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Mantara® PGx DNA Test Report

[redacted]

Surname:	[redacted]	Date of birth:	[redacted]
First name:	[redacted]	Sample ID:	[redacted]
Sex:	[redacted]	Sampling date:	[redacted]

How to use this report

The information in this report is intended for interpretation by a medically-trained doctor or other qualified prescriber.

This report should be discussed with your doctor/qualified prescriber prior to making any changes to your prescription medication.
Do not make any changes to your medication without the agreement of your doctor/qualified prescriber.

Please also read the Disclaimer section later in this report.

Result and evaluation of all pharmacogenomic analyses

Pharmacogenomic variants affecting drug response (see below for detailed results)

Gene	Phenotype / status
CYP2B6	CYP2B6 POOR METABOLIZER
CYP2C9	CYP2C9 *1/*2
CYP2D6	CYP2D6 ULTRARAPID METABOLIZER
F5	FACTOR V LEIDEN HETEROZYGOUS

Drugs with therapeutic recommendations (in alphabetical order)

- Amitriptyline
- Atomoxetine
- Clomipramine
- Codeine
- Doxepin
- Efavirenz
- Eliglustat
- Flecainide
- Haloperidol
- Imipramine
- Metoprolol
- Nortriptyline
- Oestrogen containing contraceptives
- Paroxetine

For questions relating to this report, please contact
the UK Responsible Person:

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- Phenytoin
- Propafenone
- Risperidone
- Tramadol
- Venlafaxine
- Zuclopenthixol

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RECOMMENDATIONS (in alphabetical order)

Amitriptyline

Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.

The risk of ineffectiveness is increased and the risk of cardiotoxic side effects may be increased. The gene variation leads to increased conversion of amitriptyline and the active metabolite nortriptyline to less active and inactive metabolites.

- increase the dose to 1.4 times the standard dose, monitor the effect and side effects or the plasma concentrations and be alert to increased plasma concentrations of the cardiotoxic Z-10-hydroxy metabolites. Plasma concentrations of Z-hydroxy nortriptyline or Z-hydroxy amitriptyline higher than 40 ng/mL are considered toxic.

- if a dose increase is not desirable due to the cardiotoxic hydroxy metabolite: avoid amitriptyline Anti-depressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Atomoxetine

Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.

The genetic variation results in an increased conversion of atomoxetine to the active metabolite 4-hydroxyatomoxetine, which has a much lower plasma concentration. As the plasma concentration of the active ingredients decreases as a result, this gene variation can result in reduced efficacy.

Recommendation:

- be extra alert to reduced efficacy of the treatment
- advise the patient to contact their doctor in the event of inadequate effect
- an alternative can be selected as a precaution
  Clonidine is not metabolised by CYP2D6.

Clomipramine

Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.

The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of clomipramine and the active metabolite desmethylclomipramine and to increased concentrations of the potentially cardiotoxic hydroxy metabolites.

- use 1.5 times the standard dose and monitor the effect and side effects of the plasma concentrations of clomipramine and desmethylclomipramine to set the maintenance dose.
  For depression, the therapeutic range is 200-400 ng/mL for the sum of the plasma concentrations of clomipramine and desmethylclomipramine.
  For anxiety disorders, the therapeutic plasma concentration of clomipramine is approximately 100 ng/mL, in combination with a plasma concentration of desmethylclomipramine lower than 200 ng/mL.
  For obsessive compulsive disorder, the therapeutic plasma concentration of clomipramine is higher than 200 ng/mL, in combination with a plasma concentration of desmethylclomipramine that is as low as possible.

- if a dose increase is not wanted due to potential cardiotoxic hydroxy metabolites: avoid clomipramine. Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Codeine

Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.

The genetic variation increases the conversion of codeine to morphine. This can result in an increase in side effects. Death has occurred in children who received analgesic doses. One adult with reduced kidney function and co-medication with two CYP3A4 inhibitors became comatose after use of codeine for a cough.

Recommendation:

- DOSES HIGHER THAN 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND/OR ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
  Codeine is contra-indicated
  - if possible, select an alternative

    - For PAIN: do not select tramadol, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.
    - For COUGH: noscapine is not metabolised by CYP2D6.
- DOSES LOWER THAN OR EQUAL TO 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND NO ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
    - no action required

Doxepin

Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of doxepin and the active metabolite nordoxepin and an increase in the plasma concentrations of the potentially cardiotoxic hydroxy metabolites.

- double the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose
  The therapeutic range is 100-250 ng/mL for the sum of doxepin and nordoxepin plasma concentrations. Values higher than 400 ng/mL are considered toxic.

- if a dose increase is not wanted due to the potentially cardiotoxic hydroxy metabolites: avoid doxepin.
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Efavirenz

Phenotype / Variant: CYP2B6 POOR METABOLIZER.
Genetic variations increase the risk of side effects. The standard dose leads to an efavirenz concentration in the toxic range in the majority of patients with this genotype.
Recommendation:

- Efavirenz in MONOpreparation, adults and children FROM 40 KG:
    - Body mass index LESS THAN or EQUAL to 25:
        - The recommended initial dose is 400 mg/day and this dose should be titrated to plasma concentration if needed (further reduction to 200 mg/day or in rare cases an increase to 600 mg/day).
          The therapeutic range established for efavirenz is 1000-4000 ng/ml.
    - Body mass index GREATER than 25:
        - The recommended initial dose is 600 mg/day and this dose should be titrated to plasma concentration if needed (reduction to 400 or 200 mg/day).
          The therapeutic range established for efavirenz is 1000-4000 ng/ml.
- Efavirenz in MONOpreparation, children LIGHTER THAN 40 KG:
    - Start with the standard dose and titrate this dose to plasma concentration if needed. In adults, therapeutic plasma concentrations were achieved at either 2/3rd of the standard dose (1/3rd of the patients) or 1/3rd of the standard dose (2/3rd of the patients). In children younger than 3 years, therapeutic plasma concentrations were achieved at doses of approximately 10 mg/kg per day (as capsules) (100 mg/day for 7-14 kg and 150 mg/day for 14-17 kg; 50-75% of the standard dose).
      The therapeutic range established for efavirenz is 1000-4000 ng/ml.
- Efavirenz in COMBINATION preparation:
    - Initiate the combination preparation and titrate the efavirenz dose to plasma concentration if needed (reduction to 400 or 200 mg/day)
      The therapeutic range established for efavirenz is 1000-4000 ng/ml.

Note: the dosing recommendations above are based on PM patients with the *6/*6 genotype. There is evidence that the *18/*18 genotype in PM patients (only present in negroid patients) may require greater dose reductions.
Considerations:
Detailed justification for the recommendation is contained in the risk analysis. The considerations used for adults are also given below.

- The median or mean plasma concentrations or AUC in PM patients are above the therapeutic range, except in 3 studies with low efavirenz plasma concentrations in EM patients (2 of the 3 studies performed in Africa and 1 study in the United States and Italy). A recent study showed a similar virological response for efavirenz 400 and 600 mg/day in patients not selected on genotype. The risk of underdose is therefore very small if the initial dose is reduced to 400 mg/day. Two small studies showed that dose reductions did not reduce the efficacy (HIV remained undetectable), but side effects did reduce in 24 PM patients.
- Compliance improves with administration of a combination preparation and the absence of unnecessary side effects due to excessive plasma concentrations.
- Consideration to CYP2B6 inducers such as rifampicin is not needed in PM patients. The significantly low or absent metabolic capacity of CYP2B6 makes induction of little to no relevance. Moreover, the effects of enzyme induction by rifampicin and enzyme inhibition by isoniazid on efavirenz plasma concentrations seem to largely cancel each other out, independent of the CYP2B6 phenotype of the patient.

Eliglustat
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
This gene variation increases the conversion of eliglustat to inactive metabolites. As a result, a normal dose is not effective. There is not enough scientific substantiation to suggest an effective dose for all UM.
Recommendation:

- Eliglustat is contra-indicated.
- choose an alternative if possible

Estradiol
Phenotype / Variant: FACTOR V LEIDEN HETEROZYGOUS.
The heterozygously present genetic polymorphism “factor V Leiden” causes an increased tendency to coagulation, resulting in an increased risk of venous thromboembolism. Contraceptives containing oestrogens can increase this risk even further.
Recommendation:

- If the patient has a FAMILY HISTORY WITH A LOT OF THROMBOSIS, or has had a PREVIOUS THROMBOSIS:
  - Advise the prescriber to avoid the use of contraceptives that contain oestrogens and prescribe a non-hormone contraceptive - such as a copper IUD - as an alternative. One could also opt for a progestogen-only contraceptive method, such as the depot injection, an IUD with levonorgestrel or an implant with etonogestrel.
- OTHER CASES:
  - Advise the patient to avoid additional risk factors for thrombosis (obesity, smoking, etc.).

Flecainide
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
The genetic variation increases conversion of flecainide to inactive metabolites. A higher dose is possibly required as a result.
Recommendation:
There are no data about the pharmacokinetics and/or the effects of flecainide in UM.

- monitor the plasma concentration as a precaution and record an ECG
- or select an alternative
  Examples of anti-arrhythmic drugs that are not metabolised via CYP2D6 (or to a lesser extent) include sotalol, disopyramide, quinidine and amiodarone.

Haloperidol
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
There are indications of a risk of reduced effectiveness.
The genetic variation leads to an increased conversion of haloperidol, resulting in a plasma concentration that is approximately 40% lower.

- use 1.5 times the standard dose or choose an alternative.
  Antipsychotics that are not metabolised by CYP2D6 - or to a much lesser extent - include, for example, flupentixol, fluphenazine, quetiapine, olanzapine or clozapine.

Imipramine
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of imipramine and the active metabolite desipramine and to increased plasma concentrations of the potentially cardiotoxic hydroxy metabolites.

- use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose

- if a dose increase is not wanted due to the potentially cardiotoxic hydroxy metabolites: avoid imipramine.
  Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Metoprolol
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
The gene variation increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.
Recommendation:

- use the maximum dose for the relevant indication as a target dose
- if the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative
  Possible alternatives include:
  - HEART FAILURE: bisoprolol or carvedilol. Bisoprolol: advantage: not metabolised by CYP2D6; disadvantage: elimination depends on the kidney function. Carvedilol: advantage: elimination does not depend on the kidney function; disadvantage: is metabolised (to a lesser extent than metoprolol) by CYP2D6.
  - OTHER INDICATIONS: atenolol or bisoprolol. Neither is metabolised by CYP2D6.

Nortriptyline
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
The risk of ineffectiveness and cardiotoxic effects may be increased. The gene variation leads to a decrease in the plasma concentration of nortriptyline and an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxynortriptyline.

- use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline and be alert to an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxynortriptyline
  Plasma concentrations of Z-hydroxynortriptyline exceeding 40 ng/mL are considered toxic.

- if a dose increase is not wanted due to the cardiotoxic hydroxy metabolite: avoid nortriptyline
  Antidepressants that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Paroxetine
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
Efficacy will probably be lacking. The genetic variation increases the conversion of paroxetine.
It is not possible to offer substantiated advice for dose adjustment based on the literature.

- avoid paroxetine
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include for example citalopram or sertraline.

Phenytoin
Phenotype / Variant: CYP2C9 *1/*2.
Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.
Recommendation:

- The loading dose does not need to be adjusted.
- For the other doses, use 75% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
- Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Propafenone
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
Genetic variation decreases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of reduced or no efficacy.
Recommendation:
It is not possible to offer adequately substantiated recommendations for dose adjustment based on the literature.

- Either monitor plasma concentrations, perform an ECG and be alert to reduced efficacy of the therapy.
- Or choose an alternative
  Antiarrhythmic drugs that are hardly if at all metabolised by CYP2D6 include, for example, sotalol, disopyramide, quinidine and amiodarone.

Risperidone
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
The percentage of patients with therapy failure increases from 16% to 37%. The gene variation leads to a high ratio of the active metabolite (9-hydroxyrisperidone (paliperidone)) compared to risperidone, which crosses the blood-brain barrier more effectively.

- choose an alternative or titrate the dose according to the maximum dose for the active metabolite (paliperidone) (oral 12 mg/day for adults and children from 15 years of age weighing at least 51 kg and 6 mg/day for children from 15 years of age weighing less than 51 kg; intramuscular 75 mg per 2 weeks)

Tramadol
Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.
The genetic variation increases the conversion of tramadol to a metabolite with a stronger opioid effect. This can result in an increase in potentially life-threatening side effects.
Recommendation:
As the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes, the effect of a dose reduction cannot be predicted with certainty.

- select an alternative
  - Do not choose codeine, as it is contra-indicated for CYP2D6 UM
  - Morphine is not metabolised by CYP2D6.
  - Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.
- if an alternative is not possible:
  - use 40% of the standard dose

- advise the patient to report side effects (such as drowsiness, confusion, constipation, nausea and vomiting, respiratory depression or urine retention).

Venlafaxine

Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.

It may be difficult to adjust the dose for patients due to altered metabolism between venlafaxine and the active metabolite O-desmethylvenlafaxine. The gene variation increases the conversion of venlafaxine to O-desmethylvenlafaxine and reduces the sum of venlafaxine plus O-desmethylvenlafaxine.

- be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine
- if necessary, increase the dose to 150% of the standard dose
- if dose adjustment does not result in efficacy without unacceptable side effects or if dose adjustment based on therapeutic drug monitoring is not possible, then venlafaxine should be avoided
  Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.

Zuclopenthixol

Phenotype / Variant: CYP2D6 ULTRARAPID METABOLIZER.

The risk of ineffectiveness may be elevated.

The genetic variation leads to an increased conversion of zuclopentixol, which causes the plasma concentration to be approximately 33% lower.

- use 1.5 times the standard dose or choose an alternative
  Antipsychotics that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, flupentixol, quetiapine, olanzapine and clozapine.

Detailed genotype / phenotype results

Gene	Genotype	Phenotype / status
CYP2B6	*6/*6	CYP2B6 POOR METABOLIZER
CYP2C19	wildtype/*17	CYP2C19 EXTENSIVE/NORMAL METABOLIZER
CYP2C9	wildtype/*2	CYP2C9 *1/*2
CYP2D6	*1/*1xN	CYP2D6 ULTRARAPID METABOLIZER
CYP3A5	*3/*3	CYP3A5 POOR METABOLIZER (MOST PREVALENT)
DPYD	wildtype/wildtype	DPD GENE ACTIVITY SCORE 2 (NORMAL METABOLISER)
F5	wildtype/1691G>A	FACTOR V LEIDEN HETEROZYGOUS
HLA-B	wildtype/wildtype	HLA-B*5701-NEGATIVE
SLCO1B1	wildtype/wildtype	SLCO1B1 NORMAL FUNCTION
TPMT	wildtype/wildtype	TPMT NORMAL METABOLISER
UGT1A1	wildtype/wildtype	UGT1A1 EXTENSIVE METABOLIZER
VKORC1	wildtype/wildtype	VKORC1 -1639GG (1173CC) (WILD TYPE)

Overview of drug substances, relevant phenotypes and availability of recommendations

Drug substance	Relevant phenotype(s) / variant(s)	Recommendation shown in this report?	Reason
Abacavir	HLA-B*5701-NEGATIVE	No	No action recommended according to guideline
Acenocoumarol	VKORC1 -1639GG (1173CC) (WILD TYPE)	No	No action recommended according to guideline
Acenocoumarol	CYP2C9 *1/*2	No	No action recommended according to guideline
Amiodarone	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Amitriptyline	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Amitriptyline	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Aripiprazole	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Atenolol	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Atomoxetine	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Atorvastatin	SLCO1B1 NORMAL FUNCTION	No	No action recommended according to guideline
Azathioprine	TPMT NORMAL METABOLISER	No	No action recommended according to guideline
Bisoprolol	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Brexpiprazol	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Capecitabine	DPD GENE ACTIVITY SCORE 2 (NORMAL METABOLISER)	No	No action recommended according to guideline
Carvedilol	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Citalopram	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Citalopram	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Clomipramine	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Clomipramine	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline

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Drug substance	Relevant phenotype(s) / variant(s)	Recommendation shown in this report?	Reason
Clonidine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Clonidine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Clopidrogrel	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Clozapine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Codeine	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Dexmethylphenidate	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Disopyramide	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Doxepin	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Doxepin	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Duloxetine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Efavirenz	CYP2B6 POOR METABOLIZER	Yes	Therapy modification recommended according to guideline
Eliglustat	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Escitalopram	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Escitalopram	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Esomeprazole	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Flecainide	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Flucloxacillin	HLA-B*5701-NEGATIVE	No	No action recommended according to guideline
Flucytosine	DPD GENE ACTIVITY SCORE 2 (NORMAL METABOLISER)	No	No action recommended according to guideline
Fluorouracil	DPD GENE ACTIVITY SCORE 2 (NORMAL METABOLISER)	No	No action recommended according to guideline
Fluoxetine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Flupentixol	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Fluvastatin	SLCO1B1 NORMAL FUNCTION	No	No action recommended according to guideline
Fluvoxamine	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Fluvoxamine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Gefitinib	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Glibenclamide	CYP2C9 *1/*2	No	No action recommended according to guideline
Gliclazide	CYP2C9 *1/*2	No	No action recommended according to guideline
Glimepiride	CYP2C9 *1/*2	No	No action recommended according to guideline
Haloperidol	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline

Drug substance	Relevant phenotype(s) / variant(s)	Recommendation shown in this report?	Reason
Imipramine	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Imipramine	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Irinotecan	UGT1A1 EXTENSIVE METABOLIZER	No	No action recommended according to guideline
Kinidine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Lansoprazole	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Mercaptopurine	TPMT NORMAL METABOLISER	No	No action recommended according to guideline
Methylphenidate	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Metoprolol	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Mirtazapine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Mirtazapine	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Moclobemide	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Nortriptyline	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Oestrogen containing contraceptives	FACTOR V LEIDEN HETEROZYGOUS	Yes	Therapy modification recommended according to guideline
Olanzapine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Omeprazole	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Oxycodone	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Pantoprazole	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Paroxetine	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Phenprocoumon	CYP2C9 *1/*2	No	No action recommended according to guideline
Phenprocoumon	VKORC1 -1639GG (1173CC) (WILD TYPE)	No	No action recommended according to guideline
Phenytoin	CYP2C9 *1/*2	Yes	Therapy modification recommended according to guideline
Pimozide	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Prasugrel	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Propafenone	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Quetiapine	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Rabeprazole	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Risperidone	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Sertraline	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Sertraline	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline

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Drug substance	Relevant phenotype(s) / variant(s)	Recommendation shown in this report?	Reason
Simvastatin	SLCO1B1 NORMAL FUNCTION	No	No action recommended according to guideline
Siponimod	CYP2C9 *1/*2	No	No action recommended according to guideline
Sotalol	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Tacrolimus	CYP3A5 POOR METABOLIZER (MOST PREVALENT)	No	No action recommended according to guideline
Tamoxifen	CYP2D6 ULTRARAPID METABOLIZER	No	No action recommended according to guideline
Tegafur	DPD GENE ACTIVITY SCORE 2 (NORMAL METABOLISER)	No	No action recommended according to guideline
Ticagrelor	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Tioguanine	TPMT NORMAL METABOLISER	No	No action recommended according to guideline
Tolbutamide	CYP2C9 *1/*2	No	No action recommended according to guideline
Tramadol	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Tramadol	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Venlafaxine	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline
Voriconazole	CYP2C19 EXTENSIVE/NORMAL METABOLIZER	No	No action recommended according to guideline
Warfarin	VKORC1 -1639GG (1173CC) (WILD TYPE)	No	No action recommended according to guideline
Warfarin	CYP2C9 *1/*2	No	No action recommended according to guideline
Zuclopenthixol	CYP2D6 ULTRARAPID METABOLIZER	Yes	Therapy modification recommended according to guideline

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Disclaimer

General information

This pharmacogenomic test report was issued following the protocol of the PREPARE (PREemptive Pharmacogenomic testing for Preventing Adverse drug Reactions) study. PREPARE's aim is to implement pharmacogenomic testing to guide drug and dose selection in seven European countries, thereby personalising medicine. PREPARE will provide evidence on the effect of pharmacogenomics-based prescribing on patient outcomes. The PREPARE protocol was initiated by the Ubiquitous Pharmacogenomics Consortium (U-PGx)(www.upgx.eu).

Therapeutic recommendations

The therapeutic recommendations in this report are developed by the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Pharmacists Association. The Dutch Pharmacogenetics Working Group formulates the optimal recommendations for each phenotype group based on the available scientific evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the healthcare professional should consider the next best option.

The recommendations in this report are solely based on the phenotypes that were inferred from the variants assayed by the genotyping test deployed in this test. The recommendations do not take into account any other factors that can influence a patient's phenotype and drug response, such as drug-drug interactions, various health conditions or environmental factors.

The absence of a recommendation for a specific drug is not to be equated with the general absence of variants that might influence an individual's response to this drug since the patient might have a rarer variant that is currently not covered by the genotyping test. In this case, prescribing decisions should be made with standard precautions.

This test is not intended as diagnostic, nor is it capable of being an advice on any specific problem or a recommendation for the prescription of any specific drug or a replacement thereof. The healthcare provider shall exercise professional judgement and careful interpretation of the test result in determining their advise to the patient and in the dose selection of drugs.

Over time, the database that contains the annotations and recommendations to generate this report will continuously be updated as new scientific evidence becomes available. Therefore, the information included in this report is dependent on the report generation date.

Additional information on the recommendation for oral/vaginal contraceptives with estrogens

The recommendation refers to all estrogen containing hormonal contraceptives for systemic use. This includes, but is not limited to, *combination preparations of estrogens* (e.g. ethinylestradiol, estradiol) *with the following progestogens*: Cyproterone, Desogestrel, Dienogest, Drospirenone, Etonogestrel, Gestodene, Levonorgestrel, Nomegestrol, Norelgestromin, Norethisterone, Norgestimate.

Genotyping test

Nucleic acid variants were detected by fluorescence-based endpoint genotyping using two allele-specific forward and one common reverse primer. Determined alleles were compared to the corresponding reference sequences. Fluorescence signals were analyzed and classified using computer-based method.
The method applied detects bi- and tri-allelic SNPs (single nucleotide polymorphism), insertions, deletions, and duplications. Assignment of a genotype is based on results at the positions investigated which are listed for each analysis.
As with any PCR-based method, results of genotyping can be influenced by genomic variants in the primer binding region. This can result in findings divergent from those obtained with alternative methods or with PCR products of the region generated with different primers. The method does not preclude point variations, deletions or duplications in regions of the gene other than those investigated.

Results of genotyping reported are frequently checked as part of continuing method development. Detected allele combinations are assigned to the most likely genotypes using computer-based methods. To confirm those findings or exclude rare genotype and phenotype classification, genotyping of (both) parents is recommended.

Tested variants

GENE	ALLELE	VARIANT	CORRESPONDING RS ID
CYP2B6	*9 (*6)	516G>T	rs3745274
CYP2B6	*4 (*6/*16)	785A>G	rs2279343
CYP2B6	*18 (*16)	983T>C	rs28399499
CYP2B6	*5	1459C>T	rs3211371
CYP2C9	*2	430C>T	rs1799853
CYP2C9	*3	1075A>C	rs1057910
CYP2C9	*5	1080C>G	rs28371686
CYP2C9	*11	1003C>T	rs28371685
CYP2C19	*2	681G>A	rs4244285
CYP2C19	*3	636G>A	rs4986893
CYP2C19	*4A/B	1A>G	rs28399504
CYP2C19	*5	1297C>T	rs56337013
CYP2C19	*6	395G>A	rs72552267
CYP2C19	*8	358T>C	rs41291556
CYP2C19	*9	431G>A	rs17884712
CYP2C19	*10	680C>T	rs6413438
CYP2C19	*17	-806C>T	rs12248560
CYP2D6	*xN	Gene duplication or multiplication	X
CYP2D6	*3	2549delA	rs35742686

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GENE	ALLELE	VARIANT	CORRESPONDING RS ID
CYP2D6	*4	1846G>A	rs3892097
CYP2D6	*5	Gene deletion	X
CYP2D6	*6	1707delT	rs5030655
CYP2D6	*8	1758G>T	rs5030865
CYP2D6	*9	2615delAAG	rs5030656
CYP2D6	*10	100C>T	rs1065852
CYP2D6	*14A/B	1758G>A	rs5030865
CYP2D6	*17	1023C>T	rs28371706
CYP2D6	*41	2988G>A	rs28371725
CYP3A5	*3	6986A>G	rs776746
CYP3A5	*6	14690G>A	rs10264272
CYP3A5	*7	27131_27132insT	rs41303343
DPYD	*2A	IVS14 + 1G>A (1905+1G>A)	rs3918290
DPYD	*13	1679T>G	rs55886062
DPYD	X	2846A>T	rs67376798
DPYD	X	1236G>A	rs56038477
F5	X	1691G>A	rs6025
HLA-B	*5701	T>G	rs2395029
SLCO1B1	*5 (*15/*17)	521T>C	rs4149056
TPMT	*2	238G>C	rs1800462
TPMT	*3B	460G>A	rs1800460
TPMT	*3C	719A>G	rs1142345
UGT1A1	*6	211(G>A)	rs4148323
UGT1A1	*27	686(C>A)	rs35350960
UGT1A1	*28/*37	A(TA)6TAA>A(TA)7TAA/A(TA)8TAA	rs8175347
VKORC1	X	1173C>T (C6484T)	rs9934438

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