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Pharmacogenetics Extended Test

Name:	SAMPLE RESULT	DOB:	SAMPLE	Requested:	06-May-2022
Ordering Provider:	SAMPLE	myDNA ID:		Collected:	04-May-2022
		AID:	SAMPLE	Reported:	08-Jun-2022

Submitted medications: **cefdinir, dexmethylphenidate, fluoxetine, sertraline**

Specimen Type: **Buccal**

REPORT SUMMARY

SUBMITTED MEDICATIONS OVERVIEW		
MEDICATION	GENE(S)	PRESCRIBING CONSIDERATIONS BASED ON THIS TEST
Fluoxetine	*CYP2C9* *CYP2D6*	Major – significant result that may require altering this medication
Sertraline	*CYP2C19*	Minor – result should be considered as may affect medication response
MEDICATIONS THAT DO NOT HAVE PRESCRIBING CONSIDERATIONS BASED ON THIS TEST		
cefdinir, dexmethylphenidate		

LEGEND: Major prescribing considerations Minor prescribing considerations Usual prescribing considerations

GENETIC TEST RESULTS OVERVIEW					
GENE	GENOTYPE	PREDICTED PHENOTYPE	GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP2D6	*4/*5	Poor metabolizer	*CYP3A5*	*3/*3	Poor metabolizer
CYP2C19	*1/*17	Rapid metabolizer	*SLCO1B1*	*1/*1	Normal transporter function
CYP2C9	*1/*3	Intermediate metabolizer	*COMT*	AG	Intermediate opioid sensitivity
VKORC1	GG	Normal VKORC1 enzyme level	*CYP2B6*	*1/*6	Intermediate metabolizer
CYP1A2	*1A/*1F	Normal metabolizer	*OPRM1*	AA	Higher opioid sensitivity
CYP3A4	*1/*22	Intermediate metabolizer			

OTHER INFORMATION

The co-administration of fluoxetine and sertraline could increase the risk of serotonin toxicity. It is advisable to monitor serotonin toxicity symptoms if these medications were used concomitantly.

ADDITIONAL INFORMATION FOR CONSIDERATION

The following table lists all submitted current medications known to influence the function of any specific gene product (enzyme) assessed on Lineagen's (d/b/a Bionano Laboratories) Pharmacogenetics Extended Test. This may be useful to consider when making prescribing decisions for any medication known to be metabolized by that specific enzyme (note that this information is NOT considered in the future medication section of this report). For example, a person's genetic test results may predict normal CYP2C19 enzyme function. However, if the person is taking fluvoxamine (a strong CYP2C19 inhibitor), their enzyme function may be reduced. This may have a clinical effect on any prescribed medication extensively metabolized by the CYP2C19 enzyme. Of note, the extent of inhibition or induction effects may depend on the dose and duration of the therapy; moderate and strong drug inhibitor classifications used herein are defined by the Food and Drug Administration (FDA).

MEDICATION	INHIBITOR – MODERATE	INHIBITOR - STRONG	INDUCER
Fluoxetine	CYP2C19	CYP2D6	

SUBMITTED MEDICATIONS

PERSONALIZED INTERPRETATION AND RECOMMENDATIONS

MEDICATION	INTERPRETATION	RECOMMENDATION
Fluoxetine	*CYP2D6* - Poor metabolizer *CYP2C9* - Intermediate metabolizer: 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 enzyme-inhibiting effect of the parent drug and metabolites (especially on CYP2D6). The CYP2D6 genotype predicts increased fluoxetine exposure and reduced formation of the active S-norfluoxetine metabolite. The CYP2C9 genotype predicts reduced metabolism via this pathway. There may be an increased risk of adverse effects.	Based on the CYP2D6 genotype, DPWG[1] recommends that no specific action on fluoxetine dosing is required for this genotype. Monitor for altered clinical effect, including adverse effects. The FDA[2] has cautioned regarding this genotype and increased risk for QT prolongation with fluoxetine. If adverse effects are a concern, consider an alternative antidepressant for which normal metabolism is predicted.
Sertraline	*CYP2C19* - Rapid metabolizer: 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[3] 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 metabolized by CYP2C19.

FUTURE MEDICATIONS

The following tables outline personalized 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. If no published guidelines are listed by the agencies or working groups listed below, data used to classify them as having major prescribing indications can be sought in the primary literature.

LEGEND:

CPIC = Clinical Pharmacogenetics Implementation Consortium TGA = Therapeutic Goods Administration (Australia)

DPWG = The Royal Dutch Pharmacists Association – Pharmacogenetics Working Group

FDA = Food and Drug Administration (US)

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

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
Atomoxetine (ADHD - miscellaneous agents)	*CYP2D6* - Poor metabolizer: Greatly reduced metabolism by CYP2D6 and greatly increased drug exposure is predicted. An increased risk of some side effects has been shown for this genotype (e.g. increased blood pressure and heart rate, QT interval prolongation, dry mouth, erectile dysfunction and insomnia) but also greater improvement of ADHD symptoms as compared to non-poor metabolizers in those who tolerate treatment. This genotype is associated with lower final dose requirements.	CPIC[4] provides a strong recommendation for children and moderate recommendation for adults for dosing of atomoxetine. 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 dose 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 4 hours after dosing to guide titration. Note: FDA-approved drug label[5] 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). For CYP2D6 poor metabolizers or patients on strong CYP2D6 inhibitors, FDA approved labelling[5] advises using a reduced dosing strategy (starting dose 0.5mg/kg/day, and only increasing to 1.2mg/kg/day after 4 weeks if required) in children and adolescent patients with body weight <70kg. For children and adolescents >70kg, and for adults, atomoxetine should be initiated at 40mg/day and only increased to 80mg/day after four weeks if necessary.
Perhexiline (Antianginals)	*CYP2D6* - Poor metabolizer: Greatly reduced metabolism and increased perhexiline exposure are predicted. There is an increased risk of concentration-dependent adverse effects (hepatotoxicity and peripheral neuropathy), especially if appropriate dose reduction and therapeutic drug monitoring do not occur.	Expect a prolonged time to reach steady-state. Early therapeutic drug monitoring is required when perhexiline is used. A greatly reduced maintenance dose requirement is expected. In addition to adjusting dose according to concentration, the AMH[6] notes that poor metabolizers may require doses as low as 50 mg once a week.
Flecainide (Antiarrhythmics)	*CYP2D6* - Poor metabolizer: Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may	The DPWG guidelines[7] suggest reducing the dose to 50% of the standard dose, recording an ECG and monitoring the plasma concentration.

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	increase the risk of concentration-dependent adverse effects.	
Propafenone (Antiarrhythmics)	*CYP2D6* - Poor metabolizer: Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The DPWG[8] suggest reducing the dose to 30% of the standard dose, recording an ECG and monitoring plasma concentrations. The FDA-approved drug label advises avoidance of use of propafenone in CP2D6 poor metabolizers who are also taking a CYP3A4 inhibitor.[9]
Tolterodine (Anticholinergics (genitourinary))	*CYP2D6* - Poor metabolizer: Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects. Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase tolterodine exposure and the risk of adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects. The FDA[10] has cautioned regarding this genotype and increased risk for QT prolongation with tolterodine.
Acenocoumarol (Anticoagulants)	*VKORC1* - Normal VKORC1 enzyme level *CYP2C9* - Intermediate metabolizer: Reduced metabolism of acenocoumarol by CYP2C9 is predicted. Normal amount of VKORC1 present (the enzyme inhibited by acenocoumarol). Overall increased sensitivity to acenocoumarol, an increased risk of both supratherapeutic INR and bleeding, and a lower dose requirement are predicted.	Based on the CYP2C9 genotype, DPWG[11] states that no specific action is required for dosing of acenocoumarol. Genetic variation may lead to a decrease in the required maintenance dose, however there is insufficient evidence that this causes problems when therapy is initiated as usual, i.e. with frequent INR monitoring.
Warfarin (Anticoagulants)	*VKORC1* - Normal VKORC1 enzyme level *CYP2C9* - Intermediate metabolizer: Reduced metabolism of warfarin by CYP2C9 is predicted. Normal amount of VKORC1 (the enzyme warfarin inhibits). Overall increased warfarin sensitivity and increased risk of supratherapeutic INR.	For patients already taking warfarin (eg more than 5 doses), dose adjustment is guided by INR. For patients initiating warfarin, there are CPIC[12] recommendations to reach the therapeutic dose. The summary of CPIC recommendations include consideration of the use of validated published pharmacogenetic algorithms[13],[14] available at warfarindosing.org that take into account clinical details as well as genetic findings. See CPIC guidelines for further details. If the patient identifies to be of African ancestry, CPIC provides recommendations for special dosing requirements for warfarin.
Vortioxetine (Antidepressants - other)	*CYP2D6* - Poor metabolizer: Negligible metabolism by CYP2D6 and increased drug exposure is	The TGA approved Product Information[15] states that a dose adjustment is not required. The FDA[16] approved labelling states that the

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	predicted. This may be associated with an increased risk of concentration-dependent adverse effects.	recommended maximum dose is 10mg for CYP2D6 poor metabolizers. Regardless of which dosing advice is followed, be alert for adverse effects.
Venlafaxine (Antidepressants - SNRIs)	*CYP2D6* - Poor metabolizer: Greatly 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. There are indications that the effectiveness of venlafaxine is reduced when used for management of depression in patients with this genotype.	The DPWG[17] 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.
Citalopram (Antidepressants - SSRIs)	*CYP2C19* - Rapid metabolizer: Increased metabolism of citalopram by CYP2C19 and reduced drug exposure are predicted. This may increase the likelihood of therapeutic failure.	CPIC guidelines[3] provide a moderate recommendation to consider an alternative antidepressant not predominantly metabolized by CYP2C19. If the clinical response has been adequate, a change to therapy may not be required.
Escitalopram (Antidepressants - SSRIs)	*CYP2C19* - Rapid metabolizer: Increased metabolism of escitalopram by CYP2C19 and reduced drug exposure are predicted. This may increase the likelihood of therapeutic failure.	CPIC guidelines[3] provide a moderate recommendation to consider an alternative antidepressant not predominantly metabolized by CYP2C19. If the clinical response has been adequate, a change to therapy may not be required.
Fluoxetine (Antidepressants - SSRIs)	*CYP2D6* - Poor metabolizer *CYP2C9* - Intermediate metabolizer: 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 enzyme-inhibiting effect of the parent drug and metabolites (especially on CYP2D6). The CYP2D6 genotype predicts increased fluoxetine exposure and reduced formation of the active S-norfluoxetine metabolite. The CYP2C9 genotype predicts reduced metabolism via this	Based on the CYP2D6 genotype, DPWG[1] recommends that no specific action on fluoxetine dosing is required for this genotype. Monitor for altered clinical effect, including adverse effects. The FDA[2] has cautioned regarding this genotype and increased risk for QT prolongation with fluoxetine. If adverse effects are a concern, consider an alternative antidepressant for which normal metabolism is predicted.

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	pathway. There may be an increased risk of adverse effects.	
Fluvoxamine (Antidepressants - SSRIs)	***CYP2D6*** **- Poor metabolizer** ***CYP1A2*** **- Normal metabolizer:** Fluvoxamine is metabolized by both CYP2D6 (predominant pathway) and CYP1A2. Negligible metabolism by CYP2D6 and normal metabolism by CYP1A2 (not affected by enzyme inducers such as cigarette smoke) are predicted. Fluvoxamine itself will inhibit CYP1A2. There may be increased exposure to fluvoxamine and potentially increased risk of adverse effects.	Based on the CYP2D6 genotype, CPIC[3] provides an optional recommendation to consider a 25-50% reduction of the recommended starting dose and titrate to response. Alternatively, CPIC recommends using an alternative drug not metabolized by CYP2D6. DPWG [18] suggests no specific action on fluvoxamine dosing is required based on this CYP2D6 genotype.
Paroxetine (Antidepressants - SSRIs)	***CYP2D6*** **- Poor metabolizer:** Greatly reduced metabolism by CYP2D6 and greatly increased drug exposure are predicted. There may be increased adverse effects.	CPIC[3] guidelines provide an optional recommendation to select an alternative drug not predominantly metabolized by CYP2D6. If using paroxetine, consider a 50% reduction of the recommended starting dose and titrate to response. It would also be reasonable to monitor for adverse effects.
Amitriptyline (Antidepressants - TCAs)	***CYP2D6*** **- Poor metabolizer** ***CYP2C19*** **- Rapid metabolizer:** Amitriptyline is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of amitriptyline are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	For use at higher doses such as in the treatment of depression, CPIC[19] provides an optional recommendation to avoid amitriptyline. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise therapeutic drug monitoring to guide dose adjustments. For use at lower doses such as in treatment of neuropathic pain, caution is advised if using any tricyclic.
Clomipramine (Antidepressants - TCAs)	***CYP2D6*** **- Poor metabolizer** ***CYP2C19*** **- Rapid metabolizer:** Clomipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of clomipramine are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[19] provides an optional recommendation to avoid clomipramine. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
Desipramine (Antidepressants - TCAs)	***CYP2D6*** **- Poor metabolizer:** Greatly reduced desipramine metabolism and increased drug	CPIC guidelines[19] provide an optional recommendation to avoid desipramine and consider an alternative antidepressant not

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	exposure are predicted. An increased risk of adverse effects is expected.	metabolized by CYP2D6. If prescribing desipramine, CPIC guidelines recommend a 50% reduction of the recommended steady-state starting dose, as well as using therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
Doxepin (Antidepressants - TCAs)	***CYP2D6* - Poor metabolizer** ***CYP2C19* - Rapid metabolizer:** Doxepin is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of doxepin are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[19] provides an optional recommendation to avoid doxepin. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
Imipramine (Antidepressants - TCAs)	***CYP2D6* - Poor metabolizer** ***CYP2C19* - Rapid metabolizer:** Imipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of imipramine are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[19] provides an optional recommendation to avoid imipramine. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
Nortriptyline (Antidepressants - TCAs)	***CYP2D6* - Poor metabolizer:** 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[19] provide a strong recommendation to avoid nortriptyline and consider an alternative antidepressant not metabolized by CYP2D6. If prescribing nortriptyline, CPIC guidelines recommend a 50% reduction of the recommended steady-state starting dose, as well as using therapeutic drug monitoring to guide dose adjustments. 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 *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
Trimipramine (Antidepressants - TCAs)	***CYP2D6*** **- Poor metabolizer** ***CYP2C19*** **- Rapid metabolizer:** Trimipramine is metabolized by CYP2C19 into an active metabolite, which is further metabolized by CYP2D6 into an inactive metabolite. Slightly increased metabolism and reduced plasma concentrations of trimipramine are predicted. Negligible metabolism by CYP2D6 and increased plasma concentrations of the active metabolite are also predicted.	CPIC[19] provides an optional recommendation to avoid trimipramine. If a tricyclic is required, therapeutic drug monitoring is advised. CPIC advises avoiding nortriptyline as well, but, if warranted, start with 50% of the steady-state starting dose and utilise therapeutic drug monitoring to guide dose adjustments. Note that these recommendations only apply to higher initial doses of tricyclic antidepressants for treatment of conditions such as depression.
Ondansetron (Antiemetics)	***CYP2D6*** **- Poor metabolizer:** Negligible metabolism via CYP2D6 and increased drug exposure are predicted. This has been associated with an improved antiemetic response. It may also increase the risk of concentration-dependent adverse effects.	CPIC[20] notes that there is insufficient evidence for the clinical impact based on this CYP2D6 genotype. The usual starting dose is suggested. It would be advisable to monitor for adverse effects, especially with the use of higher doses.
Tropisetron (Antiemetics)	***CYP2D6*** **- Poor metabolizer:** Significantly reduced metabolism via CYP2D6 and increased drug exposure are predicted. This has been associated with an improved antiemetic response. It may also increase the risk of concentration-dependent adverse effects.	CPIC[20] notes that there is insufficient evidence for the clinical impact based on this CYP2D6 genotype. The usual starting dose is suggested. It would be advisable to monitor for adverse effects, especially with the use of higher doses.
Phenytoin (Antiepileptics)	***CYP2C9*** **- Intermediate metabolizer:** Reduced phenytoin metabolism and increased drug exposure are predicted. This genotype has been associated with an increased risk of concentration-dependent adverse effects.	Based on the CYP2C9 genotype, CPIC guidelines[21] provide a moderate recommendation to use the typical initial or loading dose and for subsequent doses to use approximately 25% less than the typical maintenance dose. Subsequent dose adjustments should be guided by therapeutic drug monitoring and clinical response. CPIC also addresses genetic testing for the presence of the HLA-B*15:02 allele (not currently tested by myDNA, but which may be requested through a local service if required) which is known to increase the risk of phenytoin-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. The guidelines state that if both HLA-B*15:02 and CYP2C9 genotypes are known, consider the HLA-B*15:02 genotype first, then CYP2C9 genotype. In the instance of an HLA-B*15:02 positive result, CPIC provide a strong recommendation to not use phenytoin in patients who have never had phenytoin

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
		before, and to also avoid carbamazepine and oxcarbazepine. Phenytoin may be used cautiously in patients who have tolerated the drug previously for longer than three months without occurrence of adverse skin reactions.
Voriconazole (Antifungals - Azoles)	*CYP2C19* - Rapid metabolizer: Increased voriconazole metabolism and reduced plasma concentrations are predicted. Using standard dosing, there is an increased risk of subtherapeutic drug concentrations.	For adult patients, CPIC guidelines[22] provide a moderate recommendation to choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B and posaconazole, as clinically appropriate. For paediatric patients with this genotype, CPIC provides a moderate recommendation to initiate therapy with the recommended standard of care dosing, with meticulous use of therapeutic drug monitoring to titrate dose to therapeutic trough concentrations. CPIC also notes that achieving voriconazole therapeutic concentrations in the paediatric population with rapid metabolizer phenotypes in a timely manner is difficult, thus an alternative antifungal agent is recommended for effective antifungal therapy to be achieved as soon as possible.
Aripiprazole (Antipsychotics)	*CYP2D6* - Poor metabolizer: Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	FDA-approved labelling [23] advises use of 50% of the usual dose. Additionally, if aripiprazole is prescribed together with a strong CYP3A4 inhibiting drug, the dose should be reduced to 25% of the usual dose. For the injectable depot (Abilify Maintena), the FDA- approved label and TGA-approved product information [24] recommends for CYP2D6 poor metabolizers to use a starting and maintenance dose of 300 mg and for CYP2D6 poor metabolizers taking CYP3A4 inhibitors, a 200 mg dose is advised. Note the DPWG[25] recommends administering no more than 10mg/day or 300 mg/month (67-75% of the standard maximum dose), for CYP2D6 poor metabolizers.
Aripiprazole Lauroxil (Antipsychotics)	*CYP2D6* - Poor metabolizer: Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	Aristada Initio®: The FDA-approved drug label[26] advises avoiding use of Aristada Initio in CYP2D6 poor metabolizers. Aristada®: For patients known to be CYP2D6 poor metabolizers and are on concomitant strong CYP3A4 inhibitors for more than 2 weeks, the FDA-approved drug label[27] advises reducing

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
		the dose to 441 mg from 662 mg, 882 mg or 1064 mg for poor metabolizers. No dosage adjustment is required in patients tolerating 441 mg of Aristada. For patients known to be CYP2D6 poor metabolizers and on concomitant strong CYP2D6 inhibitors, no dose adjustment is required.
Brexpiprazole (Antipsychotics)	*CYP2D6* - Poor metabolizer: Poor metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	DPWG guidelines and FDA-approved labelling[28], [29] advise initial treatment with 50% of the usual dose and adjusting according to clinical response. Additionally, if brexpiprazole is prescribed together with a strong CYP3A4 inhibiting drug, the dose should be reduced to 25% of the usual dose.[29]
Haloperidol (Antipsychotics)	*CYP2D6* - Poor metabolizer: Poor reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The DPWG[30] suggests reducing the initial dose of haloperidol by 50% and adjusting to effect, or using an alternative drug.
Iloperidone (Antipsychotics)	*CYP2D6* - Poor metabolizer: Significantly reduced metabolism of iloperidone by CYP2D6 is predicted and therefore increased drug exposure is possible, leading to an increased risk of adverse effects. The FDA-approved drug label notes that poor metabolizers are expected to have higher drug exposures than extensive metabolizers. [31]	The FDA-approved drug label advises that poor metabolizers should have their dose reduced by one-half.[31]
Pimozide (Antipsychotics)	*CYP2D6* - Poor metabolizer: Negligible metabolism by CYP2D6 and significantly increased drug exposure are predicted. This may increase the risk of concentration dependant adverse effects.	FDA-approved[32] labelling advises: 1) in children, not exceeding a dose of 0.05mg/kg/day and not increasing the dose earlier than 14 days; 2) in adults, not exceeding a dose of 4mg/day and not increasing the dose earlier than 14 days. The DWPG[33] recommends using no more than 50% of the standard maximum dose.
Risperidone (Antipsychotics)	*CYP2D6* - Poor metabolizer: Poor metabolism and increased drug exposure to risperidone is predicted. This has been associated with both an increased risk of certain adverse effects and a stronger decrease in symptoms when used in schizophrenia. An increased proportion of therapeutic failure has been observed with this genotype.	The DPWG[34] suggests using 67% of the standard dose. If problematic side effects originating from the central nervous system occur despite this reduced dose, a further reduction in dose to 50% of the standard dose is advised.

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
Thioridazine (Antipsychotics)	*CYP2D6* - Poor metabolizer: Negligible metabolism by CYP2D6 and significantly increased drug exposure are predicted, with the increased risk of adverse effects. The reduction in clearance of thioridazine is 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 QTc interval, and presence of congenital prolongation of the QT interval.	The FDA-approved drug label states that thioridazine is contraindicated in patients with reduced activity of CYP2D6.[35]
Dextromethorphan (Antitussives)	*CYP2D6* - Poor metabolizer: Greatly reduced metabolism and increased drug exposure are predicted. This may increase the risk of adverse effects.	No genotype-guided dosing recommendation available. Monitor for adverse effects.
Efavirenz (Antivirals)	*CYP2B6* - Intermediate metabolizer: Reduced metabolism of efavirenz and higher dose-adjusted trough concentrations compared with normal metabolizers is predicted. This has been associated with an increased risk of concentration-dependent adverse effects, including CNS adverse events.	CPIC[36] provides a moderate recommendation to consider initiating efavirenz with decreased dose of 400 mg/day. If therapeutic drug monitoring is available and a decreased dose of efavirenz is prescribed, consider obtaining steady-state plasma efavirenz concentrations to ensure they are in the suggested therapeutic range. The potential benefits and risks of the reduced dose and pill number should be considered.
Metoprolol (Beta blockers)	*CYP2D6* - Poor metabolizer: Negligible metabolism by CYP2D6 and greatly increased metoprolol exposure are predicted. Clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.	Be alert to adverse effects such as bradycardia. Where a more gradual reduction in heart rate is desired, or where there are greater concerns for symptomatic bradycardia, DPWG[37] has recommendations to increase the dose in smaller steps and/or prescribe no more than 25% of the standard dose. If currently well tolerated and clinical response has been adequate, a change to therapy may not be required.
Timolol (Beta blockers)	*CYP2D6* - Poor metabolizer: Negligible metabolism by CYP2D6 and increased drug exposure are predicted. The poor metabolizer phenotype has been associated with increased clinical effects, including systemic beta-blocking adverse effects, observed with ophthalmic timolol aqueous (but not gel) preparations.	Monitor for systemic beta blocker adverse effects such as bradycardia and bronchospasm.
Dapoxetine	*CYP2D6* - Poor metabolizer: Negligible metabolism by CYP2D6	The TGA[38] approved product information recommends caution with prescribing, given

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
(Drugs for sexual dysfunction)	and increased drug exposure are predicted. This may increase the risk of adverse effects. Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase dapoxetine exposure and the risk of adverse effects.	the increased predicted drug exposure. Consider alternative therapy. If using dapoxetine, monitor closely for adverse effects.
Tamoxifen (Immunomodulators and antineoplastics)	*CYP2D6* - Poor metabolizer: 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 and higher mortality, whilst others have not shown such effects.	For the adjuvant treatment of ER+ breast cancer, CPIC [39] provides a strong recommendation to use alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women. Note that higher dose tamoxifen (40mg/d) increases but does not normalize endoxifen concentrations, and can be considered if there are contraindications to aromatase inhibitor therapy.
Eliglustat (Miscellaneous)	*CYP2D6* - Poor metabolizer: Negligible metabolism of eliglustat by CYP2D6 and greatly increased drug exposure are predicted. Increased risk of adverse effects, especially if appropriate dose adjustments are not made.	The recommended dose of eliglustat depends on whether CYP3A4 and/or CYP2D6 inhibiting medications are co-prescribed. See the TGA approved Product Information[40] for details before prescribing.
Tamsulosin (Miscellaneous)	*CYP2D6* - Poor metabolizer: Reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects. Concomitant use with CYP3A4 inhibiting drugs may be expected to further increase tamsulosin exposure and the risk of adverse effects.	Monitor for adverse effects. The FDA[41] has cautioned regarding this genotype and recommends the 0.4mg dose should not be used with strong inhibitors of CYP3A4 and should be used with caution in combination with strong or moderate inhibitors of CYP2D6 or in patients known to be CYP2D6 poor metabolizers, particularly at a dose higher than 0.4mg.
Deutetrabenazine (Neurological drugs)	*CYP2D6* - Poor metabolizer: Reduced metabolism by CYP2D6 and significantly increased drug exposure are predicted as compared with extensive. metabolizers,[42] This could lead to increased adverse effects including QT prolongation.	The FDA-approved drug label advises that the in poor metabolizers: 1. Total daily dose should not exceed 36 mg (maximum single dose of 18 mg) 2. A clinically relevant QT prolongation may occur in some patients treated with deutetrabenazine. [42] As such, monitoring for adverse effects is recommended.
Siponimod (Neurological drugs)	*CYP2C9* - Intermediate metabolizer: A reduced metabolism of siponimod and higher plasma	DPWG[43] and the FDA-approved drug label[44] recommend the use of 50% of the normal maintenance dose in patients with the CYP2C9 *1/*3 genotype. The FDA-approved drug label

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	concentration is predicted with the *1/*3 genotype, and by extension, other genotypes with comparable genetic variations to *1/*3.	states that in patients with the CYP2C9 *1/*3 genotype, treatment initiation should be with a 4-day titration, starting at 0.25 mg daily and gradually increasing until the maintenance dose of 1 mg on Day 5 of treatment. They also advise reconsideration or recommend against concomitant use of siponimod with moderate or strong CYP3A4 inducers in such patients due to a decrease in siponimod exposure. It would be reasonable to apply this recommendation to patients with a comparable genetic variation.
Tetrabenazine (Neurological drugs)	*CYP2D6* - Poor metabolizer: Greatly reduced metabolism by CYP2D6 and increased drug exposure are predicted. This may increase the risk of concentration-dependent adverse effects.	The FDA[45] approved drug label advises a maximum daily dose of 50mg, with a maximum recommended single dose of 25mg.
Piroxicam (NSAIDs)	*CYP2C9* - Intermediate metabolizer: Reduced metabolism by CYP2C9 and increased drug exposure are predicted.[46] This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding[47].	CPIC guidelines[48] have a moderate recommendation to choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 variants in vivo (such as aspirin, ketorolac, naproxen or sulindac), or choose an NSAID metabolized by CYP2C9 but with a shorter half-life (such as celecoxib, flurbiprofen, ibuprofen or lornoxicam).
Tenoxicam (NSAIDs)	*CYP2C9* - Intermediate metabolizer: Reduced metabolism by CYP2C9 and increased drug exposure are predicted. This has been associated with an increased risk of adverse effects, including gastrointestinal bleeding.	CPIC guidelines[48] have a moderate recommendation to choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 variants in vivo (such as aspirin, ketorolac, naproxen or sulindac), or choose an NSAID metabolized by CYP2C9 but with a shorter half-life (such as celecoxib, flurbiprofen, ibuprofen or lornoxicam).
Codeine (Opioid Analgesics)	*CYP2D6* - Poor metabolizer *OPRM1* - Higher opioid sensitivity: Greatly reduced metabolism of codeine into its active metabolite morphine. This results in lower systemic active metabolite concentrations and may result in reduced efficacy.[49] Whilst this OPRM1 genotype has been associated with increased sensitivity to morphine and by extrapolation, to codeine as well, based on the CYP2D6 Poor metabolizer status, this result is	Based on the CYP2D6 genotype CPIC[50] provides a strong recommendation to avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid. There is no additional genotype-guided dosing recommendation based on the OPRM1 result.

MEDICATIONS WITH *MAJOR* PRESCRIBING CONSIDERATIONS		
MEDICATION (DRUG CATEGORY)	INTERPRETATION	RECOMMENDATION
	unlikely to be significant for codeine.	
Tramadol (Opioid Analgesics)	*CYP2D6* - Poor metabolizer: Negligible 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[50] provide a strong recommendation to avoid tramadol use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-codeine opioid.
Amphetamine (Psychostimulants)	*CYP2D6* - Poor metabolizer: Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is involved in the formation of an active metabolite 4-hydroxy-amphetamine. Reduced metabolism by CYP2D6 is predicted which could lead to variations in amphetamine metabolism.[51] The increased levels of amphetamine may lead to an increased risk of adverse effects.[52]	The FDA advises consideration of use of a lower starting dosage, or use of an alternative agent.[52] Monitor for adverse effects.

MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Angiotensin receptor blockers	Irbesartan	*CYP2C9*	Increased therapeutic and/or adverse effects	-
	Losartan	*CYP2C9*	Reduced / inadequate response	-
Anticholinergics (genitourinary)	Darifenacin	*CYP2D6*	Adverse effects	-
	Fesoterodine	*CYP2D6*	Adverse effects	-
Anticholinesterases	Donepezil	*CYP2D6*	Adverse effects	-
	Galantamine	*CYP2D6*	Adverse effects	FDA[53]
Antidepressants - other	Bupropion	*CYP2B6*	Altered response	-
	Mirtazapine	*CYP2D6* *CYP1A2*	Adverse effects	DPWG[54]
Antidepressants - SNRIs	Duloxetine	*CYP2D6* *CYP1A2*	Adverse effects	-
Antidepressants - SSRIs	Sertraline	*CYP2C19*	Reduced / inadequate response	CPIC[3]
Antidepressants - TCAs	Amoxapine	*CYP2D6*	Increased therapeutic and/or adverse effects	FDA[55]
	Protriptyline	*CYP2D6*	Increased therapeutic and/or adverse effects	FDA[56]
Antidiabetics	Gliclazide	*CYP2C9* *CYP2C19*	Increased therapeutic and/or adverse effects	DPWG[57]

MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
	Glimepiride	*CYP2C9*	Increased therapeutic and/or adverse effects	DPWG[58]
	Glipizide	*CYP2C9*	Increased therapeutic and/or adverse effects	-
	Glyburide	*CYP2C9*	Increased therapeutic and/or adverse effects	DPWG[59]
Antiemetics	Metoclopramide	*CYP2D6*	Adverse effects	FDA[60]
Antiepileptics	Brivaracetam	*CYP2C19*	Reduced / inadequate response	-
Antihistamines	Chlorpheniramine	*CYP2D6*	Adverse effects	-
	Dexchlorpheniramine	*CYP2D6*	Adverse effects	-
	Promethazine	*CYP2D6*	Adverse effects	-
Antiplatelet drugs	Clopidogrel	*CYP2C19*	Adverse effects	CPIC[61]
Antipsychotics	Chlorpromazine	*CYP2D6*	Adverse effects	-
	Clozapine	*CYP2D6* *CYP1A2*	Adverse effects	FDA[62]
	Perphenazine	*CYP2D6*	Adverse effects	FDA[63]
	Quetiapine	*CYP3A4*	Adverse effects	-
Antivirals	Nevirapine	*CYP2B6*	Adverse effects	-
Benzodiazepines	Clobazam	*CYP2C19*	Reduced / inadequate response	-
	Diazepam	*CYP2C19*	Reduced / inadequate response	-
Beta blockers	Carvedilol	*CYP2D6*	Adverse effects	DPWG[64]
	Propranolol	*CYP2D6* *CYP1A2*	Adverse effects	-
Immunomodulators and antineoplastics	Gefitinib	*CYP2D6*	Adverse effects	FDA[65], DPWG[66]
Miscellaneous	Avatrombopag	*CYP2C9*	Altered response	FDA[67]
	Cevimeline	*CYP2D6*	Adverse effects	FDA[68]
	Cyclophosphamide	*CYP2C19*	Increased therapeutic and/or adverse effects	-
	Dronabinol	*CYP2C9*	Adverse effects	-
	Flibanserin	*CYP2C19*	Reduced / inadequate response	-
	Lesinurad	*CYP2C9*	Adverse effects	-
	Lofexidine	*CYP2D6*	Adverse effects	FDA[69]
	Meclizine	*CYP2D6*	Adverse effects	FDA[70]
	Proguanil	*CYP2C19*	Adverse effects	-
Neurological drugs	Carisoprodol	*CYP2C19*	Reduced / inadequate response	-
	Valbenazine	*CYP2D6*	Adverse effects	FDA[71]
NSAIDs	Celecoxib	*CYP2C9*	Increased therapeutic and/or adverse effects	CPIC[48]
	Flurbiprofen	*CYP2C9*	Adverse effects	CPIC[48]
	Ibuprofen	*CYP2C9*	Adverse effects	CPIC[48]
	Lornoxicam	*CYP2C9*	Adverse effects	CPIC[48]
	Mefenamic Acid	*CYP2C9*	Adverse effects	-
	Meloxicam	*CYP2C9*	Adverse effects	CPIC[48]
Opioid Analgesics	Hydrocodone	*CYP2D6*	Reduced / inadequate response	CPIC[50]
	Methadone	*CYP2B6*	Adverse effects	-
	Oxycodone	*CYP2D6*	Reduced / inadequate response	DPWG[72]
Proton pump inhibitors	Dexlansoprazole	*CYP2C19*	Reduced / inadequate response	CPIC[73]
	Esomeprazole	*CYP2C19*	Reduced / inadequate response	-
	Lansoprazole	*CYP2C19*	Reduced / inadequate response	CPIC[73]

MEDICATIONS WITH *MINOR* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
	Omeprazole	*CYP2C19*	Reduced / inadequate response	CPIC[73]
	Pantoprazole	*CYP2C19*	Reduced / inadequate response	CPIC[73]
	Rabeprazole	*CYP2C19*	Reduced / inadequate response	-
Psychostimulants	Dextroamphetamine	*CYP2D6*	Adverse effects	FDA[74]
	Lisdexamfetamine	*CYP2D6*	Adverse effects	FDA[75]
Statins	Atorvastatin	*SLCO1B1* *CYP3A4*	Increased therapeutic and/or adverse effects	-
	Fluvastatin	*SLCO1B1* *CYP2C9*	Increased therapeutic and/or adverse effects	-
	Simvastatin	*SLCO1B1* *CYP3A4*	Increased therapeutic and adverse effects	CPIC[76]

MEDICATIONS WITH *USUAL* PRESCRIBING CONSIDERATIONS				
DRUG CATEGORY	MEDICATION	GENE(S) INVOLVED	POTENTIAL CLINICAL ISSUES	PUBLISHED GUIDELINES
Antiepileptics	Lacosamide	*CYP2C19*	Reduced / inadequate response	-
Antipsychotics	Olanzapine	*CYP1A2*	No altered effect predicted by genotype	-
Beta blockers	Nebivolol	*CYP2D6*	Monitor for adverse effects	FDA[77]
Calcineurin inhibitors	Tacrolimus	*CYP3A5*	No altered effect predicted by genotype	CPIC[78]
Drugs for alcohol dependence	Naltrexone	*OPRM1*	Limited association with reduced response	CPIC[50]
Endocrine drugs	Elagolix	*SLCO1B1*	No altered effect predicted by genotype	-
Hypnotics	Melatonin	*CYP1A2*	No altered effect predicted by genotype	-
Immunomodulators and antineoplastics	Erdafitinib	*CYP2C9*	No altered effect predicted by genotype	-
Miscellaneous	Atazanavir	*CYP3A5*	No altered effect predicted by genotype	-
	Mirabegron	*CYP2D6*	No altered effect predicted by genotype	FDA[79], EMA[80]
NSAIDs	Diclofenac	*CYP2C9*	Increased drug exposure	CPIC[48]
	Indomethacin	*CYP2C9*	Increased drug exposure	CPIC[48]
Opioid Analgesics	Morphine	*OPRM1* *COMT*	Associated with increased sensitivity to morphine	CPIC[50]
Statins	Pravastatin	*SLCO1B1*	No altered effect predicted by genotype	-
	Rosuvastatin	*SLCO1B1*	No altered effect predicted by genotype	-

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PHARMACOGENOMIC INTERPRETATION

EXPLANATION OF GENETIC RESULTS		
GENE	GENOTYPE	PREDICTED FUNCTION
CYP2D6	*4/*5	*CYP2D6* - Poor metabolizer Due to the presence of one null allele and one deletion , this individual is predicted to have a poor metabolizer phenotype. For a drug extensively metabolized 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/*17	*CYP2C19* - Rapid metabolizer Due to the presence of one normal function allele and one increased function allele, this individual is predicted to have a rapid metabolizer phenotype. For a drug extensively metabolized by CYP2C19, drug exposure and clinical effects may either be slightly decreased (for an active drug) or slightly increased (for a prodrug). This individual is at risk of therapeutic failure (active drug) or adverse effects (prodrug).
CYP2C9	*1/*3	*CYP2C9* - Intermediate metabolizer Due to the presence of one normal function allele and one null allele, this individual is predicted to have an intermediate metabolizer phenotype. For a drug extensively metabolized 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).
VKORC1	GG	*VKORC1* - Normal VKORC1 enzyme level The VKORC1 enzyme is predicted to be present in normal amounts and the response to warfarin will be normal. The *CYP2C9* genotype should also be considered together with the *VKORC1* genotype for calculating the initial warfarin dose.
CYP1A2	*1A/*1F	*CYP1A2* - Normal metabolizer Due to the presence of only one copy of the *1F allele, this individual is predicted to have a normal metabolizer 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.
CYP3A4	*1/*22	*CYP3A4* - Intermediate metabolizer This individual carries one copy of the reduced function *22 allele and is predicted to have an intermediate metabolizer phenotype. Reduced metabolism of certain CYP3A4 substrate drugs (e.g. quetiapine) is expected. This may result in increased drug exposure and clinical effects.
CYP3A5	*3/*3	*CYP3A5* - Poor metabolizer Due to the presence of two no function alleles, this individual is predicted to have a poor metabolizer phenotype (CYP3A5 non-expresser). CYP3A5 is known to metabolize certain drugs, including tacrolimus. Note that this individual's genotype 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.

EXPLANATION OF GENETIC RESULTS		
GENE	GENOTYPE	PREDICTED FUNCTION
COMT	AG	*COMT* - Intermediate opioid sensitivity The AG genotype contains one variant allele (A) and one normal allele (G) for the COMT gene, which encodes the COMT enzyme that metabolizes catecholamines. Individuals with the AG genotype treated with opioids for pain may have an increased response and a lower dose requirement when compared to those with the GG genotype, but a decreased response and higher dose requirement when compared to those with the AA genotype. Contradictory studies exist for this association. A patient's opioid dosage and response is also influenced by other genetic and clinical factors.
CYP2B6	*1/*6	*CYP2B6* - Intermediate metabolizer Due to the presence of one normal functioning allele and one reduced or non-functioning allele, this individual is predicted to have an intermediate metabolizer phenotype. For a drug extensively metabolized by CYP2B6, 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).
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[81],[82] 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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Gene by Gene Ltd in a CAP and CLIA accredited laboratory (CAP Number 7212851, CLIA Number 45D1102202).
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TEST 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 of classification listed in this report 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 many medications covered in this report, international, peer reviewed prescribing guidelines are available and these are included in our report.

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 eleven gene test (i.e. seven genes encoding CYP450 metabolising enzymes relevant to a large number of medications, VKORC1 which relates to warfarin sensitivity, SLCO1B1 which relates to statin induced myopathy and OPRM1, COMT which relate to morphine sensitivity).
- Current Medications – 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 service, we have a team of genetic counselors available to answer any questions you may have about this report or about pharmacogenomics in general. If you have any queries, please call our GC team at 801-931-6191.

TEST METHODOLOGY AND LIMITATIONS: Gene by Gene is a College of American Pathologists (CAP) accredited and Clinical Laboratory Improvement Amendments (CLIA) certified clinical laboratory (accredited lab No 45D1102202) qualified to perform high-complexity testing. This test is comprised of the Veridose Core and Veridose CYP2D6 CNV panels developed by Agena, and its performance characteristics have been determined by Gene by Gene. It has not been cleared or approved by the FDA. FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. The genomic regions listed in this report were tested using the Agena MassARRAY® 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 counseling is recommended to properly review and explain these results to the tested individual.

Response to medications is complex and may also be influenced by factors which are not tested for (e.g. patient adherence to prescription regimen, concurrent illness, drug-drug interactions). The test only determines details of response to medications listed by the health professional. 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. The interpretation and clinical recommendations are based on the above results as reported by Gene by Gene and also uses information provided to myDNA Life Inc. by the referring healthcare professional via Lineagen Inc. (d/b/a Bionano Laboratories). 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 current list of reported haplotypes are below. Unless otherwise indicated, the *1 allele denotes the absence of any variant and is designated as the wild type: CYP2D6 *2 (LRG_303:g.7870C>T; 9200G>C), *3 (LRG_303:g.7569del), *4 (LRG_303:g.[5119C>T; 6866G>A; 9200G>C]), *5 (del(CYP2D6)), *6 (LRG_303:g.6727del), *7 (LRG_303:g.7955A>C), *8 (LRG_303:g.[6778G>T; 7870C>T; 9200G>C), *9 (LRG_303:g. 7635_7637del), *10 (LRG_303:g.[5119C>T; 9200G>C]), *11 (LRG_303:g.[9200G>C ;590G>C]), *12 (LRG_303:g.[5143G>A; 7870C>T; 9200G>C]), *114 (LRG_303:g.[5119C>T; 6778G>A ; 7870C>T; 9200G>C]), *14 (LRG_303:g.[6778G>A ;7870C>T; 9200G>C]),*15 (LRG_303:g.5156dup), *17 (LRG_303:g.[6041C>T; 7870C>T; 9200G>C], *18 (NC_000022.11:g.42126666_42126667insAGTGGGCAC), *19 (LRG_303:g.[7559_7562del; 9200G>C;]), *20 (LRG_303:g.[6996dup; 9200G>C]), *29 (LRG_303:g.[7870C>T;8203G>A;9200G>C], *36 (NC_000022.10:g.[42526694G>A ;42522624_42522669con42536337_42536382]), *41(LRG_303:g.[7870C>T; 8008G>A; 9200G>C]), *69 (LRG_303:g.[5119C>T; 8008G>A; 9200G>C]); CYP2C19 *2 (NG_008384.3:g.24179G>A), *3 (NG_008384.3:g.22973G>A), *4A (NG_008384.3:g.5026A>G), *4B (NG_008384.3:g.[4220C>T; 5026A>G), *5 (NG_008384.3:g. 95058C>T), *6 (NG_008384.3:g.17773G>A), *7 (NG_008384.3:g.24319T>A), *8 (NG_008384.3:g.17736T>C), *17 (NG_008384.3:g.4220C>T); CYP2C9 *2 (LRG_1195:g.9133C>T), *3(LRG_1195:g.48139A>C),*4 (LRG_1195:g.48140T>C), *5 (LRG_1195:g.48144C>G), *6 (LRG_1195:g.16126del), *8 (LRG_1195:g. 9152G>A), *11 (LRG_1195:g. 48067C>T), *12 (LRG_1195:g.55863C>T), *13 (LRG_1195:g.8801T>C), *15 (LRG_1195:g.14625C>A), *25 (LRG_1195:g.9056_9065del), *27 (LRG_1195:g. 9152G>T); VKORC1 - rs9923231 NM_024006.5:c.-1639G>A; CYP1A2 *1C (LRG_1274:g.2035G>A), *1F (LRG_1274:g.5732C>A), *1K (LRG_1274:g.[5166C>T; 5732C>A]), *1L (LRG_1274:g.[2035G>A; 5732C>A]), *7 (LRG_1274:g.9427G>A), *11 (LRG_1274:g.6452C>A); CYP3A4 *2 (NG_008421.1:g.20826T>C), *17 (NG_008421.1:g.20728T>C), *22 (NG_008421.1:g.20493C>T); CYP3A5 *1A(NG_007938.1:g.12083G>A) *2(NG_007938.1:g.[12083G>A; 32386C>A]), *3 (NG_007938.1:g), *6 (NG_007938.1:g.[12083G>A; 19787G>A]), *7 (NG_007938.1:g.[12083G>A;32228dup]); SLCO1B1 - rs4149056 NM_006446.4:c.521T>C; COMT – rs4680 (LRG_1010:g.27009G>A); CYP2B6 *6 (LRG_1267:g.20638G>T), *18 (LRG_1267:g.26018T>C) and OPRM1 - rs1799971 NM_000914.4:c.118A>G.