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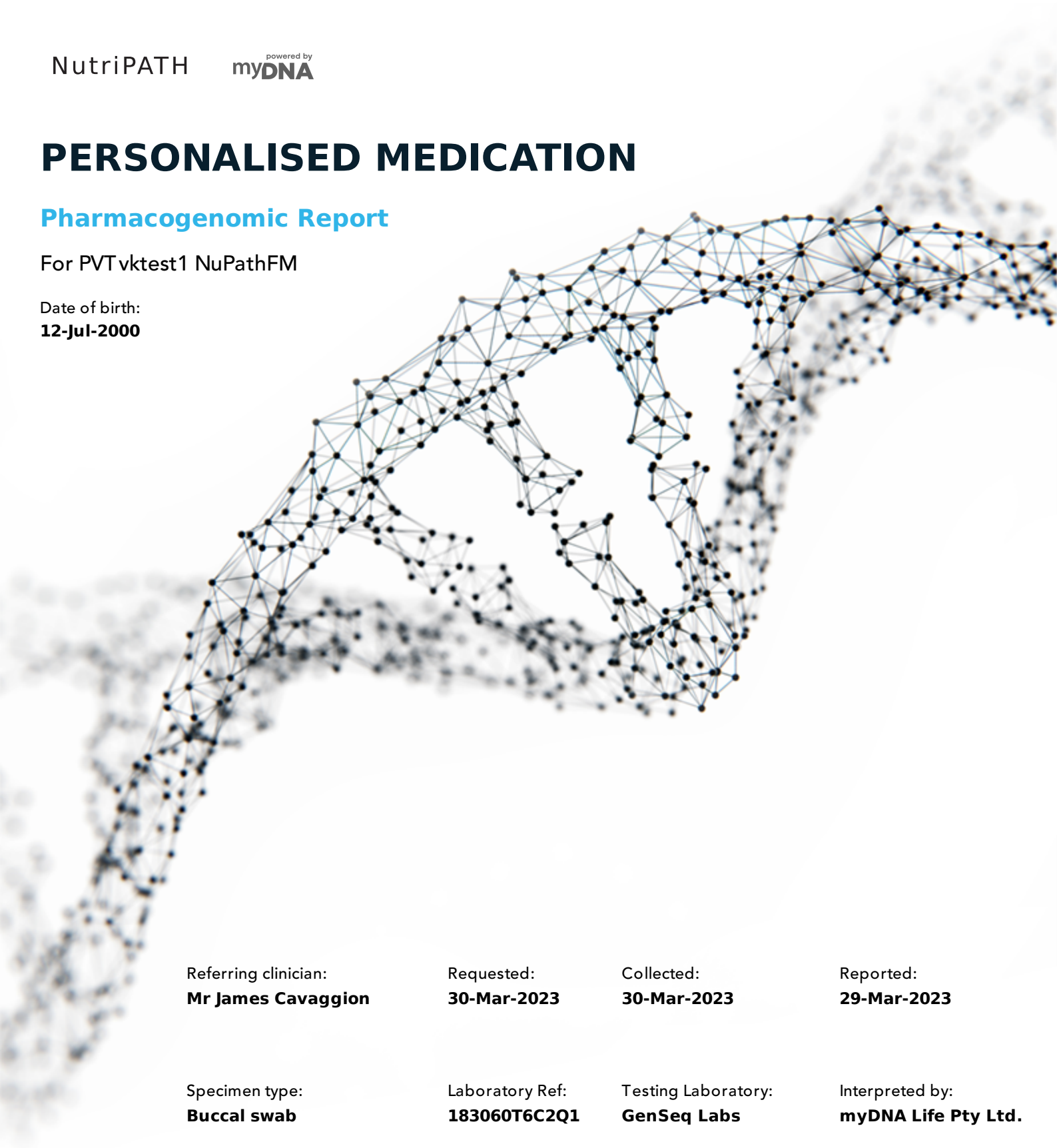
PERSONALISED MEDICATION

Pharmacogenomic Report

For PVTvktest1 NuPathFM

Date of birth:
12-Jul-2000



Referring clinician:	Requested:	Collected:	Reported:
Mr James Cavaggion	**30-Mar-2023**	**30-Mar-2023**	**29-Mar-2023**
Specimen type:	Laboratory Ref:	Testing Laboratory:	Interpreted by:
Buccal swab	**183060T6C2Q1**	**GenSeq Labs**	**myDNA Life Pty Ltd.**

ABOUT THIS REPORT

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

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

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

MAJOR PRESCRIBING CONSIDERATIONS

A potentially significant effect on drug response is predicted. There may be guidelines or a drug label recommending consideration be given to a change in the dose, the medication type, or further monitoring in order to minimize the risk of the potential clinical issue noted.
Of note, "Major" prescribing considerations do not always preclude the use of a specific medication or necessitate a dosage change if the drug is currently effective and well tolerated, this will be dependent on the individual gene-drug interaction and the clinical circumstances.

MINOR PRESCRIBING CONSIDERATIONS

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

USUAL PRESCRIBING CONSIDERATIONS

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

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

PHARMACOGENOMIC GUIDELINES

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

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

REPORT BREAKDOWN

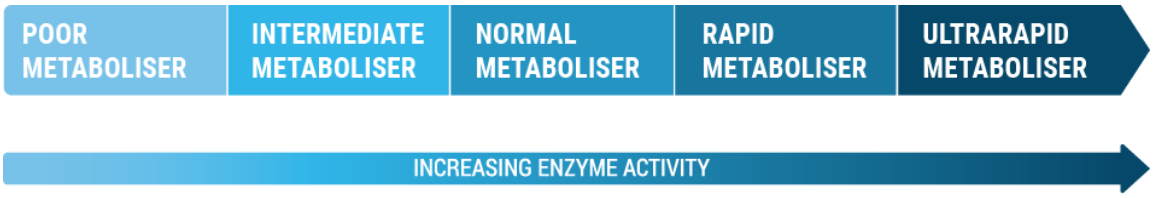
The report consists of the following 6 sections:

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

PHARMACOGENOMIC TEST RESULTS SUMMARY

GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP1A2	*1F/*1F	**Ultrarapid metaboliser (with inducer present)**
CYP2C19	*1/*2	**Intermediate metaboliser**
CYP2C9	*1/*1	**Normal metaboliser**
CYP2D6	*4/*41	**Intermediate metaboliser**
CYP3A4	*1/*1	**Normal metaboliser**
CYP3A5	*3/*3	**Poor metaboliser**
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
TOBACCO SMOKE			CYP1A2

PERSONALISED MEDICATION GUIDE

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

Legend

Consider alternative medication ⚠ | Major prescribing consideration | Minor prescribing consideration | Usual prescribing consideration

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

CLASS	MAJOR	MINOR	USUAL
Antiemetics		Metoclopramide Ondansetron Tropisetron	
Antiepileptics			Fosphenytoin Phenytoin
Antifungals - Azoles		Voriconazole	
Antihistamines		Chlorpheniramine Dexchlorpheniramine Promethazine	
Antiplatelet drugs	Clopidogrel ⚠		
Antipsychotics	Zuclopenthixol ⚠	Aripiprazole Brexpiprazole Chlorpromazine Clozapine Haloperidol Olanzapine Risperidone	Flupenthixol Quetiapine
Antitussives		Dextromethorphan	
Benzodiazepines		Clobazam Diazepam	
Beta blockers		Carvedilol Metoprolol Propranolol Timolol	Nebivolol
Calcineurin inhibitors			Tacrolimus
Drugs for alcohol dependence			Naltrexone
Drugs for sexual dysfunction		Dapoxetine	
Hypnotics			Melatonin
Immunomodulators and antineoplastics	Tamoxifen ⚠	Gefitinib	
Miscellaneous		Cyclophosphamide Eliglustat Proguanil Tamsulosin	Atazanavir
Neurological drugs		Tetrabenazine	Siponimod

CLASS	MAJOR	MINOR	USUAL
NSAIDs			Celecoxib Diclofenac Ibuprofen Indomethacin Mefenamic Acid Meloxicam Piroxicam
Opioid Analgesics	Codeine Tramadol	Oxycodone	Morphine
Proton pump inhibitors		Lansoprazole Omeprazole Pantoprazole Rabeprazole	Esomeprazole
Psychostimulants		Dexamphetamine Lisdexamfetamine	
Statins			Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin

PERSONALISED PRESCRIBING CONSIDERATIONS

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

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
FLECAINIDE Antiarrhythmics	**CYP2D6 - Intermediate metaboliser:** 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[1] 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.
VENLAFAXINE Antidepressants - SNRIs ⚠	**CYP2D6 - Intermediate metaboliser:** 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[2] 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 metaboliser:** 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[3] 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.[4]
ESCITALOPRAM Antidepressants - SSRIs	**CYP2C19 - Intermediate metaboliser:** 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[3] 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.[4]
AMITRIPTYLINE Antidepressants - TCAs	**CYP2D6 - Intermediate metaboliser** **CYP2C19 - Intermediate metaboliser:** Amitriptyline is metabolised by CYP2C19 into an active metabolite, which is further metabolised 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[5] 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.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CLOMIPRAMINE Antidepressants - TCAs	**CYP2D6 - Intermediate metaboliser** **CYP2C19 - Intermediate metaboliser:** Clomipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Reduced metabolism of both clomipramine and its active metabolite are predicted.	CPIC[5] 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.
DOSULEPIN Antidepressants - TCAs	**CYP2D6 - Intermediate metaboliser** **CYP2C19 - Intermediate metaboliser:** Dosulepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Reduced metabolism of both Dosulepin and its active metabolite are predicted.	CPIC[5] 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 metaboliser** **CYP2C19 - Intermediate metaboliser:** Doxepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Reduced metabolism of both doxepin and its active metabolite are predicted.	CPIC[5] 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 metaboliser** **CYP2C19 - Intermediate metaboliser:** Imipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised 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[5] 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 metaboliser:** 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[5] 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.
CLOPIDOGREL Antiplatelet drugs ⚠	**CYP2C19 - Intermediate metaboliser:** 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.[6]	For management of acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI), CPIC guidelines[6] 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[6] 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.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ZUCLOPENTHIXOL Antipsychotics ⚠	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism and increased drug exposure are predicted. This may increase the risk of adverse effects.	The DPWG[7] advises starting with 75% of the standard dose or selecting an alternative drug according to current guidelines.
TAMOXIFEN Immunomodulators and antineoplastics ⚠	**CYP2D6 - Intermediate metaboliser:** Reduced formation of tamoxifen's active metabolite endoxifen by CYP2D6 is predicted. There is conflicting evidence on the effect of this genotype on cancer outcomes. Some studies have shown an increased risk of disease recurrence, 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[8] 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 (e.g. 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 metaboliser** **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.	Based on the CYP2D6 genotype CPIC[9] 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. DPWG [10] provides a recommendation to be alert to possible reduced analgesic effects. In the case of reduced effectiveness, increase the dose or choose a non-tramadol alternative. There is no additional genotype-guided dosing recommendation based on the OPRM1 result.
TRAMADOL Opioid Analgesics	**CYP2D6 - Intermediate metaboliser:** 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[9] 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. DPWG guidelines[10] provide a recommendation to be alert to possible reduced analgesic effects. In the case of reduced effectiveness, increase the dose or choose a non-codeine alternative.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
ATOMOXETINE ADHD - miscellaneous agents	**CYP2D6 - Intermediate metaboliser:** 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[11] 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[12] 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).
PERHEXILINE Antianginals	**CYP2D6 - Intermediate metaboliser:** 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 metaboliser:** 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.
TOLTERODINE Anticholinergics (genitourinary)	**CYP2D6 - Intermediate metaboliser:** 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 metaboliser:** 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 metaboliser:** 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
WARFARIN Anticoagulants	**VKORC1 - Moderately reduced VKORC1 enzyme level** **CYP2C9 - Normal metaboliser:** Normal 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 (e.g. more than 5 doses), dose adjustment is guided by INR. For patients initiating warfarin, there are CPIC[13] recommendations to reach the therapeutic dose. The summary of CPIC recommendations include consideration of the use of validated published pharmacogenetic algorithms[14],[15] 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.
AGOMELATINE Antidepressants - other	**CYP1A2 - Ultrarapid metaboliser (with inducer present):** Increased agomelatine metabolism and reduced plasma concentrations are predicted[16], [17]. This effect is expected to be enhanced with exposure to enzyme inducers such as tobacco smoking, daily consumption of cruciferous vegetables or chargrilled meat, and certain medications (e.g. omeprazole). The clinical significance of this has not yet been established.	No genotype-guided dosing recommendation available. It would be reasonable to monitor for an adequate clinical response.
MIANSERIN Antidepressants - other	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This could potentially increase the risk of adverse effects.	No genotype guided dosing recommendation is available. Be alert for adverse effects.
MIRTAZAPINE Antidepressants - other	**CYP2D6 - Intermediate metaboliser** **CYP1A2 - Ultrarapid metaboliser (with inducer present):** Mirtazapine is metabolised 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.[18]
MOCLOBEMIDE Antidepressants - other	**CYP2C19 - Intermediate metaboliser:** Reduced metabolism by CYP2C19 and increased moclobemide exposure are predicted. There may be an increased risk of adverse effects.	DPWG[19] suggests that no specific action on moclobemide dosing is required with this genotype. Monitor for adverse effects.
VORTIOXETINE Antidepressants - other	**CYP2D6 - Intermediate metaboliser:** 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 metaboliser** **CYP1A2 - Ultrarapid metaboliser (with inducer present):** Duloxetine is metabolised 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 metaboliser** **CYP2C9 - Normal metaboliser:** The metabolism of fluoxetine is complex due to the involvement of several CYP enzymes (especially CYP2D6 and CYP2C9), the formation of active metabolites and the 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 normal metabolism via this pathway. However, fluoxetine and its metabolites can strongly inhibit CYP2D6 function, potentially converting the phenotype to a poor metaboliser which can last for up to 9 weeks after cessation of fluoxetine (this is particularly relevant if commencing a drug extensively metabolised 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[20] 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 metaboliser** **CYP1A2 - Ultrarapid metaboliser (with inducer present):** Fluvoxamine is metabolised 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[3] provides a moderate recommendation to initiate therapy with the recommended starting dose. DPWG [21] 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 metaboliser:** 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[3] 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 metaboliser:** Reduced metabolism when compared to extensive metabolisers is predicted.[3] However, the DPWG classifies this genetic result as having a minor influence on sertraline plasma concentration and no effect on side effects.[4]	CPIC guidelines[3] 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.[4]
GLICLAZIDE Antidiabetics	**CYP2C9 - Normal metaboliser** **CYP2C19 - Intermediate metaboliser:** This CYP2C9 genotype has been linked to a normal clinical response to gliclazide. This CYP2C19 genotype predicts increased drug plasma concentrations. The overall effect of both genotypes is not known for sure, although an enhanced clinical response would be plausible (e.g. hypoglycaemia, better reduction in HbA1c).	No genotype-guided dosing recommendation available. Monitor for adverse effects.
METOCLOPRAMIDE Antiemetics	**CYP2D6 - Intermediate metaboliser:** 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.
ONDANSETRON Antiemetics	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism via CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	CPIC[22] 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.
TROPISETRON Antiemetics	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism via CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	CPIC[22] 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.
VORICONAZOLE Antifungals - Azoles	**CYP2C19 - Intermediate metaboliser:** Reduced voriconazole metabolism and higher drug concentrations are predicted.	CPIC guidelines[23] provide a moderate recommendation to initiate therapy with the recommended standard of care dosing. DPWG guidelines[24] recommend monitoring of plasma concentrations.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CHLORPHENIRAMINE Antihistamines	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism of chlorpheniramine and increased drug exposure are predicted. There may potentially be an increased risk of adverse effects, such as drowsiness, although evidence for this is limited.	No genotype-guided dosing recommendation available. Consider using a lower starting dose. Monitor for adverse effects.
DEXCHLORPHENIRAMINE Antihistamines	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism of dexchlorpheniramine and increased drug exposure are predicted. There may potentially be an increased risk of adverse effects, such as drowsiness, although evidence for this is limited.	No genotype-guided dosing recommendation available. Consider using a lower starting dose. Monitor for adverse effects.
PROMETHAZINE Antihistamines	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism of promethazine and increased drug exposure are predicted. There may potentially be an increased risk of adverse effects, such as drowsiness, although evidence for this is limited.	No genotype-guided dosing recommendation available. Consider using a lower starting dose. Monitor for adverse effects.
ARIPIPRAZOLE Antipsychotics	**CYP2D6 - Intermediate metaboliser:** 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[25] suggests that no specific action on aripiprazole dosing is required with this genotype.
BREXPIPRAZOLE Antipsychotics	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	DPWG guidelines[26] suggest that no specific action on brexpiprazole dosing is required based on this genotype. Monitor for adverse effects.
CHLORPROMAZINE Antipsychotics	**CYP2D6 - Intermediate metaboliser:** 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 metaboliser** **CYP1A2 - Ultrarapid metaboliser (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.[27] 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.[28]
HALOPERIDOL Antipsychotics	**CYP2D6 - Intermediate metaboliser:** 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[29] suggests that no specific action on haloperidol dosing is required with this genotype.
OLANZAPINE Antipsychotics	**CYP1A2 - Ultrarapid metaboliser (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.[28]
RISPERIDONE Antipsychotics	**CYP2D6 - Intermediate metaboliser:** 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[30] 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 metaboliser:** 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
CLOBAZAM Benzodiazepines	**CYP2C19 - Intermediate metaboliser:** Clobazam is metabolised by CYP3A4 into an active metabolite, N-desmethylclobazam, which is responsible for most of the therapeutic effect. N-desmethylclobazam is further metabolised by CYP2C19 into an inactive metabolite. 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 metaboliser:** Diazepam is metabolised 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 metabolised by CYP2C19, such as oxazepam or lorazepam.
CARVEDILOL Beta blockers	**CYP2D6 - Intermediate metaboliser:** 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[31] suggests that no specific action on carvedilol dosing is required based on this genotype. Monitor for adverse effects.
METOPROLOL Beta blockers	**CYP2D6 - Intermediate metaboliser:** 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[32] 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 metaboliser** **CYP1A2 - Ultrarapid metaboliser (with inducer present):** Propranolol is metabolised 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 metaboliser:** 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
DAPOXETINE Drugs for sexual dysfunction	**CYP2D6 - Intermediate metaboliser:** 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 dapoxetine exposure and the risk of adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
GEFITINIB Immunomodulators and antineoplastics	**CYP2D6 - Intermediate metaboliser:** 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[33] suggests that no specific action on gefitinib dosing is required with this genetic result.
CYCLOPHOSPHAMIDE Miscellaneous	**CYP2C19 - Intermediate metaboliser:** 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.
ELIGLUSTAT Miscellaneous	**CYP2D6 - Intermediate metaboliser:** 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.[34]	The recommended dose of eliglustat depends on whether CYP3A4 and/or CYP2D6 inhibiting medications are co-prescribed. Refer to DPWG guidelines,[34] FDA-approved drug label[35] or TGA-approved product information[36] for prescribing details.
PROGUANIL Miscellaneous	**CYP2C19 - Intermediate metaboliser:** 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 metaboliser:** 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.
TETRABENAZINE Neurological drugs	**CYP2D6 - Intermediate metaboliser:** Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA[37] approved drug label advises a maximum daily dose of 100mg, with a maximum recommended single dose of 37.5mg.
OXYCODONE Opioid Analgesics	**CYP2D6 - Intermediate metaboliser:** 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.	Due to weak evidence for adverse effects and analgesia, CPIC guidelines[9] have no recommendations to support oxycodone dosing. DPWG guidelines[10] also suggest that no specific action on oxycodone dosing is required. Be alert to a reduced analgesic response.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
LANSOPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metaboliser:** 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 metabolisers.	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.[38]
OMEPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metaboliser:** 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 metabolisers.	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.[38]
PANTOPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metaboliser:** 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 metabolisers.	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.[38]
RABEPRAZOLE Proton pump inhibitors	**CYP2C19 - Intermediate metaboliser:** 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.[39]
DEXAMPHETAMINE Psychostimulants	**CYP2D6 - Intermediate metaboliser:** Dexamphetamine is eliminated by both the kidney (as unchanged drug) and the liver, with CYP2D6 playing a significant role. Reduced metabolism via CYP2D6 and increased dexamphetamine 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.
LISDEXAMFETAMINE Psychostimulants	**CYP2D6 - Intermediate metaboliser:** Lisdexamfetamine is a prodrug of dextroamphetamine (also known as dexamfetamine). Dextroamphetamine is eliminated by both the kidney (as unchanged drug) and the liver, with CYP2D6 playing a significant role. 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
IRBESARTAN Angiotensin receptor blockers	**CYP2C9 - Normal metaboliser:** Normal metabolism of irbesartan by CYP2C9 is predicted.	Standard dosing and prescribing measures apply.
LOSARTAN Angiotensin receptor blockers	**CYP2C9 - Normal metaboliser:** Normal formation of losartan's active metabolite by CYP2C9 and a typical clinical response is predicted.	Standard dosing and prescribing measures apply.
PRASUGREL Anticoagulants	**CYP2C19 - Intermediate metaboliser:** DPWG[40] states that there is no gene-drug interaction for CYP2C19 and prasugrel.	No genotype-guided dosing recommendation available for this genotype. Standard dosing and prescribing measures apply.
TICAGRELOR Anticoagulants	**CYP2C19 - Intermediate metaboliser:** DPWG[41] states that there is no gene-drug interaction for ticagrelor and CYP2C19.	No genotype-guided dosing recommendation available for this genotype. Standard dosing and prescribing measures apply.
GLIBENCLAMIDE Antidiabetics	**CYP2C9 - Normal metaboliser:** Normal metabolism of glibenclamide by CYP2C9 is predicted.	Standard dosing and prescribing measures apply.
GLIMEPIRIDE Antidiabetics	**CYP2C9 - Normal metaboliser:** Normal metabolism of glimepiride by CYP2C9 is predicted.	Standard dosing and prescribing measures apply.
GLIPIZIDE Antidiabetics	**CYP2C9 - Normal metaboliser:** Normal metabolism of glipizide by CYP2C9 is predicted.	Standard dosing and prescribing measures apply.
TOLBUTAMIDE Antidiabetics	**CYP2C9 - Normal metaboliser:** Normal metabolism of tolbutamide by CYP2C9 is predicted.	DPWG[42] states that there is no action needed for this gene-drug interaction.
FOSPHENYTOIN Antiepileptics	**CYP2C9 - Normal metaboliser:** Fosphenytoin is a prodrug of phenytoin. Normal metabolism of phenytoin by CYP2C9 is predicted.	Based on the CYP2C9 genotype, CPIC guidelines[43] provide a strong recommendation that no adjustments are needed from typical dosing strategies; subsequent doses should be adjusted according to 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.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
PHENYTOIN Antiepileptics	**CYP2C9 - Normal metaboliser:** Normal metabolism of phenytoin by CYP2C9 is predicted.	Based on the CYP2C9 genotype, CPIC guidelines[43] provide a strong recommendation that no adjustments are needed from typical dosing strategies; subsequent doses should be adjusted according to 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.
FLUPENTHIXOL Antipsychotics	**CYP2D6 - Intermediate metaboliser:** DPWG guidelines[44] state that there is no gene-drug interaction for flupenthixol and CYP2D6.	No dosage recommendation is currently available based on the genetic findings.
QUETIAPINE Antipsychotics	**CYP3A4 - Normal metaboliser:** Normal metabolism of quetiapine by CYP3A4 is predicted.	Standard dosing and prescribing measures apply.
NEBIVOLOL Beta blockers	**CYP2D6 - Intermediate metaboliser:** 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 metaboliser:** 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[45] 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.[45]
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.[46]	CPIC guidelines[9] 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.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
MELATONIN Hypnotics	**CYP1A2 - Ultrarapid metaboliser (with inducer present):** Increased metabolism of melatonin and reduced exposure, especially in the presence of inducers such as tobacco smoking, daily consumption of cruciferous vegetables or chargrilled meat and certain medications (e.g. omeprazole).[47] 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.
ATAZANAVIR Miscellaneous	**CYP3A5 - Poor metaboliser:** 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.
SIPONIMOD Neurological drugs	**CYP2C9 - Normal metaboliser:** Normal metabolism of siponimod by CYP2C9 is predicted.	The FDA-approved drug label[48] states that in patients with the CYP2C9 *1/*1 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.
CELECOXIB NSAIDs	**CYP2C9 - Normal metaboliser:** Normal metabolism of celecoxib by CYP2C9 is predicted.	CPIC guidelines[49] have a strong recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required.
DICLOFENAC NSAIDs	**CYP2C9 - Normal metaboliser:** Diclofenac is partially metabolised by CYP2C9 and metabolism via this pathway is expected to be normal[50].	CPIC guidelines[49] state that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.
IBUPROFEN NSAIDs	**CYP2C9 - Normal metaboliser:** Normal metabolism of ibuprofen by CYP2C9 is predicted[51].	CPIC guidelines[49] have a strong recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required.
INDOMETHACIN NSAIDs	**CYP2C9 - Normal metaboliser:** Indomethacin is only partially metabolised by CYP2C9 and metabolism via this pathway is expected to be normal.[52]	CPIC guidelines[49] state that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.
MEFENAMIC ACID NSAIDs	**CYP2C9 - Normal metaboliser:** Normal metabolism of mefenamic acid by CYP2C9 is predicted.[53]	Standard dosing and prescribing measures apply.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
MELOXICAM NSAIDs	**CYP2C9 - Normal metaboliser:** Normal metabolism of meloxicam by CYP2C9 is predicted.	CPIC guidelines[49] have a strong recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required.
PIROXICAM NSAIDs	**CYP2C9 - Normal metaboliser:** Normal metabolism of piroxicam by CYP2C9 is predicted.	CPIC guidelines[49] have a strong recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required.
MORPHINE Opioid Analgesics	**OPRM1 - Higher opioid sensitivity:** Whilst this 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.	CPIC[9] 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 metaboliser:** 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.[54]
ATORVASTATIN Statins	**SLCO1B1 - Normal transporter function:** The SLCO1B1 genotype is associated with typical atorvastatin exposure and myopathy risk.[55] 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[55] provide a strong recommendation to use the desired starting dose and adjust doses based on disease-specific guidelines.
FLUVASTATIN Statins	**SLCO1B1 - Normal transporter function** **CYP2C9 - Normal metaboliser:** This SLCO1B1 genotype is associated with typical statin exposure and myopathy risk.[55] This CYP2C9 genotype predicts normal metabolism of fluvastatin. 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[55] provide a strong recommendation to prescribe the desired starting dose and adjust doses based on disease-specific guidelines.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION DRUG CATEGORY	INTERPRETATION	RECOMMENDATION
LOVASTATIN Statins	**SLCO1B1 - Normal transporter function:** This SLCO1B1 genotype is associated with a typical myopathy risk and statin exposure.[55] 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[55] provide a strong recommendation to use the desired starting dose and adjust doses based on disease-specific guidelines.
PITAVASTATIN Statins	**SLCO1B1 - Normal transporter function:** This SLCO1B1 genotype is associated with a typical myopathy risk and statin exposure.[55] 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[55] 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.[55] 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[55] 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[55] 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.[55] 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[55] 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
CYP1A2	*1F/*1F	**Ultrarapid metaboliser (with inducer present):** Due to the presence of two *1F alleles, this individual is predicted to have an ultrarapid metaboliser phenotype. Enzyme activity is highest in the presence of inducers, such as tobacco smoke, regular consumption of cruciferous vegetables or chargrilled meats, and certain drugs. For a drug extensively metabolised by CYP1A2, drug exposure and clinical effects may either be reduced (for an active drug) or increased (for a prodrug).
CYP2C19	*1/*2	**Intermediate metaboliser:** Due to the presence of one normal function allele and one no function allele, this individual is predicted to have an intermediate metaboliser phenotype. For a drug extensively metabolised 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/*1	**Normal metaboliser:** Due to the presence of two normal function alleles, this individual is predicted to have a normal metaboliser phenotype. For a drug extensively metabolised by CYP2C9, drug exposure and clinical effects may be expected to lie within the normal range.
CYP2D6	*4/*41	**Intermediate metaboliser:** Due to the presence of one reduced function allele and one no function allele, this individual is predicted to have an intermediate metaboliser phenotype. For a drug extensively metabolised 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 metaboliser:** The *22 allele is not present and this individual is expected to have a normal metaboliser phenotype. Whilst many drugs are known to be metabolised by CYP3A4, relatively few genetic variations have been found that affect metabolism of a limited number of these drugs.
CYP3A5	*3/*3	**Poor metaboliser:** Due to the presence of two no function alleles, this individual is predicted to have a poor metaboliser phenotype (CYP3A5 non-expresser). CYP3A5 is known to metabolise certain drugs, including tacrolimus. Note that this individual's genotype is the most common one amongst Caucasians.
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[56,57] 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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GenSeq Labs (NATA 20082)

DISCLAIMER

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

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

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

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

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

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

TEST METHODOLOGY AND LIMITATIONS

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

TEST PANEL OF GENES AND VARIANTS

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