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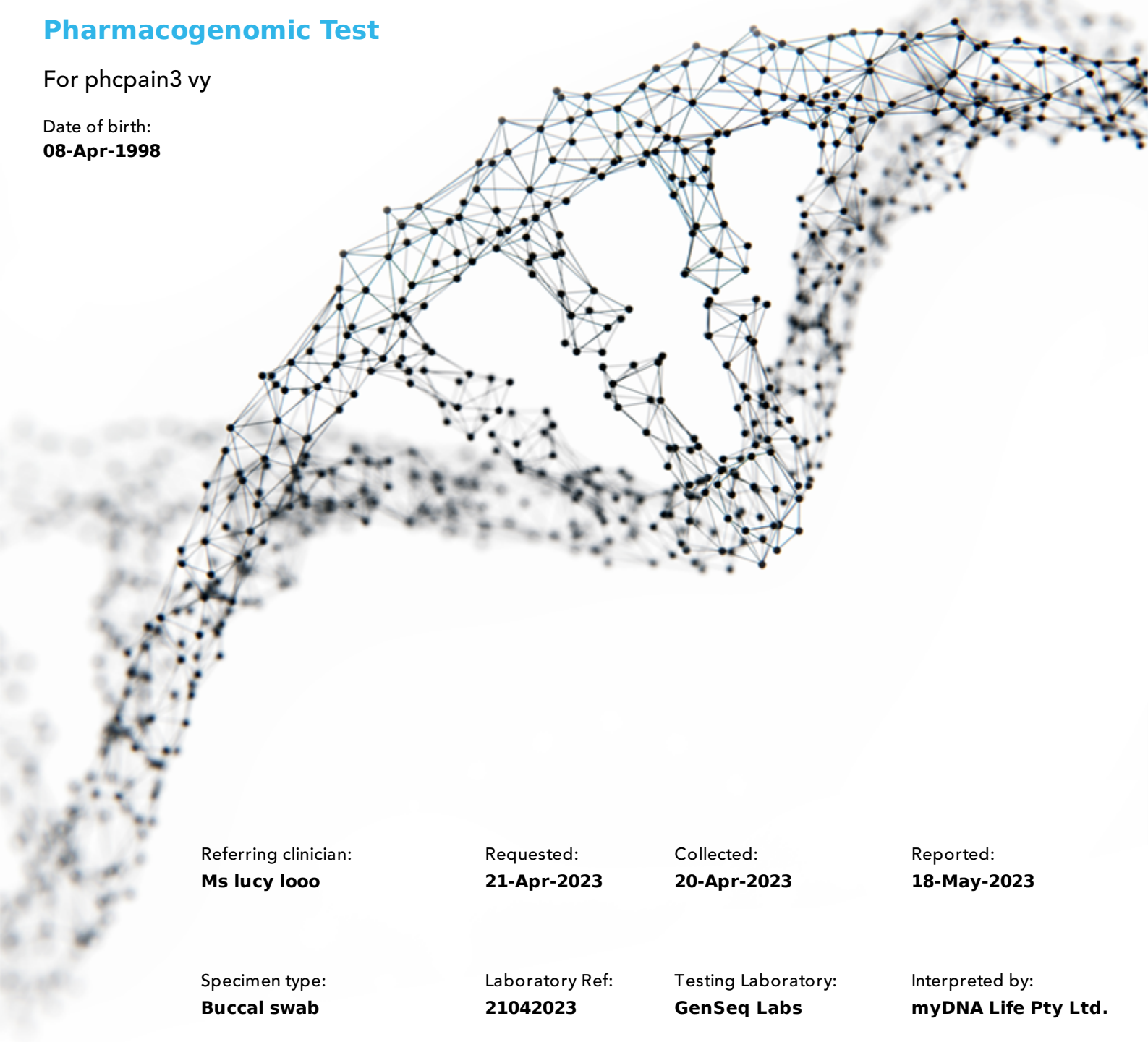
myDNA PAIN MEDICATION REPORT

Pharmacogenomic Test

For phcpain3 vy

Date of birth:
08-Apr-1998



Referring clinician:	Requested:	Collected:	Reported:
Ms lucy looo	**21-Apr-2023**	**20-Apr-2023**	**18-May-2023**

Specimen type:	Laboratory Ref:	Testing Laboratory:	Interpreted by:
Buccal swab	**21042023**	**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 test.

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 four 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.

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.

NO PHARMACOGENOMIC PRESCRIBING CONSIDERATIONS

These medications do not have significant gene-drug interactions identified and standard prescribing considerations apply.

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

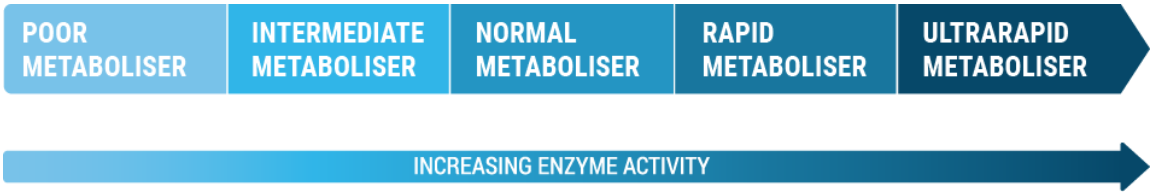
The report consists of the following 4 sections:

1. Genetic test results summary – presents the patient's genotypes for the genes relevant to the medications covered by this report.
2. Medication tables arranged according to the four categories of MAJOR, MINOR, USUAL or NO PHARMACOGENOMIC prescribing considerations.
3. Details of test results – for example, 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 (drug exposure).
4. References – list of key peer-reviewed literature that has been used to produce the report.

TEST RESULTS SUMMARY

GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP1A2	*1A/*1F	**Normal metaboliser**
CYP2C19	*2/*17	**Intermediate metaboliser**
CYP2C9	*1/*2	**Intermediate metaboliser**
CYP2D6	*10/*41	**Intermediate metaboliser**
OPRM1	AA	**Higher opioid sensitivity**

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



NSAIDS - Important Genes (CYP2C9)

Each nsaid below has been allocated to a major, minor, usual, or no prescribing considerations quadrant based on the pharmacogenomic test results. NOTE: These classifications and recommendations do not account for the effect of any inhibitors or inducers and this is not an all-inclusive list of nsaids.

MAJOR PRESCRIBING CONSIDERATIONS

- NONE

MINOR PRESCRIBING CONSIDERATIONS

- CELECOXIB
- IBUPROFEN
- MELOXICAM
- PIROXICAM

USUAL PRESCRIBING CONSIDERATIONS

- DICLOFENAC
- INDOMETHACIN
- MEFENAMIC ACID

NO PHARMACOGENOMIC PRESCRIBING CONSIDERATIONS

- NAPROXEN

OPIOID ANALGESICS - Important Genes (CYP2D6, OPRM1)

Each opioid analgesic below has been allocated to a major, minor, usual, or no prescribing considerations quadrant based on the pharmacogenomic test results. NOTE: These classifications and recommendations do not account for the effect of any inhibitors or inducers and this is not an all-inclusive list of opioid analgesics.

MAJOR PRESCRIBING CONSIDERATIONS

- CODEINE
- TRAMADOL

MINOR PRESCRIBING CONSIDERATIONS

- OXYCODONE

USUAL PRESCRIBING CONSIDERATIONS

- MORPHINE

NO PHARMACOGENOMIC PRESCRIBING CONSIDERATIONS

- TAPENTADOL

OTHER MEDICATIONS - Important Genes (CYP1A2, CYP2C19, CYP2D6)

This section includes medications that are used in pain management which belong to the following groups: Tricyclic antidepressants, Serotonin noradrenaline reuptake inhibitors, Antiepileptics. Each medication below has been allocated to a major, minor, usual, or no prescribing considerations quadrant based on the pharmacogenomic test results. NOTE: These classifications and recommendations do not account for the effect of any inhibitors or inducers and this is not an all-inclusive list of pain management medications.

MAJOR PRESCRIBING CONSIDERATIONS

- AMITRIPTYLINE (TCA)
- NORTRIPTYLINE (TCA)

MINOR PRESCRIBING CONSIDERATIONS

- DULOXETINE (SNRI)

USUAL PRESCRIBING CONSIDERATIONS

- NONE

NO PHARMACOGENOMIC PRESCRIBING CONSIDERATIONS

- PREGABALIN
- GABAPENTIN

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

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
CELECOXIB	**CYP2C9 - Intermediate metaboliser:** There may be mildly reduced metabolism and increased celecoxib exposure.[1] This is more likely to be clinically significant if high doses are used or drug-drug interactions occur.	CPIC guidelines[2] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
IBUPROFEN	**CYP2C9 - Intermediate metaboliser:** Mildly reduced metabolism by CYP2C9 and increased drug exposure are predicted[3]. This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[2] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
MELOXICAM	**CYP2C9 - Intermediate metaboliser:** Slightly reduced metabolism by CYP2C9 and increased drug exposure are predicted.[4] This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[2] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.
PIROXICAM	**CYP2C9 - Intermediate metaboliser:** Mildly reduced metabolism by CYP2C9 and increased drug exposure are predicted.[3] This effect is expected to be relatively minor, but may be exacerbated by high dosages or drug-drug interactions.	CPIC guidelines[2] have a moderate recommendation to initiate therapy with the recommended starting dose. In accordance with prescribing information, use the lowest effective dose for the shortest duration required. Monitor for adverse effects.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
DICLOFENAC	**CYP2C9 - Intermediate metaboliser:** Diclofenac is only partially metabolised by CYP2C9. This genotype is not expected to increase diclofenac exposure significantly[5].	CPIC guidelines[2] state that there is insufficient evidence to provide a recommendation to guide clinical practice at this time. Standard dosing and prescribing measures apply.
INDOMETHACIN	**CYP2C9 - Intermediate metaboliser:** Indomethacin is only partially metabolised by CYP2C9. This genotype is not expected to increase indomethacin exposure significantly.[6]	CPIC guidelines[2] 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	**CYP2C9 - Intermediate metaboliser:** Mefenamic acid is metabolised by CYP2C9.[7] This genotype predicts a small increase in mefenamic acid exposure.	Standard dosing and prescribing measures apply.

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.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
CODEINE	**CYP2D6 - Intermediate metaboliser** **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. 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. Codeine is contraindicated in children under 12 years of age.[8]	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	**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	INTERPRETATION	RECOMMENDATION
OXYCODONE	**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.

USUAL PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
MORPHINE	**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.

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.

MAJOR PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
AMITRIPTYLINE TCA	**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[11] 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.
NORTRIPTYLINE TCA	**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[11] 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.

MINOR PRESCRIBING CONSIDERATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
DULOXETINE SNRI	**CYP2D6 - Intermediate metaboliser** **CYP1A2 - Normal metaboliser:** Duloxetine is metabolised by both CYP1A2 and CYP2D6, with CYP1A2 likely to have the major role. Reduced metabolism by CYP2D6 and normal metabolism by CYP1A2 (less affected by exposure to enzyme inducers such as tobacco smoke) are predicted. This may lead to a small increase in exposure to duloxetine.	No genotype-guided dosing recommendation available. Be alert to adverse effects.

GENETIC TEST RESULTS

GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP1A2	*1A/*1F	**Normal metaboliser:** Due to the presence of only one copy of the *1F allele, this individual is predicted to have a normal metaboliser phenotype. Normal metabolism of CYP1A2 substrate drugs is predicted. Furthermore, metabolism is not expected to be increased by exposure to inducers such as tobacco smoking and certain dietary components and drugs.
CYP2C19	*2/*17	**Intermediate metaboliser:** This individual is predicted to have an intermediate metaboliser phenotype due to the presence of one no function allele and one increased function allele. 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/*2	**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). As the decreased function 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.
CYP2D6	*10/*41	**Intermediate metaboliser:** Due to the presence of two copies of reduced function alleles, 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).
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[12,13] 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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SPEAK TO A SPECIALIST

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This report has been prepared by the myDNA Clinical Team

Laboratory Results provided by:

GenSeq Labs (NATA 20082)

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]) 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 and OPRM1 genes. All variants are named using the HGVS nomenclature.