of quetiapine is predicted.	Standard dosing and prescribing measures apply.
NEBIVOLOL Beta blockers	**CYP2D6 - Intermediate metabolizer:** Reduced nebivolol metabolism by CYP2D6 and increased drug exposure are predicted. However, this has not been convincingly linked to increased beta blocking effects.	No genotype-guided dosing recommendation is available. 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 genotype 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[60] 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.[60]
NALTREXONE Drugs for alcohol dependence	**OPRM1 - Higher 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 AA genotype may be associated with a reduced response to naltrexone (compared to patients with the AG or GG genotype) in the management of alcohol use disorder in a few studies, however in other studies and a recent meta-analysis, this was not observed.[61]	CPIC guidelines[18] state that there is insufficient evidence to provide a recommendation for naltrexone dosing based on OPRM1 genotype. It would be reasonable to monitor for a reduced clinical response and appropriate modifications to therapy if required.
ELAGOLIX Endocrine drugs	**SLCO1B1 - Normal transporter function:** The SLCO1B1 C variant was not detected.	Standard dosing and prescribing measures apply.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
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).[62] 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:** There may be slightly reduced metabolism by CYP2C9, however no increase in drug exposure was observed compared with the normal genotype.[63]	No genotype-guided dosing recommendation available. Standard dosing and prescribing measures apply.
ATAZANAVIR Miscellaneous	**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 genotype 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.	Usual prescribing considerations apply.
MIRABEGRON Miscellaneous	**CYP2D6 - Intermediate metabolizer:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may could potentially increase the risk of concentration-dependent adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
SIPONIMOD Neurological drugs	**CYP2C9 - Intermediate metabolizer:** There may be slightly reduced metabolism and thus slightly increased exposure to siponimod. However this is unlikely to be clinically significant.	DPWG[64] suggests that no specific action on siponimod dosing is required for the CYP2C9 *1/*2 genotype. The FDA-approved drug label[65] states that in patients with the CYP2C9 *1/*2 genotype, treatment initiation should be with a 5-day titration using the starter pack, starting at 0.25 mg daily and gradually increasing until the maintenance dose of 2 mg on Day 6 of treatment. It would be reasonable to apply this recommendation to patients with a comparable genetic variation.
DICLOFENAC NSAIDs	**CYP2C9 - Intermediate metabolizer:** Diclofenac is only partially metabolized by CYP2C9. This genotype is not expected to increase diclofenac exposure significantly[66].	CPIC guidelines[52] state that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.
INDOMETHACIN NSAIDs	**CYP2C9 - Intermediate metabolizer:** Indomethacin is only partially metabolized by CYP2C9. This genotype is not expected to increase indomethacin exposure significantly.[67]	CPIC guidelines[52] state 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
MEFENAMIC ACID NSAIDs	**CYP2C9 - Intermediate metabolizer:** Mefenamic acid is metabolized by CYP2C9.[68] This genotype predicts a small increase in mefenamic acid exposure.	Standard dosing and prescribing measures apply.
MORPHINE Opioid Analgesics	**OPRM1 - Higher opioid sensitivity** **COMT - Higher opioid sensitivity:** OPRM1 - Whilst the AA genotype has been associated with increased sensitivity to morphine (including reduced morphine consumption, lower pain scores, and a higher rate of nausea) 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. There is some limited data indicating that individuals with the combination of OPRM1 A and COMT A alleles may require a smaller dose of morphine than individuals with other genotype combinations, however not all studies suggest this.	CPIC[18] states that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply. It may be reasonable to consider the possibility of increased clinical effects during dose titration.
ESOMEPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metabolizer:** This genotype predicts reduced metabolism of esomeprazole by CYP2C19, and increased plasma concentrations. However, there is insufficient evidence to support a significant effect on therapeutic effectiveness or side effects.	The DPWG suggests that no specific action on esomeprazole dosing is required with this genotype.[4]
ATORVASTATIN Statins	**SLCO1B1 - Normal transporter function:** The SLCO1B1 genotype is associated with typical atorvastatin exposure and myopathy risk.[19] Other factors that may 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[19] provide a strong recommendation to use the desired starting dose and adjust doses based on disease-specific guidelines.
LOVASTATIN Statins	**SLCO1B1 - Normal transporter function:** This SLCO1B1 genotype is associated with a typical myopathy risk and statin exposure.[19] Other factors that may 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[19] provide a strong recommendation to use the desired starting dose and adjust doses based on disease-specific guidelines.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
PITAVASTATIN Statins	**SLCO1B1 - Normal transporter function:** This SLCO1B1 genotype is associated with a typical myopathy risk and statin exposure.[19] Other factors that may 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[19] provide a strong recommendation to prescribe the desired starting dose and adjust doses based on disease-specific guidelines.
PRAVASTATIN Statins	**SLCO1B1 - Normal transporter function:** This SLCO1B1 genotype is associated with a typical myopathy risk and statin exposure.[19] Other factors that may increase this myopathy risk include: the choice of statin being prescribed, 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[19] provide a strong recommendation to use the desired starting dose and adjust doses based on disease-specific guidelines.
ROSUVASTATIN Statins	**SLCO1B1 - Normal transporter function:** This SLCO1B1 genotype is associated with a typical myopathy risk and statin exposure. Other factors that may 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[19] provide a strong recommendation to prescribe the desired starting dose and adjust dose based on disease-specific guidelines.
SIMVASTATIN Statins	**SLCO1B1 - Normal transporter function:** This SLCO1B1 genotype is associated with typical statin exposure and myopathy risk.[19] Other factors that may 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[19] provide a strong recommendation to use the desired starting dose and adjust doses based on disease-specific guidelines.

DETAILED PHARMACOGENOMIC TEST RESULTS

GENE	GENOTYPE	PREDICTED PHENOTYPE
COMT	AA	**Higher opioid sensitivity:** The AA genotype contains two variant alleles for the COMT gene, which encodes the COMT enzyme that metabolizes catecholamines. Individuals with the AA genotype treated with opioids for pain may have an increased response and a lower dose requirement, compared to those with AG or GG genotypes. Contradictory studies exist for this association. A patient's opioid dosage and response is also influenced by other genetic and clinical factors.
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:** Due to the presence of one normal functioning allele and one reduced or non-functioning allele, this individual is predicted to have 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/*2	**Intermediate metabolizer:** Due to the presence of one normal function allele and one no function allele, this individual is predicted to have an intermediate metabolizer phenotype. For a drug extensively metabolized by CYP2C19, 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).
CYP2C9	*1/*2	**Intermediate metabolizer:** Due to the presence of one normal function allele and one decreased function 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). As the decreased function allele is associated with only a small reduction in enzyme function, this variation may only be significant for certain medications, with high dosages or if drug-drug interactions occur.
CYP2D6	*1/*4	**Intermediate metabolizer:** Due to the presence of one normal function allele and one no function allele, this individual is predicted to have an intermediate metabolizer phenotype. For a drug extensively metabolized by CYP2D6, drug exposure and clinical effects may either be increased (for an active drug) or 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.
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 genotype is the most common one amongst Caucasians.

GENE	GENOTYPE	PREDICTED PHENOTYPE
OPRM1	AA	**Higher opioid sensitivity:** The AA genotype contains two normal alleles for the OPRM1 gene which encodes the mu opioid receptor. Whilst the evidence around OPRM1 genetic variation continues to develop, it appears that this result is associated with increased sensitivity to certain opioids (in particular, morphine) compared to those with the variant allele (G). These findings are supported by a number of cohort studies and at least two meta-analyses[69],[70] however, this is not shown in all studies. For naltrexone in the management of alcohol use disorder, some studies have shown an association of this result with a reduced response compared to those with the variant allele. Note the frequency of the variant allele (G) is higher in people of Asian ancestry (around 40%) than European ancestry (around 15%).
SLCO1B1	*1/*1	**Normal transporter function:** The decreased function *5 allele is not present and this individual is predicted to have normal function of the *SLCO1B1* encoded transporter. The transporter is important for the clearance of certain drugs, including simvastatin.
VKORC1	AG	**Moderately reduced VKORC1 enzyme level:** The VKORC1 enzyme is predicted to be present in moderately reduced amounts and the response to warfarin will be enhanced. The *CYP2C9* genotype should also be considered together with the *VKORC1* genotype for calculating the initial warfarin dose.

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SPEAK TO OUR SPECIALISTS

As part of our clinical service, we have a team of clinical experts available to answer any questions you may have about this report or about pharmacogenomics in general. If you have any such queries, please contact us at clinical@mydna.life

Electronic Signature:

This report has been prepared by the myDNA Clinical Team

Laboratory Results provided by:

Gene by Gene Ltd in a CAP and CLIA accredited laboratory (CAP Number 7212851, CLIA Number 45D1102202).

1445 North Loop West, Suite 800 Houston, TX 77008

Dr. Rachel Beddard, MD, Medical Director

DISCLAIMER

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

Clinical monitoring should occur for all psychotropic medications. It is not intended to imply that drugs listed in this report are approved for certain indications or that they have comparable efficacy or safety. Note that prescribing of propranolol, oxcarbazepine or other listed medications for psychiatric conditions may be considered off-label and approved drug labels should be consulted for guidance regarding their use.

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

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

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

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

TEST METHODOLOGY AND LIMITATIONS

Gene by Gene is a College of American Pathologists (CAP) accredited and Clinical Laboratory Improvement Amendments (CLIA) certified clinical laboratory (accredited lab No 45D1102202) qualified to perform high-complexity testing. This test is comprised of the Veridose Core and Veridose CYP2D6 CNV panels developed by Agena, and its performance characteristics have been determined by Gene by Gene. It has not been cleared or approved by the FDA. FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. The genomic regions listed in this report were tested using the Agena MassARRAY® System; there is a possibility that the tested individual is a carrier for additional, undetected variants that may affect results. Although molecular tests are highly accurate, rare diagnostic errors may occur that interfere with analysis. Sources of these errors include sample mix-up, trace contamination, and other technical errors. The presence of additional variants nearby may interfere with variant detection. Genetic counseling is recommended to properly review and explain these results to the tested individual. Response to medications is complex and may also be influenced by factors which are not tested for (e.g. patient adherence to prescription regimen, concurrent illness, drug-drug interactions). The test only determines details of response to medications listed by the health professional. Allergic reactions cannot be detected by this genetic test. The test does not detect all known variants in the genes tested. If an individual carries a rare variant not covered by the test, the phenotype may be inaccurately reported. Unless instructed by their doctor, patients are advised not to alter the dose or stop any medications. The interpretation and clinical recommendations are based on the above results as reported by Gene by Gene and also uses information provided to myDNA Life Inc. by the referring healthcare professionals. This report also assumes correct labelling of sample tubes and that the sample is from the indicated patient.

TEST PANEL OF GENES AND VARIANTS

The 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: 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]); OPRM1 - rs1799971 NM_000914.4:c.118A>G; SLCO1B1 - rs4149056 NM_006446.4:c.521T>C and VKORC1 - rs9923231 NM_024006.5:c.-1639G>A.