NutriPATH

# PGX PAIN - PERSONALISED PAIN MEDICATION REPORT

## For Test Patient

| | | | |
|---|---|---|---|
| Date of birth: | myDNA ID: | Lab Ref: | Sample Type: |
| 00-00-0000 | 0000 | 00-0000000 | |
| 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 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:

- 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.

# REPORT SUMMARY

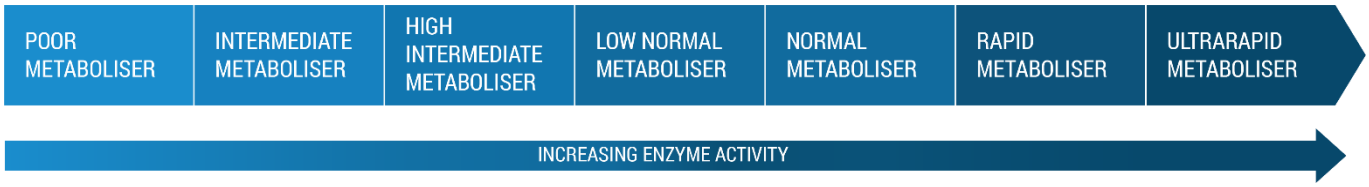
## CLINICAL NOTES

## GENETIC TEST RESULTS SUMMARY

| GENE | GENOTYPE | PHENOTYPE |
|---|---|---|
| *CYP2D6* | *4/*4 | Poor metaboliser |
| *CYP2C19* | *1/*1 | Normal metaboliser |
| *CYP2C9* | *1/*3 | Intermediate metaboliser |
| *CYP1A2* | *1F/*1F | Ultrarapid metaboliser (with inducer present) |
| *OPRM1* | GG | Lower opioid sensitivity |

*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 this test. Laboratory work by Genseq Labs



# NSAIDS

The following tables outline personalised recommendations for nsaids.

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

## MEDICATIONS WITH ***MINOR*** PRESCRIBING CONSIDERATIONS

| MEDICATION | INTERPRETATION | RECOMMENDATION |
|---|---|---|
| Celecoxib | ***CYP2C9*** **- Intermediate metaboliser:** Reduced metabolism and increased celecoxib exposure are predicted[1]. This may increase the risk of concentration-dependent adverse effects such as gastrointestinal bleeding[2]. | No genotype-guided dosing recommendation available. Monitor for adverse effects. Consider general measures to manage the risk of toxicity such as considering alternative treatments, using the lowest effective dose and gastroprotective agents as clinically appropriate. |
| Diclofenac | ***CYP2C9*** **- Intermediate metaboliser:** Diclofenac is only partially metabolised by CYP2C9. This genotype predicts a small increase in diclofenac exposure[3] which may potentially increase the risk of adverse effects[4], especially with high dosages or if drug-drug interactions occur. | Standard dosing and prescribing measures apply. Monitor for adverse effects. |
| Ibuprofen | ***CYP2C9*** **- Intermediate metaboliser:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted[5]. This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding[5]. | No genotype-guided dosing recommendation available. Monitor for adverse effects. Consider general measures to manage the risk of toxicity such as considering alternative treatments, using the lowest effective dose and gastroprotective agents as clinically appropriate. |
| Indomethacin | ***CYP2C9*** **- Intermediate metaboliser:** Indomethacin is only partially metabolised by CYP2C9. This genotype predicts a small increase in indomethacin exposure[6] which may potentially increase the risk of adverse effects, especially with high dosages or if drug-drug interactions occur. | Standard dosing and prescribing measures apply. Monitor for adverse effects. |

| | | |
|---|---|---|
| Mefenamic Acid | *CYP2C9* - **Intermediate metaboliser:** Mefenamic acid is metabolised by CYP2C97. This genotype predicts an increase in mefenamic acid exposure which may potentially increase the risk of adverse effects8, especially with high dosages or if drug-drug interactions occur. | Standard dosing and prescribing measures apply. Monitor for adverse effects. |
| Meloxicam | *CYP2C9* - **Intermediate metaboliser:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted[9]. This may be associated with an increased risk of adverse effects, including gastrointestinal bleeding[2]. | No genotype-guided dosing recommendation available. Monitor for adverse effects. Consider general measures to manage the risk of toxicity such as considering alternative treatments, using the lowest effective dose and gastroprotective agents as clinically appropriate. |
| Piroxicam | *CYP2C9* - **Intermediate metaboliser:** Reduced metabolism by CYP2C9 and increased drug exposure are predicted[5]. This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding[2]. | No genotype-guided dosing recommendation available. Monitor for adverse effects. Consider general measures to manage the risk of toxicity such as considering alternative treatments, using the lowest effective dose and gastroprotective agents as clinically appropriate. |

# OPIOID ANALGESICS

The following tables outline personalised recommendations for opioid analgesics.

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

## MEDICATIONS WITH ***MAJOR*** PRESCRIBING CONSIDERATIONS

| MEDICATION | INTERPRETATION | RECOMMENDATION |
|---|---|---|
| Codeine | ***CYP2D6*** **- Poor metaboliser**<br>***OPRM1*** **- Lower opioid sensitivity:**<br>Greatly reduced metabolism of codeine into its active metabolite morphine. There is a high likelihood of an inadequate analgesic response to codeine.<br><br>The OPRM1 genotype predicts reduced sensitivity to morphine and, by extrapolation, to codeine as well. | Based on the CYP2D6 genotype CPIC[10] provides a strong recommendation to avoid codeine use due to the lack of efficacy. CPIC states that tramadol and to a lesser extent oxycodone are not suitable alternatives. (However, given that oxycodone itself has analgesic activity, it may be effective even in a CYP2D6 poor metaboliser). Examples of opioids not metabolised via CYP2D6 (and therefore not affected by this genetic variation) include morphine and buprenorphine.<br><br>Based on the OPRM1 genotype, there is no genotype-guided dosing recommendation available. |
| Tramadol | ***CYP2D6*** **- Poor metaboliser:**<br>Negligible formation of tramadol's active metabolite is predicted. There is a high likelihood of an inadequate analgesic response to tramadol.<br><br>Note that tramadol is a serotonergic drug. There is an increased risk of serotonin toxicity when used together with other serotonergic drugs. | The DPWG[11] suggests selecting an alternative opioid or to be alert to an inadequate response. Opioids not metabolised by CYP2D6 include morphine and buprenorphine. The DPWG guideline states that codeine and oxycodone are not suitable alternatives, however oxycodone may still have analgesic effect. |

# MEDICATIONS WITH ***MINOR*** PRESCRIBING CONSIDERATIONS

| MEDICATION | INTERPRETATION | RECOMMENDATION |
|---|---|---|
| Morphine | *OPRM1* - **Lower opioid sensitivity:** This genotype has been associated with significantly reduced sensitivity to morphine. In the immediate post-operative setting, it has been associated with significantly higher morphine consumption, higher pain scores, as well as a lower rate of nausea. In the chronic pain setting (including cancer pain), it has also been associated with significantly higher morphine consumption. | No genotype-guided dosing recommendation available. It would be reasonable to monitor for a poorer response to morphine and to consider appropriate modifications to therapy if required. |
| Oxycodone | *CYP2D6* - **Poor metaboliser:** Negligible exposure to oxycodone's active metabolite, oxymorphone, is predicted. Analgesia may be adequate (as oxycodone itself is active) or it may be reduced. | DPWG guidelines recommend selecting an alternative drug or being alert to a reduced analgesic response. If an alternative is sought, consider an opioid not metabolised by CYP2D6 such as morphine or buprenorphine. Codeine and tramadol are not suitable alternatives. |

# 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 ***MAJOR*** PRESCRIBING CONSIDERATIONS

| MEDICATION | INTERPRETATION | RECOMMENDATION |
|---|---|---|
| Amitriptyline (TCA) | ***CYP2D6*** **- Poor metaboliser**<br>***CYP2C19*** **- Normal metaboliser:**<br>Amitriptyline is metabolised by CYP2C19 into an active metabolite, which is further metabolised by CYP2D6 into an inactive metabolite. Normal metabolism of amitriptyline and negligible metabolism (via CYP2D6) of the active metabolite are predicted. Higher plasma concentrations of the active metabolite may increase the risk of adverse effects. | For use at higher doses such as in the treatment of depression, CPIC[12] provides a strong recommendation to avoid amitriptyline use and consider use of an alternative not metabolised by CYP2D6. If a tricyclic is required, consider 50% reduction of the recommended starting dose. Consider therapeutic drug monitoring to guide dose adjustments.<br><br>For use at lower doses such as in treatment of neuropathic pain, initial dose adjustments are not recommended but close monitoring for adverse effects is advisable. |
| Nortriptyline (TCA) | ***CYP2D6*** **- Poor metaboliser:**<br>Greatly reduced nortriptyline metabolism and increased drug exposure are predicted. An increased risk of adverse effects is expected. | For use at higher doses such as in the treatment of depression, CPIC guidelines[12] provide a strong recommendation to avoid nortriptyline and consider an alternative antidepressant not metabolised by CYP2D6. If prescribing nortriptyline, CPIC guidelines recommend a 50% reduction of the recommended starting dose, as well as using therapeutic drug monitoring to guide dose adjustments.<br><br>For use at lower doses such as in treatment of neuropathic pain, initial dose adjustments are not recommended but close monitoring for adverse effects is advisable. |

# MEDICATIONS WITH ***MINOR*** PRESCRIBING CONSIDERATIONS

| MEDICATION | INTERPRETATION | RECOMMENDATION |
|---|---|---|
| Duloxetine (SNRI) | *CYP2D6* - **Poor metaboliser**<br>*CYP1A2* - **Ultrarapid metaboliser (with inducer present):**<br>Duloxetine is metabolised by both CYP1A2 and CYP2D6, with CYP1A2 likely to have the major role. Negligible 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. Be alert to an inadequate response, especially in smokers. |

# GENETIC TEST RESULTS

| GENE | GENOTYPE | PHENOTYPE |
|---|---|---|
| *CYP2D6* | *4/*4 | Poor metaboliser<br>Due to the presence of two null alleles, this individual is predicted to have a poor metaboliser phenotype. For a drug extensively metabolised by CYP2D6, drug exposure and clinical effects may either be greatly increased (for an active drug) or greatly decreased (for a prodrug). The individual is at risk of experiencing adverse effects (active drug) or therapeutic failure (prodrug). |
| *CYP2C19* | *1/*1 | Normal metaboliser<br>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 CYP2C19, drug exposure and clinical effects may be expected to lie within the normal range. |
| *CYP2C9* | *1/*3 | Intermediate metaboliser<br>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)<br>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). |
| *OPRM1* | GG | Lower opioid sensitivity<br>The GG genotype contains two variant alleles for the OPRM1 gene which encodes the mu opioid receptor. Whilst the evidence around OPRM1 genetic variation continues to develop, it appears that the G allele is associated with a reduced response to certain opioids (in particular, morphine). These findings are supported by a number of cohort studies and at least two meta-analyses[13],[14] however, this is not shown in all studies. For naltrexone in the management of alcohol use disorder, some studies have shown an association of the G allele with superior clinical outcomes. Note the frequency of the variant allele (G) is higher in people of Asian ancestry (around 40%) than European ancestry (around 15%). |

# REFERENCES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REPORT PREPARED BY:


**Associate Professor Les Sheffield**
Accredited Pathology Practitioner
MB.BS. FRACP

**Sam Mostafa**
Consultant Pharmacist
BPharm, AACPA, MPS