PERSONALISED CARDIOVASCULAR MEDICATION REPORT

For Test Patient

Date of birth:	myDNA ID:	Pathology No:
1-Jan-0000	**9016**	**00-6846545**
Collected:	Received:	Reported:
1-Jan-0000	**1-Jan-0000**	**31-May-2017**

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 – significant result that may require altering this medication

● Minor – result should be considered as may affect medication response

● Usual – usual prescribing considerations apply

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:

» Genetic test results summary – presents the patients genotypes for the genes relevant to the medications covered by this report

» Medication tables arranged according to the three categories

» Details of test results – an explanation of how the genotypes have been used to predict CYP enzyme function and the likely general effect on drug metabolism and plasma concentrations (exposure)

» References – the major references used for the report. More detailed references are available by contacting myDNA.

As part of our clinical service, we have a team of clinical experts available to answer any questions you may have about this report or about pharmacogenomics in general.

If you have any such queries, please contact our team by emailing info@nutripath.com.au.
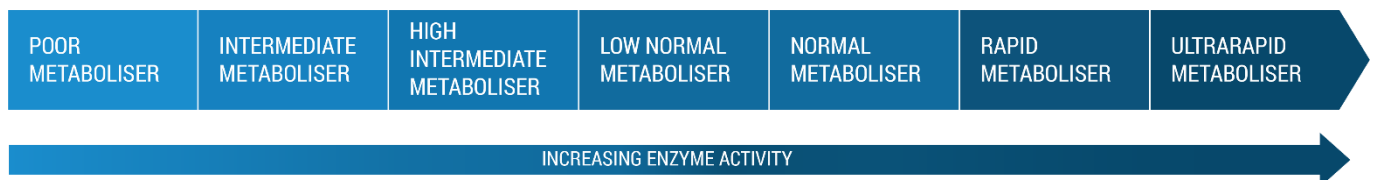
GENETIC TEST RESULTS SUMMARY

GENE	GENOTYPE	PHENOTYPE
CYP2D6	*1/*2X2	Ultrarapid metaboliser
CYP2C19	*2/*17	High intermediate metaboliser
CYP2C9	*1/*2	High intermediate metaboliser
VKORC1	AA	Highly increased warfarin sensitivity
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present)
CYP3A4	*1/*1	Normal metaboliser
SLCO1B1	CC	Low transporter function

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

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

POOR METABOLISER	INTERMEDIATE METABOLISER	HIGH INTERMEDIATE METABOLISER	LOW NORMAL METABOLISER	NORMAL METABOLISER	RAPID METABOLISER	ULTRARAPID METABOLISER

INCREASING ENZYME ACTIVITY

STATINS

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
🔴 Simvastatin	*SLCO1B1* - **Low transporter function** *CYP3A4* - **Normal metaboliser:** This SLCO1B1 result is associated with a high risk of myopathy (up to twenty-fold at 80mg daily).[4] Other factors expected to further increase this risk include higher doses, certain co-administered drugs, female sex, patient frailty, renal failure and hypothyroidism. Normal metabolism of simvastatin by CYP3A4 is predicted.	Based on the SLCO1B1 genotype, CPIC guidelines[5] provide a strong recommendation to be alert to the increased risk of myopathy, to consider low-dose therapy (e.g. 20mg daily) and if this is inappropriate, to consider an alternate statin. If using simvastatin, creatine kinase (CK) measurement may be considered. No genotype-guided dosing recommendation based on the CYP3A4 genotype is available.

MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
🟠 Atorvastatin	*SLCO1B1* - **Low transporter function** *CYP3A4* - **Normal metaboliser:** This SLCO1B1 genotype may be associated with an increased risk of atorvastatin related myopathy. However, at this stage, the evidence does not prove a strong association. If an increased risk is proven in future studies, it is likely to be substantially smaller than that with simvastatin. However, other factors increase the myopathy risk regardless of genotype, including choice of statin, higher doses, certain co-administered drugs, female sex, patient frailty, renal failure and hypothyroidism. Normal metabolism of atorvastatin by CYP3A4 is predicted.	No genotype-guided dosing recommendation based on the SLCO1B1 genotype. Suggest careful dose titration and clinical monitoring. No guidelines for dose modification available based on the CYP3A4 genotype.

MEDICATIONS WITH _USUAL_ PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
● Fluvastatin	_SLCO1B1_ – Low transporter function _CYP2C9_ – High intermediate metaboliser: There is no evidence linking SLCO1B1 genotype and the risk of myopathy with fluvastatin, pravastatin or rosuvastatin. Other factors known to increase the myopathy risk include the choice of statin being prescribed, higher doses, certain co-administered drugs, female sex, patient frailty, renal failure and hypothyroidism. The CYP2C9 genotype predicts slightly reduced metabolism of fluvastatin by this enzyme, which is unlikely to be clinically significant.	Standard dosing and prescribing measures apply.
● Pravastatin	_SLCO1B1_ – Low transporter function: There is no evidence linking SLCO1B1 genotype and the risk of myopathy with fluvastatin, pravastatin or rosuvastatin. Other factors known to increase the myopathy risk include the choice of statin being prescribed, higher doses, certain co-administered drugs, female sex, patient frailty, renal failure and hypothyroidism.	Standard dosing and prescribing measures apply.
● Rosuvastatin	_SLCO1B1_ – Low transporter function: There is no evidence linking SLCO1B1 genotype and the risk of myopathy with fluvastatin, pravastatin or rosuvastatin. Other factors known to increase the myopathy risk include the choice of statin being prescribed, higher doses, certain co-administered drugs, female sex, patient frailty, renal failure and hypothyroidism.	Standard dosing and prescribing measures apply.

NOTE: These tables do not account for the effect of any inhibitors or inducers. The table is not an all-inclusive list of all medications.

BETA BLOCKERS

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
● Metoprolol	*CYP2D6* – **Ultrarapid metaboliser:** Increased metabolism by CYP2D6 and reduced drug exposure are predicted. This could potentially lead to a reduced clinical effect.	Be alert to a reduced clinical response. For the treatment of heart failure the DPWG suggests using an alternative beta blocker (e.g. bisoprolol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and adverse effects. For other indications, the DPWG suggest either an alternative drug or up-titration of the metoprolol dose guided by clinical response. If currently well tolerated and clinical response has been adequate, a change to therapy may not be required.

MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
● Carvedilol	*CYP2D6* – **Ultrarapid metaboliser:** Increased carvedilol metabolism by CYP2D6 and reduced drug exposure are predicted. This may potentially lead to a reduction in clinical effects, although direct evidence is lacking.	If currently efficacious and tolerated, no change is required. No genotype-guided dosing recommendation available. Be alert to reduced clinical effect.
● Nebivolol	*CYP2D6* – **Ultrarapid metaboliser:** Increased metabolism of nebivolol by CYP2D6 and reduced exposure are predicted. This could potentially lead to a reduction in clinical response, although direct evidence is lacking.	No genotype-guided dosing recommendation available. However, be alert for reduced effect.
● Propranolol	*CYP1A2* – **Ultrarapid metaboliser (with inducer present)** *CYP2D6* – **Ultrarapid metaboliser:** Propranolol is metabolised by both CYP2D6 and CYP1A2 and also has an active metabolite. This genotype predicts increased metabolism by both CYP2D6 and CYP1A2 (the latter mainly in the presence of inducers such as cigarette smoke) and reduced overall exposure to propanolol. This may lead to an altered clinical effect.	No genotype-guided dosing guideline available. Monitor for altered clinical effect in patients exposed to CYP1A2 inducers.

NOTE: These tables do not account for the effect of any inhibitors or inducers. The table is not an all-inclusive list of all medications.

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
● Warfarin (Anticoagulant)	*VKORC1* – **Highly increased warfarin sensitivity** *CYP2C9* – **High intermediate metaboliser:** Slightly reduced metabolism of warfarin by CYP2C9 is predicted. Significantly reduced amount of VKORC1 (the enzyme warfarin inhibits). Overall increased warfarin sensitivity and increased risk of supratherapeutic INR.	For patients commencing warfarin, the FDA-approved drug label[1] recommends a starting dose of 3 - 4mg daily. INR monitoring and INR-guided dose adjustment should begin soon after commencement of warfarin. For patients already taking warfarin, dose adjustment should be guided by INR.
● Clopidogrel (Antiplatelet)	*CYP2C19* – **High 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 cardiovascular events in clopidogrel treated patients who have had an acute coronary syndrome (ACS) and undergone a percutaneous coronary intervention (PCI). There is also more limited evidence linking this genotype with recurrent stroke when clopidogrel is used in the management of ischaemic stroke.[2]	CPIC guidelines[3] provide a moderate recommendation to use an alternative P2Y12 blocking antiplatelet drug for management of acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI). Prasugrel or ticagrelor may be suitable alternatives, depending on the clinical circumstances. There are no genotype-guided recommendations for ischaemic stroke. If an alternative to clopidogrel is being considered, refer to published stroke guidelines.

MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
● Irbesartan (ARB)	*CYP2C9* – **High intermediate metaboliser:** Slightly reduced metabolism of irbesartan by CYP2C9 and slightly increased drug exposure are predicted. There is some evidence for an increased antihypertensive effect.	Standard dosing and prescribing measures apply.

MEDICATIONS WITH _USUAL_ PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
🟢 Losartan (ARB)	_CYP2C9_ - **High intermediate metaboliser:** Near normal formation of losartan's active metabolite and a normal clinical response are predicted.	Standard dosing and prescribing measures apply.

NOTE: These tables do not account for the effect of any inhibitors or inducers. The table is not an all-inclusive list of all medications.

GENE	GENOTYPE	PHENOTYPE
CYP2D6	*1/*2X2	**Ultrarapid metaboliser** Due to the presence of three copies of a normal function allele, this individual is predicted to have an ultrarapid metaboliser phenotype. For a drug extensively metabolised by CYP2D6, drug exposure and clinical effects may either be decreased (for an active drug) or increased (for a prodrug). This individual is at risk of therapeutic failure (active drug) or adverse effects (prodrug).
CYP2C19	*2/*17	**High intermediate metaboliser** Due to the presence of one null allele and one increased function allele, this individual is predicted to have a high 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).
CYP2C9	*1/*2	**High intermediate metaboliser** Due to the presence of one normal function allele and one reduced function allele, this individual is predicted to have a high intermediate metaboliser phenotype. For a drug extensively metabolised by CYP2C9, drug exposure and clinical effects may either be increased (for an active drug) or decreased (for a prodrug). As the *2 allele is associated with only a small reduction in enzyme function, this variation may only be significant for certain medications, with high dosages or if drug-drug interactions occur.
VKORC1	AA	**Highly increased warfarin sensitivity** The VKORC1 enzyme is predicted to be present in significantly 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	**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 will be further increased in the presence of inducers (e.g. 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	**Normal metaboliser** The *22 allele is not present and this individual is expected to have an 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.
SLCO1B1	CC	**Low transporter function** Due to the presence of two reduced function alleles, this individual is predicted to have low function of the *SLCO1B1* encoded transporter. Reduced clearance of certain medications such as simvastatin is expected.

1. DailyMed - COUMADIN- warfarin sodium tablet . 2016. DailyMed - COUMADIN- warfarin sodium tablet . [ONLINE] Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d91934a0-902e-c26c-23ca-d5accc4151b6#_Refs12.5. [Accessed 11 October 2016].

2. Wang Y, Zhao X, Lin J, Li H, Johnston S, Lin Y et al. Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischaemic Attack. JAMA 2016;316(1):70-78.

3. Scott S, Sangkuhl K, Stein C, Hulot J, Mega J, Roden D et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. Clin Pharmacol Ther. 2013;94(3):317-323.

4. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, et al. SLCO1B1 variants and statin-induced myopathy-a genomewide study. N Eng J Med. 2008 Aug 21;359(8):789-99.

5. Ramsey LB, Johnson SG, Caudle KE, Haidar CE, Voora D, Wilke RA, et al. The Clinical Pharmacogenetics Implementation Consortium Guidelines for SLCO1B1 and Simvastatin-Induced Myopathy: 2014 Update. Clin Pharmacol Ther. Online publication 9 July 2014. doi:10.1038/clpt.2014.125

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