

10 July 2023

Dear Healthcare Professional,

Please find attached your patient's myDNA report.

Patient Full Name: Angus Swendson

Patient Address:

DOB: 11-Feb-1980

Reference ID:

THIS WAS PROVIDED TO PAWAN IN OCTOBER OR NOVEMBER OF 2024

Your patient has undertaken a myDNA Medication test and has nominated you to receive a copy of their results.

The myDNA medication test is a pharmacogenomic test which looks at common genetic variants in a number of genes with likely clinical significance and potential to enhance safe and effective prescribing of a range of medications. The information provided by the test is mainly around drug metabolism and how genotype-predicted changes influence plasma concentrations, and clinical effects (both therapeutic and adverse). The reports prepared by the myDNA clinical team, provide suggestions on medication selection, dose modification and other clinically relevant information. This information is based on the published literature, as well as peer-reviewed pharmacogenomic guidelines where available.

This report is not sent directly to the patient as per TGA requirements. The results and report are sent to the patient's community pharmacist to deliver to the patient and share with their doctor. Following the delivery of the results by their pharmacist, the patient is provided a copy of their report and can also access simple explanations of their results via an online myDNA App.

As pharmacogenomics is a relatively new area of medicine which clinicians are incorporating into their practice, our service believes it is vital to provide timely support. Therefore, we have a clinical team available by phone to answer any questions you may have about this report, including interpretation and clinical utility, or about pharmacogenomics in general. The clinical team can be reached on 1300 436 373 or clinical@mydna.life.

Kind Regards,

A/Prof Les Sheffield
Medical Director
MyDNA Life Australia

PERSONALISED MEDICATION REPORT

For Angus Swendson

Date of birth: Order Number:
11-Feb-1980

Sample type:
Buccal

Collected: Received:
19-Jun-2023 **21-Jun-2023**

Reported:
10-Jul-2023

ABOUT THIS REPORT

Overview

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 significant effect to drug response is predicted. There may be guidelines recommending consideration be given to a change in the dose or the medication type, in order to minimise the risk of the potential clinical issue noted.
- Minor prescribing considerations – Altered drug response is possible, but the clinical significance is either thought to be minor or there is insufficient data available. Consider monitoring for the clinical issue noted in this report and any guideline prescribing recommendations.
- Usual prescribing considerations – Genetic results are not predicted to affect drug response, 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.

For many medications covered in this report, international, peer reviewed prescribing guidelines are available and these are included in our report.

The two major guidelines are those of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Royal Dutch Pharmacists Association – Pharmacogenetics Working Group (DPWG).

Report breakdown

The report consists of the following sections:

- » Report Summary – identifies which of the patient's listed medications have pharmacogenomic information relevant to the genes tested, with an indication of the clinical importance of this information (i.e. "Major", "Minor" or "Usual" prescribing considerations).
- » Genetic Test Results Overview – genotype result for the eight gene test (i.e. six genes encoding CYP450 metabolising enzymes relevant to a large number of medications, *VKORC1* which relates to warfarin sensitivity and *SLCO1B1* which relates to statin induced myopathy).
- » Medications of Interest – details of the interaction between the patient's genetic results and their medication, based on the current scientific literature, as well as clinical recommendations, many sourced from peer-reviewed, published guidelines.
- » Potential Drug Interactions – identifies which of the patient's listed medications can significantly inhibit or induce CYP enzymes, as they may modify the genotype-predicted enzyme function.
- » Future Medications – lists medications that the patient is not currently taking that have potentially clinically significant prescribing considerations based on the patient's genetic test results (also classified as having "Major", "Minor" or "Usual" prescribing considerations).

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 call our clinical team on +61 3 8582 0301.

Personalised Medication Report

for Angus Swendson

Unless instructed by their doctor, patients are advised not to alter the dose or stop any medications.

Name: Angus Swendson
 Address: 16 Barton Drive, Mount Eliza, VIC, 3930
 DOB: 11-Feb-1980
 Order Number:
 Collected: 19-Jun-2023
 Received: 21-Jun-2023
 Reported: 10-Jul-2023

Copy to: TerryWhite Chemmart Mt Eliza

Sample type and quality: Buccal. The sample quality was assessed and deemed to be satisfactory according to the laboratory's acceptance criteria.

Clinical Notes:

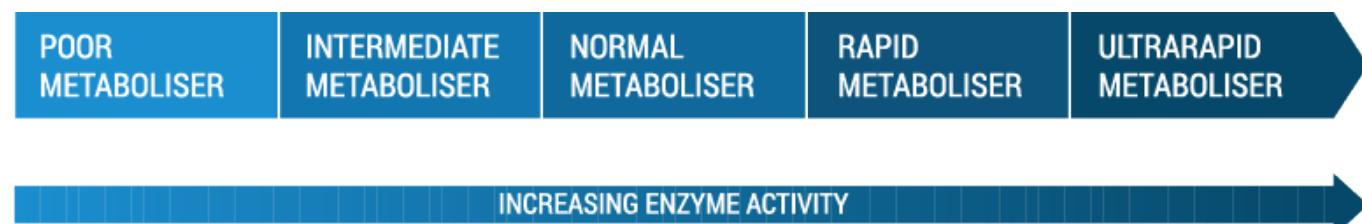


REPORT SUMMARY

MEDICATIONS OF INTEREST OVERVIEW					
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON myDNA TEST					
fluticasone / salmeterol (Seretide), tobacco smoke					
GENETIC TEST RESULTS OVERVIEW					
GENE	GENOTYPE	PREDICTED PHENOTYPE	GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP2D6	*4/*41	Intermediate metaboliser	CYP3A4	*1/*1	Normal metaboliser
CYP2C19	*1/*1	Normal metaboliser	CYP3A5	*3/*3	Poor metaboliser
CYP2C9	*1/*1	Normal metaboliser	SLCO1B1	*1/*1	Normal transporter function
VKORC1	GA	Moderately reduced VKORC1 enzyme level	OPRM1	AA	Higher opioid sensitivity
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present)			

Detailed interpretations of genetic test results are provided in the [pharmacogenomic interpretation](#) section below.

The following diagram provides the range of enzyme activity predicted by the myDNA test.



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



FUTURE MEDICATIONS

The following tables outline personalised recommendations for future medications.

NOTE: 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.

MEDICATIONS WITH MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
Atomoxetine (ADHD - miscellaneous agents)	CYP2D6 - Intermediate metaboliser: Reduced metabolism by CYP2D6 and increased drug exposure is predicted. This may increase the risk of adverse effects.	CPIC ¹ provides a moderate recommendation for dosing in children and adults. Refer to CPIC guidelines for details. In summary, Adults: initiate at 40 mg/day. If no clinical response and no adverse events after 2 weeks, increase to 80 mg/day. If inadequate response after 2 weeks, consider use of plasma concentrations 2-4 hours after dosing to guide titration. Children: initiate at 0.5mg/kg/day. If no clinical response and no adverse events after 2 weeks, consider use of plasma concentrations 2-4 hours after dosing to guide titration. Note: FDA-approved drug label ² 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).
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 ³ 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 metaboliser: Reduced metabolism by CYP2D6	The DPWG ⁴ suggests either: 1) adjusting the dose in response to plasma concentration, recording an ECG and being alert to side

MEDICATIONS WITH MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	effects, or 2) selecting an alternative drug (e.g., sotalol, amiodarone).
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 ⁵ 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.
Amitriptyline (Antidepressants - TCAs)	CYP2D6 - Intermediate metaboliser CYP2C19 - Normal metaboliser: Amitriptyline is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of amitriptyline and reduced metabolism of the active metabolite are predicted.	For use at higher doses such as in the treatment of depression, CPIC ⁶ provides a moderate 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.
Clomipramine (Antidepressants - TCAs)	CYP2D6 - Intermediate metaboliser CYP2C19 - Normal metaboliser: Clomipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of clomipramine and reduced metabolism of the active metabolite are predicted.	CPIC ⁶ 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.
Desipramine (Antidepressants - TCAs)	CYP2D6 - Intermediate metaboliser: 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 ⁶ 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.

MEDICATIONS WITH MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
Dosulepin (Antidepressants - TCAs)	CYP2D6 - Intermediate metaboliser CYP2C19 - Normal metaboliser: Dosulepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of Dosulepin and reduced metabolism of the active metabolite are predicted.	CPIC ⁶ 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 - Normal metaboliser: Doxepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of doxepin and reduced metabolism of the active metabolite are predicted.	CPIC ⁶ 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 - Normal metaboliser: Imipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of imipramine and reduced metabolism of the active metabolite are predicted.	CPIC ⁶ 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 ⁶ 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 metaboliser CYP2C19 - Normal metaboliser: Trimipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of trimipramine and reduced metabolism of the active metabolite are predicted.	CPIC ⁶ 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.
Pimozide (Antipsychotics)	CYP2D6 - Intermediate metaboliser: Reduced metabolism by CYP2D6	DPWG ⁷ recommends using no more than 80% of the standard maximum dose. Monitor for adverse effects.

MEDICATIONS WITH MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	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 pointes); the recommendations for a lower dose aim to reduce the risk of excessively high plasma concentration of drug.	
Thioridazine (Antipsychotics)	CYP2D6 - Intermediate metaboliser: 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. ⁸ 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.
Zuclopentixol (Antipsychotics)	CYP2D6 - Intermediate metaboliser: Reduced metabolism and increased drug exposure are predicted. This may increase the risk of adverse effects.	The DPWG ⁹ 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 ¹⁰ provides a moderate* 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.

*A moderate recommendation means there is close or uncertain balance as to whether the

MEDICATIONS WITH MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
		evidence is high quality and desirable effects clearly outweigh undesirable effects.
Codeine (Opioid Analgesics)	<p>CYP2D6 - Intermediate metaboliser</p> <p>OPRM1 - Higher opioid sensitivity: Reduced metabolism of codeine by CYP2D6 into its active metabolite morphine is predicted. This could lead to a reduction in analgesic response to codeine.</p> <p>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.</p> <p>Codeine is contraindicated in children under 12 years of age.¹¹</p>	<p>Based on the CYP2D6 genotype CPIC¹² 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. DPWG¹³ 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.</p> <p>There is no additional genotype-guided dosing recommendation based on the OPRM1 result.</p>
Tramadol (Opioid Analgesics)	<p>CYP2D6 - Intermediate metaboliser: Reduced formation of tramadol's active metabolite is predicted. This could lead to a reduction in analgesic response.</p> <p>Note that tramadol is a serotonergic drug. There is an increased risk of serotonin toxicity when used together with other serotonergic drugs.</p>	<p>CPIC guidelines¹² 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.</p> <p>DPWG guidelines¹³ 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.</p>

MEDICATIONS WITH MINOR PRESCRIBING CONSIDERATIONS

DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
ADHD - miscellaneous agents	Viloxazine	CYP2D6	Adverse effects	-
Antianginals	Perhexiline	CYP2D6	Adverse effects	-
Anticholinergics (genitourinary)	Darifenacin	CYP2D6	Adverse effects	-
	Fesoterodine	CYP2D6	Adverse effects	-
	Tolterodine	CYP2D6	Adverse effects	-
Anticholinesterases	Donepezil	CYP2D6	Adverse effects	-
	Galantamine	CYP2D6	Adverse effects	-
Anticoagulants	Acenocoumarol	VKORC1 CYP2C9	Increased acenocoumarol sensitivity	DPWG ¹⁴
	Warfarin	VKORC1 CYP2C9	Increased warfarin sensitivity	CPIC ¹⁵
Antidepressants - other	Agomelatine	CYP1A2	Reduced / inadequate response	-
	Mianserin	CYP2D6	Adverse effects	-
	Mirtazapine	CYP2D6 CYP1A2	Altered response	DPWG ¹⁶
	Vortioxetine	CYP2D6	Adverse effects	-

MEDICATIONS WITH MINOR PRESCRIBING CONSIDERATIONS

DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Antidepressants - SNRIs	Duloxetine	CYP2D6 CYP1A2	Altered response	-
Antidepressants - SSRIs	Fluoxetine	CYP2D6 CYP2C9	Altered response	DPWG ¹⁷
	Fluvoxamine	CYP2D6 CYP1A2	Adverse effects	CPIC ¹⁸ , DPWG ¹⁹
	Paroxetine	CYP2D6	Adverse effects	CPIC ¹⁸ , DPWG ²⁰
Antidepressants - TCAs	Amoxapine	CYP2D6	Increased therapeutic and/or adverse effects	FDA ²¹
	Protriptyline	CYP2D6	Increased therapeutic and/or adverse effects	-
Antiemetics	Metoclopramide	CYP2D6	Adverse effects	-
	Ondansetron	CYP2D6	Increased therapeutic and/or adverse effects	CPIC ²²
	Tropisetron	CYP2D6	Adverse effects	CPIC ²²
Antihistamines	Chlorpheniramine	CYP2D6	Adverse effects	-
	Dexchlorpheniramine	CYP2D6	Adverse effects	-
	Promethazine	CYP2D6	Adverse effects	-
Antipsychotics	Aripiprazole	CYP2D6	Adverse effects	DPWG ²³
	Aripiprazole Lauroxil	CYP2D6	Adverse effects	FDA ^{24 25}
	Brexpiprazole	CYP2D6	Adverse effects	DPWG ²⁶
	Chlorpromazine	CYP2D6	Adverse effects	-
	Clozapine	CYP2D6 CYP1A2	Altered response	-
	Haloperidol	CYP2D6	Adverse effects	DPWG ²⁷
	Iloperidone	CYP2D6	Adverse effects	-
	Olanzapine	CYP1A2	Reduced / inadequate response	-
	Perphenazine	CYP2D6	Adverse effects	-
	Risperidone	CYP2D6	Adverse effects	DPWG ²⁸
Antitussives	Dextromethorphan	CYP2D6	Adverse effects	-
Beta blockers	Carvedilol	CYP2D6	Adverse effects	DPWG ²⁹
	Metoprolol	CYP2D6	Increased therapeutic and/or adverse effects	DPWG ³⁰
	Propranolol	CYP2D6 CYP1A2	Altered response	-
	Timolol	CYP2D6	Adverse effects	-
	Pitolisant	CYP2D6	Adverse effects	-
Drugs for anxiety and sleep disorders	Dapoxetine	CYP2D6	Adverse effects	-
Drugs for sexual dysfunction	Gefitinib	CYP2D6	Adverse effects	DPWG ³¹
Miscellaneous	Cevimeline	CYP2D6	Adverse effects	-
Neurological drugs	Eliglustat	CYP2D6	Adverse effects	DPWG ³² , FDA ³³ , TGA ³⁴
	Lofexidine	CYP2D6	Adverse effects	-
	Meclizine	CYP2D6	Adverse effects	FDA ³⁵
	Tamsulosin	CYP2D6	Increased therapeutic and/or adverse effects	-
	Deutetrabenazine	CYP2D6	Adverse effects	-
	Tetrabenazine	CYP2D6	Adverse effects	FDA ³⁶
	Valbenazine	CYP2D6	Adverse effects	-

MEDICATIONS WITH MINOR PRESCRIBING CONSIDERATIONS

DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Opioid Analgesics	Hydrocodone	CYP2D6	Altered response	CPIC ¹²
	Oliceridine	CYP2D6	Increased therapeutic and/or adverse effects	-
	Oxycodone	CYP2D6	Reduced / inadequate response	CPIC ¹² , DPWG ³⁷
Proton pump inhibitors	Dexlansoprazole	CYP2C19	Reduced / inadequate response	CPIC ³⁸
	Lansoprazole	CYP2C19	Reduced / inadequate response	CPIC ³⁸
	Omeprazole	CYP2C19	Reduced / inadequate response	CPIC ³⁸
	Pantoprazole	CYP2C19	Reduced / inadequate response	CPIC ³⁸
Psychostimulants	Amphetamine	CYP2D6	Adverse effects	FDA ³⁹
	Dextroamphetamine	CYP2D6	Adverse effects	-
	Lisdexamfetamine	CYP2D6	Adverse effects	-

MEDICATIONS WITH USUAL PRESCRIBING CONSIDERATIONS

DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Angiotensin receptor blockers	Irbesartan	CYP2C9	No altered effect predicted by genotype	-
	Losartan	CYP2C9	No altered effect predicted by genotype	-
Anticoagulants	Prasugrel	CYP2C19	No altered effect predicted by genotype	DPWG ⁴⁰
	Ticagrelor	CYP2C19	No altered effect predicted by genotype	DPWG ⁴¹
Antidepressants - other	Moclobemide	CYP2C19	No altered effect predicted by genotype	-
Antidepressants - SSRIs	Citalopram	CYP2C19	No altered effect predicted by genotype	CPIC ¹⁸
	Escitalopram	CYP2C19	No altered effect predicted by genotype	CPIC ¹⁸
	Sertraline	CYP2C19	No altered effect predicted by genotype	CPIC ¹⁸
Antidiabetics	Gliclazide	CYP2C9 CYP2C19	No altered effect predicted by genotype	-
	Glimepiride	CYP2C9	No altered effect predicted by genotype	-
	Glipizide	CYP2C9	No altered effect predicted by genotype	-
	Glyburide	CYP2C9	No altered effect predicted by genotype	-
	Nateglinide	CYP2C9	No altered effect predicted by genotype	-
	Tolbutamide	CYP2C9	No altered effect predicted by genotype	DPWG ⁴²
Antiepileptics	Brivaracetam	CYP2C19	No altered effect predicted by genotype	FDA ⁴³
	Fosphenytoin	CYP2C9	No altered effect predicted by genotype	CPIC ⁴⁴
	Lacosamide	CYP2C19	No altered effect predicted by genotype	-
	Phenytoin	CYP2C9	No altered effect predicted by genotype	CPIC ⁴⁴

MEDICATIONS WITH <u>USUAL</u> PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Antifungals - Azoles	Voriconazole	CYP2C19	No altered effect predicted by genotype	CPIC ⁴⁵
Antineoplastics	Atazanavir	CYP3A5	No altered effect predicted by genotype	-
	Cyclophosphamide	CYP2C19	No altered effect predicted by genotype	-
Antiplatelet drugs	Clopidogrel	CYP2C19	No altered effect predicted by genotype	CPIC ⁴⁶
Antipsychotics	Flupenthixol	CYP2D6	No altered effect predicted by genotype	DPWG ⁴⁷
	Quetiapine	CYP3A4	No altered effect predicted by genotype	-
Benzodiazepines	Clobazam	CYP2C19	No altered effect predicted by genotype	-
	Diazepam	CYP2C19	No altered effect predicted by genotype	-
Beta blockers	Nebivolol	CYP2D6	Monitor for adverse effects	-
Calcineurin inhibitors	Tacrolimus	CYP3A5	No altered effect predicted by genotype	CPIC ⁴⁸
Drugs for alcohol dependence	Naltrexone	OPRM1	Limited association with reduced response	CPIC ¹²
Endocrine drugs	Elagolix	SLCO1B1	No altered effect predicted by genotype	-
Haemostatic agents	Avatrombopag	CYP2C9	No altered effect predicted by genotype	FDA ⁴⁹
Hypnotics	Melatonin	CYP1A2	Reduced drug exposure (in presence of CYP1A2 inducer)	-
Immunomodulators and antineoplastics	Abrocitinib	CYP2C19	No altered effect predicted by genotype	-
	Belzutifan	CYP2C19	No altered effect predicted by genotype	-
	Erdafitinib	CYP2C9	No altered effect predicted by genotype	-
Miscellaneous	Dronabinol	CYP2C9	No altered effect predicted by genotype	-
	Flibanserin	CYP2C19	No altered effect predicted by genotype	-
	Mirabegron	CYP2D6	No altered effect predicted by genotype	-
	Proguanil	CYP2C19	No altered effect predicted by genotype	-
Neurological drugs	Carisoprodol	CYP2C19	No altered effect predicted by genotype	-
	Siponimod	CYP2C9	No altered effect predicted by genotype	FDA ⁵⁰
NSAIDs	Celecoxib	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹
	Diclofenac	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹
	Flurbiprofen	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹
	Ibuprofen	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹
	Indomethacin	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹

MEDICATIONS WITH USUAL PRESCRIBING CONSIDERATIONS

DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
	Lornoxicam	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹
	Mefenamic Acid	CYP2C9	No altered effect predicted by genotype	-
	Meloxicam	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹
	Piroxicam	CYP2C9	No altered effect predicted by genotype	CPIC ⁵¹
Opioid Analgesics	Morphine	OPRM1	Associated with increased sensitivity to morphine	CPIC ¹²
Proton pump inhibitors	Esomeprazole	CYP2C19	No altered effect predicted by genotype	-
	Rabeprazole	CYP2C19	No altered effect predicted by genotype	-
Statins	Atorvastatin	SLCO1B1	No altered effect predicted by genotype	CPIC ⁵²
	Fluvastatin	SLCO1B1 CYP2C9	No altered effect predicted by genotype	CPIC ⁵²
	Lovastatin	SLCO1B1	No altered effect predicted by genotype	CPIC ⁵²
	Pitavastatin	SLCO1B1	No altered effect predicted by genotype	CPIC ⁵²
	Pravastatin	SLCO1B1	No altered effect predicted by genotype	CPIC ⁵²
	Rosuvastatin	SLCO1B1	No altered effect predicted by genotype	CPIC ⁵²
	Simvastatin	SLCO1B1	No altered effect predicted by genotype	CPIC ⁵²

LEGEND:

CPIC = Clinical Pharmacogenetics Implementation Consortium

DPWG = The Royal Dutch Pharmacists Association –

Pharmacogenetics Working Group

TGA = Therapeutic Goods Administration (Australia)

FDA = Food and Drug Administration (US)

CPIC and DPWG guidelines are available on the PharmGKB website www.pharmgkb.org/view/dosing-guidelines.do



PHARMACOGENOMIC INTERPRETATION

EXPLANATION OF GENETIC RESULTS

GENE	GENOTYPE	PREDICTED FUNCTION
CYP2D6	*4/*41	<p>CYP2D6 - Intermediate metaboliser</p> <p>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).</p>
CYP2C19	*1/*1	<p>CYP2C19 - Normal metaboliser</p> <p>Due to the presence of two copies of normal function alleles, this individual is predicted to have a normal metaboliser phenotype. For a drug extensively metabolised by CYP2C19, drug exposure and clinical effects may be expected to lie within the normal range.</p>

EXPLANATION OF GENETIC RESULTS

GENE	GENOTYPE	PREDICTED FUNCTION
CYP2C9	*1/*1	CYP2C9 - 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.
VKORC1	GA	VKORC1 - 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.
CYP1A2	*1F/*1F	CYP1A2 - 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).
CYP3A4	*1/*1	CYP3A4 - 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	CYP3A5 - Poor metaboliser Due to the presence of two no function alleles, this individual is predicted to have a poor metaboliser phenotype (CYP3A5 non-expressor). CYP3A5 is known to metabolise certain drugs, including tacrolimus. Note that this individual's phenotype is the most common one amongst Caucasians.
SLCO1B1	*1/*1	SLCO1B1 - 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.
OPRM1	AA	OPRM1 - 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 ^{53,54} 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%).



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Electronic Signature:

Approved Pathology Practitioner: A/Professor Les Sheffield (23077)
This report has been prepared by the myDNA Clinical Team

Laboratory Results provided by: GenSeq

TEST SEND OUT: Pharmacogenomics testing and clinical interpretation was performed by GenSeq Labs (a subsidiary of MyDNA) in a NATA accredited laboratory (NATA accredited lab No 20082)

TEST METHODOLOGY AND LIMITATIONS: 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. Response to medications is complex and may also be influenced by factors which are not tested for (e.g. compliance, concurrent illness, drug-drug interactions.). The test only determines response to indicated medications. 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.

TEST PANEL OF GENES AND VARIANTS: The following clinically actionable alleles are tested: 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]); 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); VKORC1 - rs9923231 NM_024006.5:c.-1639G>A; CYP1A2 *1F(LRG_1274:g.5732C>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); SLCO1B1 - rs4149056 NM_006446.4:c.521T>C and OPRM1 - rs1799971 NM_000914.4:c.118A>G. 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, SLCO1B1 and OPRM1 genes. All variants are named using the HGVS nomenclature.

MYDNA CLINICAL SUPPORT

For all health practitioner enquiries please contact myDNA clinical support

T: +61 3 8582 0301

E: clinical@mydna.life