NutriPATH

RECOMMENDATIONS FOR HEALTHCARE PROFESSIONALS

PERSONALISED MENTAL HEALTH MEDICATION REPORT

For Test Patient

Genetic interpretation by:

NutriPATH

Date of birth:	myDNA ID:	Pathology No:
00-00-0000	00000	00000000
Collected:	Received:	Reported:
00-00-0000	00-00-0000	00-00-0000

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 – 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)

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.

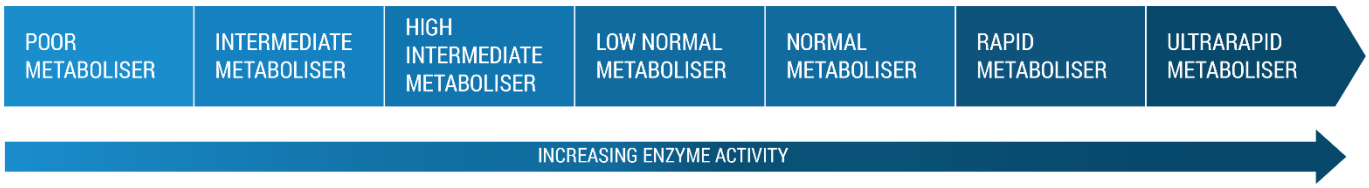
RESULTS SUMMARY

GENETIC TEST RESULTS SUMMARY

GENE	GENOTYPE	PHENOTYPE
CYP2D6	*1/*2	Normal metaboliser
CYP2C19	*17/*17	Ultrarapid metaboliser
CYP2C9	*1/*3	Intermediate metaboliser
CYP1A2	*1F/*1F	Ultrarapid metaboliser (with inducer present)
CYP3A4	*1/*1	Normal metaboliser

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.



ANTIDEPRESSANTS

The following tables outline personalised recommendations for antidepressants.

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

MEDICATIONS WITH ***MAJOR*** PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Citalopram (SSRI)	***CYP2C19*** - **Ultrarapid metaboliser:** Increased metabolism of citalopram by CYP2C19 and reduced drug exposure are predicted. This may increase the likelihood of therapeutic failure.	CPIC guidelines[1] provide a moderate recommendation to consider an alternative antidepressant not predominantly metabolised by CYP2C19. If the clinical response has been adequate, a change to therapy may not be required.
Escitalopram (SSRI)	***CYP2C19*** - **Ultrarapid metaboliser:** Increased metabolism of escitalopram and reduced drug exposure are predicted. This may increase the likelihood of therapeutic failure.	CPIC guidelines[1] provide a moderate recommendation to consider an alternative antidepressant not predominantly metabolised by CYP2C19. If the clinical response has been adequate, a change to therapy may not be required.
Amitriptyline (TCA)	***CYP2D6*** - **Normal metaboliser** ***CYP2C19*** - **Ultrarapid metaboliser:** Amitriptyline is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Increased metabolism and reduced plasma concentrations of amitriptyline are predicted. There may be an increased risk of therapeutic failure with amitriptyline. Normal metabolism of the active metabolite is predicted.	For use at higher doses such as in the treatment of depression, CPIC[2] provides an optional recommendation to consider an alternative drug not metabolized by CYP2C19, such as nortriptyline. If amitriptyline is required, consider therapeutic drug monitoring to guide dose adjustments. For use at lower doses such as in treatment of neuropathic pain, if currently well tolerated and clinical response has been adequate, a change to therapy may not be required. Nortriptyline may be more suitable from a metabolism perspective.

MEDICATION	INTERPRETATION	RECOMMENDATION
Clomipramine (TCA)	***CYP2D6*** **- Normal metaboliser** ***CYP2C19*** **- Ultrarapid metaboliser:** Clomipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Increased metabolism and reduced plasma concentrations of clomipramine are predicted. Normal metabolism of the active metabolite is predicted.	CPIC[2] provides an optional recommendation to consider an alternative drug not metabolized by CYP2C19, such as nortriptyline. If clomipramine is required, consider therapeutic drug monitoring to guide dose adjustments.
Dothiepin (TCA)	***CYP2D6*** **- Normal metaboliser** ***CYP2C19*** **- Ultrarapid metaboliser:** Dothiepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Increased metabolism and reduced plasma concentrations of dothiepin are predicted. Normal metabolism of the active metabolite is predicted.	CPIC[2] provides an optional recommendation to consider an alternative drug not metabolized by CYP2C19, such as nortriptyline. If dothiepin is required, consider therapeutic drug monitoring to guide dose adjustments.
Doxepin (TCA)	***CYP2D6*** **- Normal metaboliser** ***CYP2C19*** **- Ultrarapid metaboliser:** Doxepin is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Increased metabolism and reduced plasma concentrations of doxepin are predicted. Normal metabolism of the active metabolite is predicted.	CPIC[2] provides an optional recommendation to consider an alternative drug not metabolized by CYP2C19, such as nortriptyline. If doxepin is required, consider therapeutic drug monitoring to guide dose adjustments.
Imipramine (TCA)	***CYP2D6*** **- Normal metaboliser** ***CYP2C19*** **- Ultrarapid metaboliser:** Imipramine is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Increased metabolism and reduced plasma concentrations of imipramine are predicted. Normal metabolism of the active metabolite is predicted.	CPIC[2] provides an optional recommendation to consider an alternative drug not metabolized by CYP2C19, such as nortriptyline. If imipramine is required, consider therapeutic drug monitoring to guide dose adjustments.

MEDICATIONS WITH ***MINOR*** PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Agomelatine	***CYP1A2*** **- Ultrarapid metaboliser (with inducer present):** Increased agomelatine metabolism and reduced plasma concentrations are predicted, especially with exposure to enzyme inducers such as tobacco smoking, daily consumption of cruciferous vegetables or chargrilled meat, and certain medications (e.g. omeprazole). One study demonstrated a significant reduction in plasma concentrations of agomelatine with this genotype.[3] The relationship of changes in plasma concentration to patient response to agomelatine is not clear.	No genotype-guided dosing recommendation available. Monitor for a reduced clinical effect.
Mirtazapine	***CYP2D6*** **- Normal metaboliser** ***CYP1A2*** **- Ultrarapid metaboliser (with inducer present):** Mirtazapine is metabolised by a number of enzymes, including CYP2D6 and CYP1A2. The CYP2D6 genotype predicts normal metabolism and the CYP1A2 genotype predicts increased metabolism and reduced plasma concentrations in the presence of inducers such as cigarette smoking.	No genotype-guided dosing recommendation available. Monitor for reduced clinical response, especially in smokers.
Moclobemide	***CYP2C19*** **- Ultrarapid metaboliser:** Increased metabolism by CYP2C19 and reduced plasma concentrations are predicted. The clinical significance of this is not known, though reduced effects could be anticipated.	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.
Duloxetine (SNRI)	***CYP2D6*** **- Normal metaboliser** ***CYP1A2*** **- Ultrarapid metaboliser (with inducer present):** Duloxetine is metabolised by both CYP1A2 and CYP2D6, with CYP1A2 likely to have the major role. Normal duloxetine metabolism by CYP2D6 and increased metabolism by CYP1A2 in patients exposed to enzyme inducers (e.g. cigarette smoke) are predicted. The combined effect is likely to be reduced duloxetine plasma concentrations and potentially a reduced clinical response.	No genotype-guided dosing recommendation available. Be alert to an inadequate response, especially in smokers.

MEDICATION	INTERPRETATION	RECOMMENDATION
Fluoxetine (SSRI)	*CYP2D6* - **Normal metaboliser** *CYP2C9* - **Intermediate 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 normal fluoxetine exposure and normal formation of the active S-norfluoxetine metabolite. The CYP2C9 genotype predicts reduced metabolism via this pathway. However, fluoxetine and its metabolites can strongly inhibit CYP2D6 function, converting the phenotype to an intermediate or 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.	No genotype-guided dosing recommendation available. Monitor for altered clinical effect. If adverse effects are a concern, consider an alternative antidepressant for which normal metabolism is predicted.
Sertraline (SSRI)	*CYP2C19* - **Ultrarapid metaboliser:** Increased metabolism by CYP2C19 could increase the probability of reduced plasma concentrations, and potentially reduce the clinical effects. However, there is limited evidence linking this genotype with increased sertraline metabolism and reduced drug exposure.	CPIC[1] provides an optional recommendation to initiate therapy with the recommended starting dose. If the clinical response is not adequate despite standard maintenance dosing, CPIC suggests considering an alternative antidepressant not predominantly metabolised by CYP2C19.

MEDICATIONS WITH ***USUAL*** PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Mianserin	*CYP2D6* - **Normal metaboliser:** Normal CYP2D6 mediated metabolism of mianserin is predicted.	Standard dosing and prescribing measures apply.
Vortioxetine	*CYP2D6* - **Normal metaboliser:** Normal metabolism of vortioxetine is predicted.	Standard dosing and prescribing measures apply.

MEDICATION	INTERPRETATION	RECOMMENDATION
Venlafaxine (SNRI)	***CYP2D6* - Normal metaboliser:** Normal metabolism of venlafaxine is predicted.	Standard dosing and prescribing measures apply.
Fluvoxamine (SSRI)	***CYP2D6* - Normal metaboliser** ***CYP1A2* - Ultrarapid metaboliser (with inducer present):** Fluvoxamine is metabolised by both CYP2D6 (predominant pathway) and CYP1A2. Normal 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. The overall effect on fluvoxamine exposure and effects is difficult to predict.	Based on the CYP2D6 genotype, CPIC[1] provides a strong recommendation to initiate therapy with the recommended starting dose.
Paroxetine (SSRI)	***CYP2D6* - Normal metaboliser:** Normal metabolism by CYP2D6 is predicted. As paroxetine is a strong inhibitor of CYP2D6, the CYP2D6 function is expected to decrease 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.	CPIC[1] guidelines provide a strong recommendation to initiate therapy with the recommended starting dose.
Nortriptyline (TCA)	***CYP2D6* - Normal metaboliser:** Normal metabolism of nortriptyline is predicted.	For use at higher doses such as in the treatment of depression, CPIC guidelines[2] provide a strong recommendation to initiate therapy with the recommended starting dose. For use at lower doses such as in treatment of neuropathic pain, standard dosing and prescribing measures apply.

ANTIPSYCHOTICS

The following tables outline personalised recommendations for antipsychotics.

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

MEDICATIONS WITH ***MINOR*** PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Clozapine	***CYP1A2*** - **Ultrarapid metaboliser (with inducer present):** 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 genotype has also been associated with a reduced clinical response to clozapine, which is more marked in smokers.[4]	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.[5]
Olanzapine	***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.[5]

MEDICATIONS WITH ***USUAL*** PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Aripiprazole	***CYP2D6*** - **Normal metaboliser:** Normal metabolism by CYP2D6 is predicted.	Standard dosing and prescribing measures apply.
Brexpiprazole	***CYP2D6*** - **Normal metaboliser:** Normal metabolism by CYP2D6 is predicted.	Standard dosing and prescribing measures apply.

MEDICATION	INTERPRETATION	RECOMMENDATION
Chlorpromazine	***CYP2D6*** **- Normal metaboliser:** Normal metabolism of chlorpromazine by CYP2D6 is predicted.	Standard dosing and prescribing measures apply.
Haloperidol	***CYP2D6*** **- Normal metaboliser:** Normal metabolism by CYP2D6 is predicted.	Standard dosing and prescribing measures apply.
Quetiapine	***CYP3A4*** **- Normal metaboliser:** Normal metabolism of quetiapine is predicted.	Standard dosing and prescribing measures apply.
Risperidone	***CYP2D6*** **- Normal metaboliser:** Normal metabolism of risperidone is predicted.	Standard dosing and prescribing measures apply.
Zuclopenthixol	***CYP2D6*** **- Normal metaboliser:** Normal metabolism of zuclopenthixol is predicted.	Standard dosing and prescribing measures apply.

OTHER MEDICATIONS

The following tables outline personalised recommendations for other medications.

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

MEDICATIONS WITH ***MINOR*** PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Clobazam (Benzodiazepine)	*CYP2C19* - **Ultrarapid 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. The CYP2C19 genotype predicts increased metabolism of clobazam's active metabolite and a possible reduction in clinical effects. (Note that the effect of variations in CYP3A4 has not been described).	No genotype-guided dosing recommendation available. Be alert to a reduced clinical response.
Diazepam (Benzodiazepine)	*CYP2C19* - **Ultrarapid metaboliser:** Diazepam is metabolised by CYP3A4 and CYP2C19 into active metabolites, including desmethyldiazepam, which has a long half-life. The CYP2C19 genotype predicts increased metabolism of both diazepam and desmethyldiazepam, reduced plasma concentrations and possibly reduced clinical effects. (Note that the effect of variations in the CYP3A4 gene on diazepam metabolism have not been described).	Monitor for reduced clinical response. If an alternative benzodiazepine is required, consider agents not extensively metabolised by CYP2C19, such as oxazepam and lorazepam.
Melatonin	*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).[6] The clinical significance of this is not known.	No genotype-guided dosing recommendation available. Monitor for a reduced clinical effect.

MEDICATIONS WITH ***USUAL*** PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Atomoxetine	*CYP2D6* - **Normal metaboliser:** Normal metabolism by CYP2D6 of atomoxetine is predicted.	Standard dosing and prescribing measures apply.
Dexamphetamine (Psychostimulant)	*CYP2D6* - **Normal metaboliser:** Dexamphetamine is eliminated by both the kidney (as unchanged drug) and the liver, with CYP2D6 playing a significant role. Normal metabolism by CYP2D6 is predicted.	Standard dosing and prescribing measures apply.
Lisdexamfetamine (Psychostimulant)	*CYP2D6* - **Normal metaboliser:** Lisdexamphetamine is a prodrug of dexamphetamine. Dexamphetamine is eliminated by both the kidney (as unchanged drug) and the liver, with CYP2D6 playing a significant role. Normal metabolism by CYP2D6 is predicted.	Standard dosing and prescribing measures apply.

GENETIC TEST RESULTS

GENE	GENOTYPE	PHENOTYPE
CYP2D6	*1/*2	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 CYP2D6, drug exposure and clinical effects may be expected to lie within the normal range.
CYP2C19	*17/*17	Ultrarapid metaboliser Due to the presence of two increased function alleles, this individual is predicted to have an ultrarapid metaboliser phenotype. For a drug extensively metabolised by CYP2C19, drug exposure and clinical effects may either be decreased (for an active drug) or increased (for a prodrug). The individual is at risk of therapeutic failure (active drug) or adverse effects (prodrug).
CYP2C9	*1/*3	Intermediate metaboliser Due to the presence of one normal function allele and one decreased function allele, this individual is predicted to have an 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). This may increase the likelihood of adverse effects (active drug) or therapeutic failure (prodrug).
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).
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.

REFERENCES

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Disclaimer: The pharmacogenomic test result in this report is just one factor that the prescribing doctor will take into consideration when determining a patient's appropriate medication and dose. These interpretations are being provided to the prescribing doctor as a tool to assist in the prescription of medication. Patients are advised not to alter the dose or stop any medications unless instructed by the doctor. The interpretation and clinical recommendations are based on the above results as reported by GenSeq Labs (NATA 20082) and also uses information provided to myDNA by the referring doctor. This report also assumes correct labelling of sample tubes and that the sample is from the above patient.