GeneAccount

You were tested for 22 genes, out of which 6 may affect the efficacy or safety of your medication: **CYP2C19, CYP2C9, CYP2D6, IFNL3, UGT1A1, VKORC1**

Your genetic factors may affect the efficacy or safety of 106 drugs.

TEST SUMMARY

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This is the report of your pharmacogenetic test results. The report contains information on the tested genetic variants and their effects on the safety and efficacy of medications. **This report should not be used to change medications without guidance from a physician. Always consult your physician before making any changes to your medications.**

First, here is a short list of terms to understand the report better:

- variant = a genetic alteration which deviates from the common form
- genotype = the composition of your genetic variants for a gene
- phenotype = a property or function caused by a genotype, e.g. “rapid metabolizer” or “increased risk”

The report is divided into three major sections: gene-specific recommendations for medications, detailed genotype results and the raw data of your variants.

It is vital to remember that drug responses may be affected by other genetic variants not included in this report. Additionally, many other individual factors, e.g. age, body weight, allergies or hypersensitivities, other drugs, foods and natural products, kidney and liver function and disease states affect the drug responses. Even though a gene might be stated here as having a normal genotype and phenotype (i.e. no variants with aberrant functionality detected), a possibility of having a deviant genotype exists e.g. due to rare non-detectable variants or technical error. Scientific knowledge also changes over time and thus it is important to check most recent version of the recommendations from GeneAccount.

Some of the genes are shown as affecting medications significantly, although their genotypes and phenotypes were normal. This confusing listing is due to the fact, that for some medications there are highly significant drug recommendations even though the genotype is normal. In these cases, the normal genotype should also be regarded when prescribing and dosing the medication. This stands for e.g. genes *CYP2C9* and *VKORC1* (recommendation for warfarin) and *CYP2D6* (recommendations for eliglustat and atomoxetine). On the other hand, for gene *CYP3A5*, the most common phenotype in the white populations is “poor metabolizer” and common drug dosages stated in drug labels apply to this group. Therefore, *CYP3A5* is shown in the list of significant gene results for individuals with “normal metabolizers” phenotype for *CYP3A5*, as this genotype / phenotype alters the dosing of certain medications significantly.

SUMMARY OF MEDICATIONS INCLUDED IN THE REPORT

DRUGS WITH GENETIC VARIATION OF SIGNIFICANT CLINICAL RELEVANCE

amitriptyline, boceprevir, clomipramine, codeine, desipramine, doxepin, eliglustat, imipramine, metoprolol, nortriptyline, paroxetine, peginterferon alfa-2a, peginterferon alfa-2b, propafenone, ribavirin, siponimod, telaprevir, tramadol, trimipramine

DRUGS WITH GENETIC VARIATION OF SOME CLINICAL RELEVANCE

atomoxetine, citalopram, clopidogrel, escitalopram, haloperidol, irinotecan, ondansetron, risperidone, tropisetron, voriconazole, warfarin

DRUGS WITH GENETIC VARIATION OF MINOR CLINICAL RELEVANCE

acenocoumarol, amoxapine, amphetamine, arformoterol, aripiprazole, aripiprazole lauroxil, atazanavir, belinostat, brexpiprazole, brivaracetam, caffeine, cariprazine, carisoprodol, carvedilol, cevimeline, clobazam, clozapine, dapsone, darifenacin, desvenlafaxine, deutetrabenazine, dextromethorphan, diazepam, digoxin, dolutegravir, donepezil, duloxetine, erlotinib, fesoterodine, flecainide, flibanserin, flupenthixol, fluvoxamine, galantamine, gefitinib, iloperidone, lacosamide, lofexidine, meclizine, methylthioninium, mirtazapine, modafinil, nebivolol, nefazodone, nilotinib, nitrofurantoin, olanzapine, oxycodone, palonosetron, pazopanib, pegloticase, perphenazine, phenprocoumon, phenytoin, pimozide, primaquine, propranolol, protriptyline, quinidine, quinine, raltegravir, ranolazine, rasburicase, sertindole, simeprevir, sofosbuvir, sulfadiazine, tafenoquine, terbinafine, tetrabenazine, tolterodine, valbenazine, venlafaxine, vincristine, vortioxetine, zuclopenthixol

DRUGS WITH NO CLINICALLY RELEVANT GENETIC VARIATION

alcohol, articaine, ascorbic acid, atorvastatin, avatrombopag, azathioprine, binimetinib , capecitabine, celecoxib, chloroprocaine, chloroquine, chlorpropamide, ciprofloxacin, cisplatin, dabrafenib, daclatasvir, diclofenac, dronabinol, efavirenz, elagolix, eltrombopag, erdafitinib, esomeprazole, estradiol, estriol, ethinylestradiol, fluorouracil, fluoxetine, flurbiprofen, flutamide, fluvastatin, fosphenytoin, glibenclamide, glimepiride, glipizide, glyceryl trinitrate, hydroxychloroquine, indacaterol, irbesartan, lansoprazole, lesinurad, levofloxacin, lidocaine, losartan, lovastatin, lusutrombopag, mafenide, mepivacaine, mercaptopurine, methadone, methotrexate, metoclopramide, mirabegron, mivacurium, moclobemide, moxifloxacin, nalidixic acid, nevirapine, norfloxacin, omeprazole, pantoprazole, pioglitazone, piroxicam, prasugrel, pravastatin, prilocaine, probenecid, rabeprazole, romiplostim, ropivacaine, rosiglitazone, rosuvastatin, rucaparib, sertraline, simvastatin, sodium nitrite, sulfamethoxazole, sulfasalazine, sulfisoxazole, suxamethonium, tacrolimus, tamoxifen, tamsulosin, tegafur, tetracaine, thioguanine, thioridazine, tibolone, ticagrelor, tolazamide, tolbutamide, umeclidinium

CLASSIFICATION OF DRUG RECOMMENDATIONS

D — Pharmacogenetic variation affects drug effectiveness or adverse reactions with significant clinical relevance. A genetic test is recommended. Check existing test results before prescribing the drug. Check dosing and administration based on test results.

C — Pharmacogenetic variation affects drug effectiveness or adverse reactions with some clinical relevance. If genetic test results are available, consider changing drug or dosing based on results. If genetic testing has not been conducted, consider ordering a test.

B — Pharmacogenetic variation may affect drug effectiveness or adverse reactions, but with minor clinical significance in most patients. Monitor drug response and possible adverse reactions. If genetic test results are available, consider changing drug or dosing based on results.

A — Pharmacogenetic variation does not significantly affect drug effectiveness or adverse reactions.

HIGHLY AFFECTED MEDICATIONS ORDERED BY THERAPEUTIC AREA

Therapeutic area		Active ingredient	Phenotype	Classification
Alimentary Tract And Metabolism	Antiemetics And Antinauseants	ondansetron	CYP2D6 UM Ultrarapid Metabolizer	C
	Other Alimentary Tract And Metabolism Products	eliglustat	CYP2D6 UM Ultrarapid Metabolizer	D
Blood And Blood Forming Organs	Antithrombotic Agents	clopidogrel	CYP2C19 IM Intermediate Metabolizer	C
		warfarin	CYP2C9 NM Normal Metabolizer	C
		warfarin	VKORC1 Reduced expression of the enzyme	C
Cardiovascular System	Beta Blocking Agents, Plain	metoprolol	CYP2D6 UM Ultrarapid Metabolizer	D
	Beta Blocking Agents And Thiazides	metoprolol	CYP2D6 UM Ultrarapid Metabolizer	D
	Beta Blocking Agents And Other Antihypertensives	metoprolol	CYP2D6 UM Ultrarapid Metabolizer	D
General Antiinfectives For Systemic Use	Antimycotics For Systemic Use	voriconazole	CYP2C19 IM Intermediate Metabolizer	C
Antineoplastic And Immunomodulating Agents	Other Cytostatics	irinotecan	UGT1A1 IM Intermediate Metabolizer	C
	Immunostimulating Agents	peginterferon alfa-2a	IFNL3 Unfavorable response genotype	D
Nervous System	Opioids	codeine	CYP2D6 UM Ultrarapid Metabolizer	D
		tramadol	CYP2D6 UM Ultrarapid Metabolizer	D
	Antipsychotics	haloperidol	CYP2D6 UM Ultrarapid Metabolizer	C
		risperidone	CYP2D6 UM Ultrarapid Metabolizer	C
	Antidepressants	amitriptyline	CYP2D6 UM Ultrarapid Metabolizer	D
		citalopram	CYP2C19 IM Intermediate Metabolizer	C
		clomipramine	CYP2D6 UM Ultrarapid Metabolizer	D
		doxepin	CYP2D6 UM Ultrarapid Metabolizer	D
		escitalopram	CYP2C19 IM Intermediate Metabolizer	C
		nortriptyline	CYP2D6 UM Ultrarapid Metabolizer	D
		paroxetine	CYP2D6 UM Ultrarapid Metabolizer	D
		trimipramine	CYP2D6 UM Ultrarapid Metabolizer	D
	Psychostimulants	atomoxetine	CYP2D6 UM Ultrarapid Metabolizer	C
	Psycholeptics And Psychoanaleptics In Combination	amitriptyline	CYP2D6 UM Ultrarapid Metabolizer	D
Respiratory System	Cough Suppressants And Expectorants, Combinations	codeine	CYP2D6 UM Ultrarapid Metabolizer	D

SUMMARY OF TESTED GENES AND THEIR PREDICTED PHENOTYPES

Gene	Diplotype	Phenotype
ABCB1	WT/var	Possibly high expression of P-GP (heterozygous)
ALDH2	*1/*1	Normal enzyme activity
BCHE	WT/WT	Normal enzyme activity
CYP1A2	*1/*1F	High inducibility
CYP2B6	*1/*1	Normal metabolism
CYP2C19	*2/*17	IM Intermediate Metabolizer
CYP2C8	*1/*1	Normal metabolism
CYP2C9	*1/*1	NM Normal Metabolizer
CYP2D6	(*1/*1)x3	UM Ultrarapid Metabolizer
CYP3A4	*1/*1	Normal metabolism
CYP3A5	*3/*3	PM Poor metabolizer
CYP4F2	*1/*3	Decreased enzyme activity
DPYD	WT/WT	NM Normal metabolizer
F2	WT/WT	No increased risk of venous thromboembolism
F5	WT/WT	No increased risk of venous thromboembolism
G6PD	B/B	No detected G6PD deficiency
GRIK4	T/C	Poor responder (heterozygous)
IFNL3	WT/var	Unfavorable response genotype
SLCO1B1	*1B/*1B	Normal function
TPMT	*1/*1	NM Normal metabolizer
UGT1A1	*1 or *36/*28 or *37	IM Intermediate Metabolizer
VKORC1	*1/*2	Reduced expression of the enzyme

acenocoumarol

B Label-recommended dosing and administration. With this genotype the sensitivity to acenocoumarol is potentially increased. There are several published genetically guided dosing algorithms (for CYP2C9 and VKORC1 genotypes) but, however, there is no consistent scientific evidence, whether they help in finding appropriate dose. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The genetic variation results in a reduction of the required dose, but with the current practice of initiating or reviewing treatment this results in little or no increased risk of bleeding or excessive anticoagulation.

VKORC1: Reduced expression of the enzyme

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

alcohol

A Minor or no flushing reaction to alcohol.

ALDH2: Normal enzyme activity

amitriptyline

D Efficacy of amitriptyline is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments. This recommendation applies to higher initial doses for treatment of conditions such as depression (and not for treatment of e.g. neuropathic pain; however, monitor the patients closely for response or consider alternative agents).

CYP2D6: UM Ultrarapid Metabolizer

A Label-recommended dosing and administration. With this genotype, the metabolism of amitriptyline is decreased.

CYP2C19: IM Intermediate Metabolizer

amoxapine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

amphetamine

B Label-recommended dosage and administration. According to the label approved by the U.S. Food and Drug Administration (FDA), although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

CYP2D6: UM Ultrarapid Metabolizer

arformoterol

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

A Label-recommended dosing and administration.

UGT1A1: IM Intermediate Metabolizer

aripiprazole

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

aripiprazole lauroxil

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

articaine

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

ascorbic acid

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

atazanavir

B With this genotype the metabolism of atazanavir is reduced but the risk of jaundice caused by atazanavir is not markedly increased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): There is no need to avoid prescribing of atazanavir based on UGT1A1 genetic test result. Inform the patient that some patients stop atazanavir because of jaundice (yellow eyes and skin) but this patient's genotype makes this unlikely (less than about a one in 20 chance of stopping atazanavir because of jaundice).

UGT1A1: IM Intermediate Metabolizer

atomoxetine

C With this genotype, the exposure to the drug is potentially decreased which may lead to insufficient efficacy. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): FOR ADULTS: Initiate with a dose of 40 mg/day and increase to 80 mg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day. If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1-2 hours after dose administered). If < 200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml. Dosages > 100 mg/day may be needed to achieve target concentrations. FOR CHILDREN: Initiate with a dose of 0.5 mg/kg/day and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1-2 hours after dose administered). If < 200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.

CYP2D6: UM Ultrarapid Metabolizer

atorvastatin

avatrombopag

A Label-recommended dosing and administration.

CYP3A4: Normal metabolism

A Label-recommended dosing and administration.

SLCO1B1: Normal function

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

azathioprine

A Start with normal starting dose and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.

TPMT: NM Normal metabolizer

belinostat

B Label-recommended dosing and administration. Drug exposure and thus the risk for adverse effects are potentially increased in patients with decreased UGT1A1 activity.

UGT1A1: IM Intermediate Metabolizer

binimetinib

A Label-recommended dosing. According to the summary of product characteristics provided by the manufacturer, UGT1A1 genotype does not have a clinically important effect on drug safety or efficacy.

UGT1A1: IM Intermediate Metabolizer

boceprevir

D This genotype is associated with an unfavorable response of hepatitis C virus (genotype 1) treatment with combination of peginterferon alpha 2 (PEG-IFN alpha) and ribavirin (RBV). According to a recommendation by an international board of experts (Clinical Pharmacogenetics Implementation Consortium) with this genotype there is approximately 30% chance for sustained virologic response after 48 weeks of treatment when treated with combination of PEG-IFN alpha and RBV. Consider implications before initiating PEG-IFN alpha and RBV containing regimens. Additionally, there is approximately 60% chance for sustained virologic response after 24–48 weeks of treatment when treated with combination of PEG-IFN alpha, RBV and protease inhibitor and approximately 50% of patients are eligibile for shortened therapy (24–28 weeks instead of 48 weeks). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

IFNL3: Unfavorable response genotype

brexpiprazole

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

brivaracetam

B With this genotype the exposure to brivaracetam is potentially increased. According to the drug label approved by U.S. Food and Drug Administration (FDA), a reduced dose may be required.

CYP2C19: IM Intermediate Metabolizer

caffeine

B With this genotype the metabolism of caffeine by CYP1A2 is potentially increased. In addition to genetic factors, the activity of CYP1A2 is affected significantly by daily habits, e.g. smoking.

CYP1A2: High inducibility

capecitabine

A Normal dihydropyrimidine dehydrogenase activity and no increased risk for fluoropyrimidine toxicity. Label-recommended dosage.

DPYD: NM Normal metabolizer

cariprazine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

carisoprodol

B With this genotype the exposure to carisoprodol is potentially increased. Use carisoprodol with caution.

CYP2C19: IM Intermediate Metabolizer

carvedilol

B Label-recommended dosing and administration. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is required for this gene-drug interaction. The plasma concentration of carvedilol can be reduced. This does not, however, result in a decrease in the effectiveness.

CYP2D6: UM Ultrarapid Metabolizer

celecoxib

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

cevimeline

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

chloroprocaine

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

chloroquine

chlorpropamide

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

ciprofloxacin

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

citalopram

C With this genotype the metabolism of citalopram is reduced. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The risk of QT prolongation and therefore also the theoretical risk of torsades de pointes is increased as the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the increased risk of QT prolongation will be offset. Do not exceed the following daily doses (50% of the standard maximum dose): 1. Adults up to 65 years: 20 mg as tablets or 16 mg as drops. 2. Adults 65 years or older: 10 mg as tablets or 8 mg as drops.

CYP2C19: IM Intermediate Metabolizer

B Label-recommended dosage. Patients with this genotype may be less likely to respond to antidepressant treatment as compared to high response genotype.

GRIK4: Poor responder (heterozygous)

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

clomipramine

D Efficacy of clomipramine is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Since tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the dosing guideline for amitriptyline/nortriptyline and CYP2D6 to other tricyclics including clomipramine: Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments. This recommendation applies to higher initial doses for treatment of conditions such as depression (and not for treatment of e.g. neuropathic pain; however, monitor the patients closely for response or consider alternative agents).

CYP2D6: UM Ultrarapid Metabolizer

B Label-recommended dosing and administration. With this genotype, the metabolism of clomipramine is decreased.

CYP2C19: IM Intermediate Metabolizer

clozapine

B Label-recommended dosage. Monitor the drug response. With this genotype the activity of CYP1A2 is potentially increased (especially in smokers) and thus the exposure to clozapine may be decreased. On the other hand, the seizure risk related to the use of clozapine is potentially increased but scientific evidence about this is limited. Several other genetic and behavioral factors, such as smoking, also affect the metabolism.

CYP1A2: High inducibility

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

dabrafenib

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

dapsone

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

cisplatin

A Label-recommended dosing and administration.

TPMT: NM Normal metabolizer

clobazam

B Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

clopidogrel

C With this genotype the metabolism of clopidogrel to active metabolites is reduced. The effect of clopidogrel in preventing thrombocyte aggregation is probably low. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Alternative antiplatelet therapy (if not contraindicated), e.g. prasugrel or ticagrelor, is recommended. This recommendation is mainly to be considered for patients with acute coronary syndrome treated with PCI and stenting, for which prasugrel and ticagrelor are also indicated.

CYP2C19: IM Intermediate Metabolizer

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

codeine

D With this genotype the metabolism of codeine to morphine is increased. According to the summary of product characteristics provided by the manufacturer, use of the drug is contraindicated in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Avoid codeine use due to potential for toxicity. Alternatives that are not affected by this CYP2D6 genotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity.

CYP2D6: UM Ultrarapid Metabolizer

daclatasvir

A According to the summary of product characteristics provided by the manufacturer IFNL3 genotype was not associated with treatment response when treating patients coinfected with hepatitis C and HIV with combination of daclatasvir and sofosbuvir.

IFNL3: Unfavorable response genotype

darifenacin

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

desipramine

D Efficacy of desipramine is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Since tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the dosing guideline for amitriptyline/nortriptyline and CYP2D6 to other tricyclics including desipramine: Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments. This recommendation applies to higher initial doses for treatment of conditions such as depression (and not for treatment of e.g. neuropathic pain; however, monitor the patients closely for response or consider alternative agents).

CYP2D6: UM Ultrarapid Metabolizer

deutetrabenazine

B Label-recommended dosing and administration. A clinically relevant QT prolongation may occur in some patients treated with deutetrabenazine who are co-administered a strong CYP2D6 inhibitor.

CYP2D6: UM Ultrarapid Metabolizer

diazepam

B Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

digoxin

B Label-recommended dosing. With this genotype, exposure to digoxin is potentially increased. Be alert for increased digoxin concentrations. Scientific evidence for this is inconsistent, though. Pay attention to concomitant use of drugs inhibiting P-glycoprotein, which seem to affect the digoxin concentrations more significantly than the genotype.

ABCB1: Possibly high expression of P-GP (heterozygous)

donepezil

B Label-recommended dosage. With this genotype the metabolism of donepezil is potentially increased.

CYP2D6: UM Ultrarapid Metabolizer

dronabinol

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

efavirenz

A Label-recommended dosing and administration.

CYP2B6: Normal metabolism

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

desvenlafaxine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

dextromethorphan

B Half-life of dextrometorphan may be shorter in ultrarapid metabolizers than in normal metabolizers. Monitor the patient's drug response.

CYP2D6: UM Ultrarapid Metabolizer

diclofenac

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

dolutegravir

B Label-recommended dosing and administration. With this genotype the exposure to dolutegravir is potentially increased but according to current knowledge it is not clinically significant.

UGT1A1: IM Intermediate Metabolizer

doxepin

D Efficacy of doxepin is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Since tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the dosing guideline for amitriptyline/nortriptyline and CYP2D6 to other tricyclics including doxepin: Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments. This recommendation applies to higher initial doses for treatment of conditions such as depression (and not for treatment of e.g. neuropathic pain; however, monitor the patients closely for response or consider alternative agents).

CYP2D6: UM Ultrarapid Metabolizer

B Label-recommended dosing and administration. With this genotype, the metabolism of doxepin is decreased.

CYP2C19: IM Intermediate Metabolizer

duloxetine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

elagolix

A Label-recommended dosing and administration.

SLCO1B1: Normal function

eliglustat

D With this genotype the patient may not achieve adequate concentrations of eliglustat to achieve a therapeutic effect. According to the summary of product characteristics provided by the manufacturer eliglustat should not be used.

CYP2D6: UM Ultrarapid Metabolizer

eltrombopag

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

erdafitinib

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

erlotinib

B Label-recommended dosage and administration. According to the summary of product characteristics provided by the manufacturer, the inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution.

UGT1A1: IM Intermediate Metabolizer

escitalopram

C With this genotype the metabolism of escitalopram is reduced. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset. Do not exceed the following doses (75% of the standard maximum dose): Adults < 65 years: 15 mg/day. Adults ≥65 years: 7.5 mg/day.

CYP2C19: IM Intermediate Metabolizer

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

B Label-recommended dosage. Patients with this genotype may be less likely to respond to antidepressant treatment as compared to high response genotype.

GRIK4: Poor responder (heterozygous)

esomeprazole

A Label-recommended dosing and administration. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is required for this gene-drug interaction. Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

CYP2C19: IM Intermediate Metabolizer

estradiol

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

estriol

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

ethinylestradiol

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

fesoterodine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

flecainide

B With this genotype the exposure to flecainide is potentially reduced. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The genetic variation increases conversion of flecainide to inactive metabolites. A higher dose is possibly required as a result. 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.

CYP2D6: UM Ultrarapid Metabolizer

flibanserin

B With this genotype the exposure to flibanserin is potentially increased. Monitor the patient for adverse effects (e.g. hypotension).

CYP2C19: IM Intermediate Metabolizer

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

fluorouracil

A Normal dihydropyrimidine dehydrogenase activity and no increased risk for fluoropyrimidine toxicity. Label-recommended dosage.

DPYD: NM Normal metabolizer

fluoxetine

A Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The ratio of fluoxetine/norfluoxetine decreases as a result of the increased activity of CYP2D6. However, this does not affect the sum of the plasma concentrations of the active substances (fluoxetine and norfluoxetine). There is no effect on adverse events or response.

CYP2D6: UM Ultrarapid Metabolizer

flupenthixol

B Label-recommended dosing and administration. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): This is not a gene-drug interaction. No studies have been published in which the kinetics and the effects of flupenthixol were studied for this phenotype.

CYP2D6: UM Ultrarapid Metabolizer

flurbiprofen

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

flutamide

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

fluvastatin

A Label-recommended dosing and administration.

SLCO1B1: Normal function

fluvoxamine

B Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): With this genotype there are no dosage recommendations due to lack of evidence on how ultrarapid metabolizer type affects fluvoxamine treatment. It may be reasonable, though, to select an alternative SSRI not normal metabolized by CYP2D6.

CYP2D6: UM Ultrarapid Metabolizer

fosphenytoin

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

galantamine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

gefitinib

B Label-recommended dosing and administration. With this genotype the exposure to the drug is potentially decreased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The gene variation may lead to a decrease in the gefitinib plasma concentration. In practice, an alternative is only chosen if non-response to gefitinib has been proved. Moreover, dose adjustments guided by the gefitinib plasma concentration are rarely performed in clinical practice as the analytical method is not available in most hospitals.

CYP2D6: UM Ultrarapid Metabolizer

glibenclamide

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

glimepiride

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

glipizide

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

glyceryl trinitrate

A Label-recommended dosing and administration.

ALDH2: Normal enzyme activity

haloperidol

C With this genotype the exposure to haloperidol is potentially decreased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause decreased plasma concentrations of haloperidol and the active metabolite reduced haloperidol. Recommendation: It is not possible to offer substantiated advice for dose adjustment due to the limited amount of available literature. Be alert to possible reduced plasma concentrations of haloperidol and reduced haloperidol and increase the dose based on results of therapeutic drug monitoring, or select alternative according to the current guidelines. Anti-psychotics that are not metabolised via CYP2D6 - or to a much lesser extent - include, for example, flupentixol, fluphenazine, quetiapine, olanzapine or clozapine.

hydroxychloroquine

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

CYP2D6: UM Ultrarapid Metabolizer

iloperidone

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

imipramine

D Efficacy of imipramine is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Since tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the dosing guideline for amitriptyline/nortriptyline and CYP2D6 to other tricyclics including imipramine: Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments. This recommendation applies to higher initial doses for treatment of conditions such as depression (and not for treatment of e.g. neuropathic pain; however, monitor the patients closely for response or consider alternative agents).

CYP2D6: UM Ultrarapid Metabolizer

B Label-recommended dosing and administration. With this genotype, the metabolism of imipramine is decreased.

CYP2C19: IM Intermediate Metabolizer

indacaterol

A Label-recommended dosing and administration.

UGT1A1: IM Intermediate Metabolizer

irbesartan

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

irinotecan

C With this phenotype the risk of toxicity with irinotecan doses above 180 mg/m2 is increased. Recommendation by a French board of experts, the National Pharmacogenetics Network (RNPGx) and the Group of Clinical Onco-pharmacology (GPCO-Unicancer): Label-recommended dosage. Rigorous laboratory and clinical surveillance recommended. Be alert to adverse effects. Dose intensification over 240 mg/m2 not recommended. The recommendation applies especially to the best characterised nonfunctional allele *28. There are also other nonfunctional alleles, e.g. *6 (for which there is increasing evidence on toxicity risk) or *37 but this recommendation is mostly based on evidence considering *28 allele.

UGT1A1: IM Intermediate Metabolizer

lacosamide

B Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

lansoprazole

A Label-recommended dosage. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The higher plasma concentration of lansoprazole results in an increase in the therapeutic effectiveness, without an increase in the incidence of side effects.

CYP2C19: IM Intermediate Metabolizer

lesinurad

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

levofloxacin

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

lidocaine

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

lofexidine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

losartan

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

lovastatin

A Label-recommended dosing and administration.

SLCO1B1: Normal function

lusutrombopag

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

mafenide

meclizine

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

mepivacaine

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

methadone

A Label-recommended dosing and administration.

CYP2B6: Normal metabolism

methylthioninium

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

metoprolol

D With this genotype the exposure to metoprolol is potentially decreased. If efficacy is insufficient, dosage recommendation by a Dutch group of experts (Dutch Pharmacogenetics Working Group) may be beneficial: 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.

CYP2D6: UM Ultrarapid Metabolizer

mirtazapine

B Label-recommended dosage. With this genotype the metabolism of mirtazapine is increased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is required for this gene-drug interaction. The effect on the plasma concentration of mirtazapine is small. No effect has been demonstrated with regard to effectiveness or side effects.

CYP2D6: UM Ultrarapid Metabolizer

moclobemide

A Label-recommended dosage. With this genotype the exposure moclobemide might be increased but there is no need for change of dose. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. Although the moclobemide plasma concentration may increase as a result of the decreased CYP2C19 activity, this does not lead to an increased incidence of side effects, in as far as is known.

CYP2C19: IM Intermediate Metabolizer

moxifloxacin

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

B Label-recommended dosing and administration. With this genotype the exposure to the drug is potentially decreased.

CYP2D6: UM Ultrarapid Metabolizer

mercaptopurine

A Start with normal starting dose and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.

TPMT: NM Normal metabolizer

methotrexate

A Label-recommended dosing and administration.

SLCO1B1: Normal function

metoclopramide

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

mirabegron

A Label-recommended dosing and administration. With this genotype the metabolism of mirabegron is potentially increased, but that doesn't seem to be clinically significant.

CYP2D6: UM Ultrarapid Metabolizer

mivacurium

A Label-recommended dosing and administration.

BCHE: Normal enzyme activity

modafinil

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

nalidixic acid

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

nebivolol

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

nefazodone

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

nevirapine

A Label-recommended dosing and administration.

CYP2B6: Normal metabolism

nilotinib

B Label-recommended dosage. The risk of hyperbilirubinemia is potentially slightly increased which should be taken into consideration.

UGT1A1: IM Intermediate Metabolizer

nitrofurantoin

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

norfloxacin

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

nortriptyline

D Efficacy of nortriptyline is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments. This recommendation applies to higher initial doses for treatment of conditions such as depression (and not for treatment of e.g. neuropathic pain; however, monitor the patients closely for response or consider alternative agents).

CYP2D6: UM Ultrarapid Metabolizer

olanzapine

B Label-recommended dosage. Monitor the drug response. With this genotype the metabolism of CYP1A2 is potentially increased (especially in smokers) which may decrease the exposure to olanzapine. In addition, several other genetic and behavioral factors, such as smoking, also affect the metabolism.

CYP1A2: High inducibility

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

omeprazole

A Label-recommended dosage. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

CYP2C19: IM Intermediate Metabolizer

ondansetron

C With this genotype the metabolism of ondansetron is potentially increased which may lead to reduced efficacy. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Select an alternative drug not predominantly metabolized by CYP2D6 (i.e. granisetron).

CYP2D6: UM Ultrarapid Metabolizer

B Label-recommended dosage. With this genotype, the anti-emetic efficacy of ondansetron is potentially decreased. Monitor the drug response and use alternative medication if needed. This considers especially chemotherapy-induced and post-operational nausea and vomiting in the early phase.

ABCB1: Possibly high expression of P-GP (heterozygous)

oxycodone

B With this genotype the speed of metabolism of oxycodone is increased but evidence of its significance in relation to efficacy or adverse drug effects is controversial. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is required for this gene-drug interaction. The increased conversion of oxycodone to the more active metabolite oxymorphone does not result in an increase in side effects in patients.

CYP2D6: UM Ultrarapid Metabolizer

palonosetron

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

pantoprazole

A Label-recommended dosage. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The higher plasma concentration of pantoprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

CYP2C19: IM Intermediate Metabolizer

paroxetine

D With this genotype the exposure to paroxetine is potentially decreased which may lead to insufficient efficacy. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Select alternative drug not predominantly metabolized by CYP2D6.

CYP2D6: UM Ultrarapid Metabolizer

B With this genotype the required dose of paroxetine may be higher than in normal metabolizers. In addition, several other genetic and behavioral factors, such as smoking, also affect the metabolism.

CYP1A2: High inducibility

pazopanib

B Label-recommended dosage. The risk of hyperbilirubinemia is potentially slightly increased which should be taken into consideration.

UGT1A1: IM Intermediate Metabolizer

peginterferon alfa-2a

D This genotype is associated with an unfavorable response of hepatitis C virus (genotype 1) treatment with combination of peginterferon alpha 2 (PEG-IFN alpha) and ribavirin (RBV). According to a recommendation by an international board of experts (Clinical Pharmacogenetics Implementation Consortium) with this genotype there is approximately 30% chance for sustained virologic response after 48 weeks of treatment when treated with combination of PEG-IFN alpha and RBV. Consider implications before initiating PEG-IFN alpha and RBV containing regimens. Additionally, there is approximately 60% chance for sustained virologic response after 24–48 weeks of treatment when treated with combination of PEG-IFN alpha, RBV and protease inhibitor and approximately 50% of patients are eligibile for shortened therapy (24–28 weeks instead of 48 weeks). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

IFNL3: Unfavorable response genotype

peginterferon alfa-2b

D This genotype is associated with an unfavorable response of hepatitis C virus (genotype 1) treatment with combination of peginterferon alpha 2 (PEG-IFN alpha) and ribavirin (RBV). According to a recommendation by an international board of experts (Clinical Pharmacogenetics Implementation Consortium) with this genotype there is approximately 30% chance for sustained virologic response after 48 weeks of treatment when treated with combination of PEG-IFN alpha and RBV. Consider implications before initiating PEG-IFN alpha and RBV containing regimens. Additionally, there is approximately 60% chance for sustained virologic response after 24–48 weeks of treatment when treated with combination of PEG-IFN alpha, RBV and protease inhibitor and approximately 50% of patients are eligibile for shortened therapy (24–28 weeks instead of 48 weeks). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

IFNL3: Unfavorable response genotype

pegloticase

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

perphenazine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

phenprocoumon

B Label-recommended dosing and administration. With this genotype the sensitivity to phenprocoumon is potentially increased. There are several published genetically guided dosing algorithms (for CYP2C9 and VKORC1 genotypes) but, however, there is no consistent scientific evidence, whether they help in finding appropriate dose. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The genetic variation results in a reduction of the required dose, but regular monitoring of patients ensures that this does not lead to a distinct increase in the risk of bleeding.

VKORC1: Reduced expression of the enzyme

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

phenytoin

B With this genotype the exposure to the drug is potentially increased which may predispose to adverse effects. According to the drug label approved by U.S. Food and Drug Administration (FDA) there may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Unusually high levels result potentially from variant CYP2C19 alleles.

CYP2C19: IM Intermediate Metabolizer

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

pimozide

B Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is required for this gene-drug interaction. This gene variation can result in lower pimozide concentrations. However, there is no evidence of reduced effectiveness.

CYP2D6: UM Ultrarapid Metabolizer

pioglitazone

A Label-recommended dosing and administration.

CYP2C8: Normal metabolism

piroxicam

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

prasugrel

A Label-recommended dosing and administration.

CYP2B6: Normal metabolism

A Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

pravastatin

A Label-recommended dosing and administration.

SLCO1B1: Normal function

A Label-recommended dosing and administration.

CYP3A5: PM Poor metabolizer

prilocaine

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

primaquine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

probenecid

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

propafenone

D With this genotype the exposure to propafenone is potentially decreased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): 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.

CYP2D6: UM Ultrarapid Metabolizer

propranolol

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

protriptyline

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

quinidine

B Quinidine is a potent inhibitor of CYP2D6 enzyme, effectively turning normal metabolizers to poor metabolizers of CYP2D6 substrates, which should be taken into consideration when administered concomitantly with other drugs metabolized by CYP2D6.

CYP2D6: UM Ultrarapid Metabolizer

quinine

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

rabeprazole

A Label-recommended dosing and administration. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. The higher plasma concentration of rabeprazole does not result in an increase in side effects.

CYP2C19: IM Intermediate Metabolizer

raltegravir

B Label-recommended dosing. According to the summary of product characteristics provided by the manufacturer, UGT1A1 genotype does not have a clinically important effect on drug safety or efficacy. However, there is evidence of higher concentrations of the drug in patients with this genotype.

UGT1A1: IM Intermediate Metabolizer

ranolazine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

rasburicase

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible.To ascertain the G6PD metabolizer type, the enzyme activity of G6PD needs to be measured (phenotyping test). If the patient has ascertained normal G6PD activity: Label-recommended dosing and administration. No reason to withhold rasburicase based on G6PD status.

G6PD: No detected G6PD deficiency

ribavirin

D This genotype is associated with an unfavorable response of hepatitis C virus (genotype 1) treatment with combination of peginterferon alpha 2 (PEG-IFN alpha) and ribavirin (RBV). According to a recommendation by an international board of experts (Clinical Pharmacogenetics Implementation Consortium) with this genotype there is approximately 30% chance for sustained virologic response after 48 weeks of treatment when treated with combination of PEG-IFN alpha and RBV. Consider implications before initiating PEG-IFN alpha and RBV containing regimens. Additionally, there is approximately 60% chance for sustained virologic response after 24–48 weeks of treatment when treated with combination of PEG-IFN alpha, RBV and protease inhibitor and approximately 50% of patients are eligibile for shortened therapy (24–28 weeks instead of 48 weeks). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

risperidone

C With this genotype the ratio of risperidone and its active metabolite is altered but their joint effect may not be changed compared to normal metabolizer. Selecting an alternative is potentially beneficial. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. Genetic variation may lead to an increase in the required maintenance dose. However, as the effect is smaller than that of the normal biological variation, action is not useful.

CYP2D6: UM Ultrarapid Metabolizer

IFNL3: Unfavorable response genotype

romiplostim

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

rosiglitazone

A Label-recommended dosing and administration.

CYP2C8: Normal metabolism

rucaparib

A Label-recommended dosing and administration.

CYP1A2: High inducibility

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

sertraline

A Label-recommended dosage. With this genotype the metabolism of sertraline is reduced.

CYP2C19: IM Intermediate Metabolizer

simvastatin

A Label-recommended dosing and administration.

CYP3A4: Normal metabolism

A Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines.

SLCO1B1: Normal function

sodium nitrite

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

sulfadiazine

B There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

sulfasalazine

ropivacaine

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

rosuvastatin

A Label-recommended dosing and administration.

SLCO1B1: Normal function

sertindole

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

simeprevir

B According to the summary of product characteristics provided by the manufacturer, this genotype is associated with less favourable hepatitis C (genotypes 1) treatment response when treating treatment-naive patients with combination of simeprevir, ribavirin, and peginterferon-alfa. Sustained virological response was achieved in 61 % of patients homozygous for less favourable response genotype whereas corresponding number for heterozygotes was 78 % compared to 95 % in patients with favourable response genotype.

IFNL3: Unfavorable response genotype

siponimod

D According to the label approved by the U.S. Food and Drug Administration (FDA), after treatment titration, with this genotype the recommended maintenance dosage is 2 mg taken orally once daily starting on day 6.

CYP2C9: NM Normal Metabolizer

sofosbuvir

B According to the summary of product characteristics provided by the manufacturer, this genotype is associated with less favourable hepatitis C (genotypes 1 and 4) treatment response when treating treatment-naive patients with combination of sofosbuvir, ribavirin, and peginterferon-alfa for 12 weeks. 87 % of patients with this genotyped achieved sustained virological response whereas 99 % of patients with favourable response genotype achieved sustained virological response.

IFNL3: Unfavorable response genotype

sulfamethoxazole

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

sulfisoxazole

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

suxamethonium

A Label-recommended dosing and administration.

BCHE: Normal enzyme activity

tafenoquine

B According to the summary of product characteristics all patients must be tested for G6PD deficiency prior to prescribing of the product. There was no detected G6PD deficiency with this gene test. However, due to possible nonfunctional alleles not included in this test, G6PD deficiency is possible. In populations at high risk for G6DP deficiency measuring the G6DP enzyme activity is recommended before initiation of the drug (e.g. those of African or Mediterranean ancestry). The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs. Pregnancy test should be performed for all females with reproductive potential and in case of pregnancy the foetus should be screened for G6PD deficiency prior to initiating the product. G6PD-deficient infant may be at increased risk for hemolytic anaemia if exposed to product through breast feeding.

G6PD: No detected G6PD deficiency

tamsulosin

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

telaprevir

D This genotype is associated with an unfavorable response of hepatitis C virus (genotype 1) treatment with combination of peginterferon alpha 2 (PEG-IFN alpha) and ribavirin (RBV). According to a recommendation by an international board of experts (Clinical Pharmacogenetics Implementation Consortium) with this genotype there is approximately 30% chance for sustained virologic response after 48 weeks of treatment when treated with combination of PEG-IFN alpha and RBV. Consider implications before initiating PEG-IFN alpha and RBV containing regimens. Additionally, there is approximately 60% chance for sustained virologic response after 24–48 weeks of treatment when treated with combination of PEG-IFN alpha, RBV and protease inhibitor and approximately 50% of patients are eligibile for shortened therapy (24–28 weeks instead of 48 weeks). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

IFNL3: Unfavorable response genotype

tetrabenazine

B Label-recommended dosing and administration. In ultrarapid metabolizers the titration time to appropriate dose may be longer than in normal metabolizers, and the needed dose is potentially increased.

CYP2D6: UM Ultrarapid Metabolizer

thioguanine

A Start with normal starting dose. Adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady state after each dose adjustment.

TPMT: NM Normal metabolizer

tibolone

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

tacrolimus

A Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): In patients with this genotype, starting dose of tacrolimus is normal, mentioned in summary of product characteristics. Do further dose adjustments according to therapeutic drug monitoring. Note! This recommendation concerns those liver transplant recipients, whose donor's genotype is identical with recipient's genotype.

CYP3A5: PM Poor metabolizer

tamoxifen

A Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day). Avoid moderate and strong CYP2D6 inhibitors.

CYP2D6: UM Ultrarapid Metabolizer

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

F5: No increased risk of venous thromboembolism

tegafur

A Normal dihydropyrimidine dehydrogenase activity and no increased risk for fluoropyrimidine toxicity. Label-recommended dosage.

DPYD: NM Normal metabolizer

terbinafine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

tetracaine

A Label-recommended dosing. The drug should be discontinued if signs of methaemoglobinaemia occur (shortness of breath, high pulse, cyanosis, or seizures).

G6PD: No detected G6PD deficiency

thioridazine

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

ticagrelor

A Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

F5: No increased risk of venous thromboembolism

tolazamide

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

tolbutamide

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer

A Label-recommended dosing and administration. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or erythrocyte count occurs.

G6PD: No detected G6PD deficiency

tolterodine

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

tramadol

D With this genotype the speed of metabolism of tramadol to an active metabolite is increased, which may lead to symptoms of overdose. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): 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).

CYP2D6: UM Ultrarapid Metabolizer

trimipramine

D Efficacy of trimipramine is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Since tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the dosing guideline for amitriptyline/nortriptyline and CYP2D6 to other tricyclics including trimipramine: Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments. This recommendation applies to higher initial doses for treatment of conditions such as depression (and not for treatment of e.g. neuropathic pain; however, monitor the patients closely for response or consider alternative agents).

CYP2D6: UM Ultrarapid Metabolizer

B Label-recommended dosing and administration. With this genotype, the metabolism of trimipramine is decreased.

CYP2C19: IM Intermediate Metabolizer

tropisetron

C With this genotype the metabolism of tropisetron is potentially increased which may lead to reduced efficacy. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Select an alternative drug not predominantly metabolized by CYP2D6 (i.e. granisetron).

CYP2D6: UM Ultrarapid Metabolizer

umeclidinium

A Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

valbenazine

B Label-recommended dosing and administration. A clinically relevant QT prolongation may occur in some patients treated with valbenazine who are co-administered a strong CYP2D6 inhibitor.

CYP2D6: UM Ultrarapid Metabolizer

venlafaxine

B Label-recommended dosing and administration. With this genotype the metabolism of venlafaxine is potentially decreased and exposure to venlafaxine increased, especially in patients with decreased metabolic activity of CYP2D6. Scientific evidence on its association with adverse effects or efficacy is scarce, though.

CYP2C19: IM Intermediate Metabolizer

B Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): 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. 1) Be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine. 2) If necessary, increase the dose to 150% of the standard dose. 3) 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.

CYP2D6: UM Ultrarapid Metabolizer

vincristine

B Label-recommended dosing and administration. With this genotype the metabolism vincristine is potentially reduced and thus the risk of drug-induced neurotoxicity increased. Scientific evidence of this is inconsistent, though.

CYP3A5: PM Poor metabolizer

voriconazole

vortioxetine

C With this genotype the exposure to voriconazole is potentially increased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Initiate therapy with recommended standard of care dosing. Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, therapeutic drug monitoring, and comorbidities.

CYP2C19: IM Intermediate Metabolizer

warfarin

C Warfarin dosing is potentially benefited by use of a dosing algorithm which includes genotype information. For the use of algorithm, check the patient's detailed genotype from the gene test report. Recommendation for patients of non-african ancestry: Calculate a dose estimate using the algorithm available at www.warfarindosing.org using the CYP2C9*2 and *3 and VKORC1 genotype information. If the patient is a carrier of CYP2C9*5, *6, *8 or *11 variant alleles, decrease the calculated dose by 15-30%. If the patient is a carrier of rs2108622 variant T allele of CYP4F2 gene, increase the calculated dose by 5-10%. Recommendation for patients of african ancestry: Calculate a dose estimate using the algorithm available at www.warfarindosing.org using the CYP2C9*2 and *3 and VKORC1 genotype information. If the patient is a carrier of CYP2C9*5, *6, *8 or *11 variant alleles, decrease the calculated dose by 15-30%. If the patient has not been tested for CYP2C9*5, *6, *8 or *11 alleles, dose clinically. Additionally, if the patient is of African American ancestry and rs12777823 gene test has been made, decrease dose by 10-25% if the patient is a carrier of A allele. Recommendation for pediatric patients: If the patient is of European ancestry, use the dose calculation application (available at http://www.warfarindoserevision.com) which takes CYP2C9 and VKORC1 genotypes in consideration. Otherwise dose clinically.

CYP2C9: NM Normal Metabolizer

C Warfarin dosing is potentially benefited by use of a dosing algorithm which includes genotype information. For the use of algorithm, check the patient's detailed genotype from the gene test report. Recommendation for patients of non-african ancestry: Calculate a dose estimate using the algorithm available at www.warfarindosing.org using the CYP2C9*2 and *3 and VKORC1 genotype information. If the patient is a carrier of CYP2C9*5, *6, *8 or *11 variant alleles, decrease the calculated dose by 15-30%. If the patient is a carrier of rs2108622 variant T allele of CYP4F2 gene, increase the calculated dose by 5-10%. Recommendation for patients of african ancestry: Calculate a dose estimate using the algorithm available at www.warfarindosing.org using the CYP2C9*2 and *3 and VKORC1 genotype information. If the patient is a carrier of CYP2C9*5, *6, *8 or *11 variant alleles, decrease the calculated dose by 15-30%. If the patient has not been tested for CYP2C9*5, *6, *8 or *11 alleles, dose clinically. Additionally, if the patient is of African American ancestry and rs12777823 gene test has been made, decrease dose by 10-25% if the patient is a carrier of A allele. Recommendation for pediatric patients: If the patient is of European ancestry, use the dose calculation application (available at http://www.warfarindoserevision.com) which takes CYP2C9 and VKORC1 genotypes in consideration. Otherwise dose clinically.

VKORC1: Reduced expression of the enzyme

B Warfarin dosing is potentially benefited by use of a dosing algorithm which includes genotype information. See separate recommendations for CYP2C9 and VKORC1 genes and CYP2C rs12777823 variant. With this CYP4F2 genotype, increase the calculated dose by 5 - 10%.

CYP4F2: Decreased enzyme activity

B Label-recommended dosing and administration. According to the summary of product characteristics provided by the manufacturer, in ultrarapid CYP2D6 metabolizers the plasma concentration of vortioxetine 10 mg/day were between those obtained in normal metabolisers at 5 mg/day and 10 mg/day. Depending on individual patient response, a dose adjustment may be considered.

CYP2D6: UM Ultrarapid Metabolizer

zuclopenthixol

B With this genotype the exposure to zuclopenthixol is potentially decreased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The genetic polymorphism leads to incfeased metabolic capacity of CYP2D6, which may cause decreased zuclopenthixol plasma concentrations. No data have been published from studies into the pharmacokinetics and effects of zuclopenthixol for this phenotype. Recommendation: As a precaution, the prescriber should be advised to be alert to a decreased zuclopenthixol plasma concentration and - if necessary - the dose should be increased on the basis of the clinical effect, or an alternative should be prescribed according to the current guidelines. Antipsychotics that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, flupenthixol, quetiapine, olanzapine and clozapine.

CYP2D6: UM Ultrarapid Metabolizer

Drug safety and efficacy (ABCB1)

ABCB1 gene encodes the P-glycoprotein (P-gp) which is a key cell membrane transporter. P-gp acts as a protective factor in several interfaces of organ systems (including the gut, the bile canaliculi and the blood-brain barrier) where it restricts the compounds entry and therefore affects the drug concentrations. P-gp activity is significantly affected by drugs which inhibit (e.g. atorvastatin, quinidine) or induce it (e.g. rifampin, carbamazepine). There are several known very common variants of the gene, but their effect on drug concentrations and responses are controversial in different studies. Other drugs affecting the activity of P-gp seem to be more significant factors in P-gp-related drug responses.

Possibly high expression of P-GP (heterozygous)

WT/var

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (ALDH2)

Mitochondrial Aldehyde dehydrogenase enzyme oxidizes aldehydes to corresponding carboxylic acids. The function of the enzyme may be deficient due to genetic variation which manifests for example as intoxication symptoms after consumption of alcohol as acetaldehyde metabolite accumulates. Most Europeans have two major isozymes, while approximately 50% of Northeast Asians have one normal copy of the ALDH2 gene and one variant copy that encodes an inactive mitochondrial isoenzyme. The insufficient activity may also decrease the efficacy of glyceryl trinitrate used.

Normal enzyme activity

*1/*1

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (BCHE)

Butyrylcholinesterase (BCHE) also known as plasma cholinesterase and pseudocholinesterase is a nonspecific cholinesterase enzyme and it is very similar to the acetylcholinesterase. Over 60 single nucleotide polymorphisms (SNPs) in the BCHE gene have been reported. Butyrylcholinesterase deficiency is significant only when present in homozygous form, which occurs in approximately one in 2500 patients. Pseudocholinesterase deficiency results in delayed metabolism of only a few compounds of clinical significance, including succinylcholine, mivacurium and cocaine. The clinically most important substrate of these is the depolarizing neuromuscular blocking agent, succinylcholine (suxamethonium), which the BCHE enzyme hydrolyses to inactive metabolites. Genetic variants that impair the BCHE enzyme activity can be divided into two groups. The other variants affect the substrate affinity of the enzyme and the other variants affect the amount of the enzyme without affecting the substrate affinity. Both types of variants increase the patient's risk of prolonged apnea when using succinylcholine, but the duration of the apnea depends on the type and the number of variants present.

Normal enzyme activity

WT/WT

Analyzed 3 of 3 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP1A2)

CYP1A2 is a hepatic enzyme which mediates metabolism of several drugs, caffeine and procarcinogens. Smoking, certain drugs and other exposures induce the expression of the enzyme. There is some genetic variation concerning CYP1A2, and due to this the speed of metabolism or the inducibility of the enzyme in an individual may be altered. This affects the efficacy of certain drugs. Environmental and drug exposures are likely more important factors altering the enzyme activity, though.

High inducibility

*1/*1F

Analyzed 4 of 4 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP2B6)

CYP2B6 is a hepatic enzyme that is responsible for the metabolism of HIV and cancer drugs as well as bupropion. There is genetic variation in the enzyme activity but there is no wide, coherent scientific evidence of the association between the variation and drug metabolism. The evidence is strongest for certain HIV drugs.

Normal metabolism

*1/*1

Analyzed 4 of 4 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP2C19)

CYP2C19 is a hepatic enzyme which mediates metabolism of several drugs. Drugs metabolized by it include e.g. psychotropic drugs and gastric acid pump blockers, and among the most important, drugs which prevent blood platelets from aggregating and thus from causing arterial blocks (clopidogrel, ticagrelor, prasugrel). There is genetic variation concerning CYP2C19, and due to this the speed of metabolism of the enzyme in an individual can be faster or slower than average. This either increases or decreases efficacy of different drugs. Frequencies of genotypes in different populations are dependent on ethnic background, and the variation of frequency for CYP2C19 genotypes is from a few percent to half of a population.

IM Intermediate Metabolizer

*2/*17

Analyzed 5 of 5 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP2C8)

CYP2C8 is a hepatic enzyme which mediates metabolism of several drugs. Drugs metabolized by it include e.g. antidiabetics, statins, pain medications and cancer therapeutics. There is genetic variation concerning CYP2C8, and due to this the speed of metabolism of the enzyme in an individual can be faster or slower than average. This either increases or decreases efficacy of different drugs. The effect of certain genotypes on metabolism depends on substrate which means that the same genotype may cause opposite effects on the metabolism rate of different drugs. Frequencies of genotypes in different populations are dependent on ethnic background, and the variation of frequency for CYP2C8 genotypes is from under one percent to tens of percents.

Normal metabolism

*1/*1

Analyzed 3 of 3 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP2C9)

CYP2C9 is a hepatic enzyme which mediates metabolism of several drugs, including warfarin and phenytoin. There is genetic variation concerning CYP2C9, and due to this the speed of metabolism by the enzyme in an individual can be slower than average. This increases efficacy of certain drugs. Altered alleles *2 and *3 of CYP2C9 gene are the most frequent and the most important functionally. They are shown to be linked to decreased enzymatic activity, slower metabolism and thus decreased required doses of certain drugs.

NM Normal Metabolizer

*1/*1

Analyzed 6 of 6 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP2D6)

CYP2D6 is a hepatic enzyme that is responsible for the metabolism of many pharmaceuticals. These include several antidepressants and pain medications, for example. There is genetic variation concerning CYP2D6, and due to this the speed of metabolism of the enzyme in an individual can be faster or slower than average. This either increases or decreases efficacy of different drugs, which alters the needed doses between individuals.

UM Ultrarapid Metabolizer

(*1/*1)x3

Analyzed 3 of 3 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP3A4)

CYP3A4 is a hepatic enzyme which mediates metabolism of more drugs than any other human enzyme. Several drugs inhibit the activity or increase the expression of the enzyme. There is some genetic variation concerning CYP3A4, and due to this the speed of metabolism of the enzyme in an individual may be altered. This increases or decreases the efficacy of certain drugs. CYP3A4 and closely related CYP3A5 have some common substates. The combined metabolism of these enzymes may define the speed of metabolism of certain drugs better than that of CYP3A4 alone.

Normal metabolism

*1/*1

Analyzed 2 of 2 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP3A5)

CYP3A5 is a hepatic enzyme that is responsible for the metabolism of many pharmaceuticals. The most important of these is tacrolimus. Due to genetic variation concerning CYP3A5 the speed of metabolism of the enzyme varies. The majority of white people are poor CYP3A5 metabolizers. This alters the needed doses of certain drugs between individuals.

PM Poor metabolizer

*3/*3

Analyzed 4 of 4 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP4F2)

People fall into different categories according to CYP4F2 genotype. Genotype information is potentially helpful when predicting warfarin dose.

Decreased enzyme activity

*1/*3

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (DPYD)

Dihydropyrimidine dehydrogenase (DPD) is a key enzyme catabolizing fluoropyrimidines, which are used as chemotherapeutics for various types of cancer. Due to genetic variation concerning DPYD, the gene encoding DPD, the speed of metabolism of the enzyme varies between individuals. DPD-deficient patients are in greater risk for adverse effects of fluoropyrimidines.

NM Normal metabolizer

WT/WT

Analyzed 4 of 4 single nucleotide polymorphisms (SNP).

Blood coagulation factor II (F2, prothrombin)

Occurrence of venous thromboembolic events is mediated by both hereditary and acquired risk factors. The most common reasons for dominantly inherited propensity for thrombotic events are point mutations in two genes encoding blood coagulation factors: factor V (F V) and factor II (prothrombin, FII). The mutation in prothrombin gene is the second most common genetic error after F V gene error predisposing to thrombotic events. Prothrombin, the precursor of thrombin, is a key enzyme involved in coagulation cascade. Thrombin transforms soluble fibrinogen to fibrin which forms the clot. It also activates thrombocytes. The point mutation in in the prothrombin gene causes elevated levels of prothrombin in the plasma and thus advances the propensity for thrombotic events. The mutation is significantly more common in patients with venous thromboembolism than in normal population. Appearance of the prothrombin mutation together with some other factor predisposing to thromboembolism increases the patients risk for thrombotic event.

No increased risk of venous thromboembolism

WT/WT

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Blood coagulation factor V (F5 Leiden)

Occurrence of venous thromboembolic events is mediated by both hereditary and acquired risk factors. The most common reasons for dominantly inherited propensity for thrombotic events are point mutations in two genes encoding blood coagulation factors: factor V (F V) and factor II (prothrombin, FII). Resistance to activated protein C (APCR), which means the inability of protein C to degrade activated clotting factor V, occurs due to so called Leiden mutation in the gene encoding F V. It is over tenfold more common than any other known hereditary factor predisposing to clotting. Depending on experiment sample, frequency of APCR is between 21-60% in patients with venous thrombotic event, and between only 3-7% in control patients. Classic risk factor including surgery, fracture, severe infection, oral contraception, pregnancy and childbirth increase the risk for venous thrombosis.

No increased risk of venous thromboembolism

WT/WT

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (G6PD)

Deficiency of glucose-6-phosphate dehydrogenase (G6PD) is an inherited enzyme defect which causes haemolytic anemia either continuously or under certain exposures (certain drugs, nutritional compounds or infections). A key compound produced by the enzyme protects erythrocytes from oxidative stress, and its significance is emphasized under circumstances where red blood cells are under unusually heavy oxidation. As oxidation increases, erythrocytes are broken up, i. e. hemolyzed. In some patients there is insufficient production of the enzyme and in some patients the enzyme is not active enough. The gene for this recessively inherited disease is located on the X chromosome, and thus the condition occurs mainly in men or boys, as females are normally asymptomatic. G6PD deficiency is the most common human enzyme defect, being present in more than 400 million people worldwide. More than 400 variations of the G6PD enzyme have been found. Severe G6PD deficiency appears in Mediterranean countries, Middle East and Asia, and milder forms in Africa. In white populations the deficiency is rare. In the Finnish major population deficiency is rare. Even if G6PD deficiency wouldn't have been detected by a genetic test, it is however possible for the patient to have G6PD deficiency due to deficient variants not included in the genetic test. Therefore, the G6PD activity can only be fully ascertained with a phenotyping test (i.e. measurement of the enzyme activity) in patients with normal genotype.

NORMAL	DEFICIENT	VARIABLE

No detected G6PD deficiency

B/B

Analyzed 7 of 7 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (GRIK4)

Gene GRIK4 encodes a kainate receptor, a subtype of glutamate receptor. The receptor contributes to glutamatergic signalling. Glutamate is the major excitatory neurotransmitter in the central nervous system. Antidepressant treatment results in part in a correction of glutamate imbalance. A single nucleotide polymorphism in GRIK4 has been shown to be associated with decreased response to antidepressant therapy.

TT	CT	CC

Poor responder (heterozygous)

T/C

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (IFNL3)

IFNL3 or IL28B gene encodes interferon lambda 3 which is a protein involved immune reactions, triggered e.g. by virus infections. There are common genetic variants in this gene or its surroundings. They are the strongest predictors of the efficacy of hepatitis C virus (HCV) therapies with peginterferon alpha (PEG-IFN alpha) and ribavirin (RBV) alone or combined with protease inhibitors. These combination therapies last several months and produce a lot of adverse effects. Therefore, before initiating the treatment, it is necessary to consider the probability of treatment failure and other factors of the patient which may alter the outcome. The outcome is also dependent on the genotype of HCV itself, and the medication recommendations related to IFNL3 variation pertain especially to virus genotype I.

FAVOURABLE	UNFAVOURABLE

Unfavorable response genotype

WT/var

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (SLCO1B1)

OATP1B1 protein, which is encoded by SLCO1B1 gene, facilitates the hepatic uptake of statins from the plasma. One variant allele of the gene (C allele) decreases the transport function of the protein and thus leads to accumulation of statins in the plasma and increased risk for myopathy. The risk for myopathy has been shown to be associated to the use of simvastatin in allele C carriers, especially in homozygotes (CC) but also in heterozygotes (CT). There may also be association with other statins and the muscle toxicity and the size of the dose is also crucial: the higher the statin dose the greater the myopathy risk.

NORMAL	DECREASED	POOR

Normal function

*1B/*1B

Analyzed 2 of 2 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (TPMT)

Thiopurine methyltransferase (TPMT) is an enzyme responsible for the metabolism of thiopurine drugs (azathioprine, mercaptopurine and thioguanine). Approximately 0.3 % of the patients have inherited low enzyme activity of TPMT, which predisposes to adverse effects of these drugs (myelosuppression, pancytopenia and possible secondary malignancies). By adjusting the patient's thiopurine dose according to his/her TPMT activity, adverse effects may be avoided. Enzyme activity can be genetically determined.

NORMAL	INTERMEDIATE	POOR

NM Normal metabolizer

*1/*1

Analyzed 4 of 4 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (UGT1A1)

UGT1A1 gene encodes the UDP-glucuronosyltransferase 1-1 enzyme which is responsible for elimination of certain drugs and bilirubin. It is also responsible glucuronidation of the active metabolite of an anticancer drug irinotecan/CPT-11 and thus elimination of it. Using irinotecan in combination with poor UGT1A1 metabolism may lead to haematological or gastrointestinal adverse effects. Additionally, the development of hyperbilirubinemia during treatment with inhibitors of UGT1A1, such as atazanavir, has also been linked to poor UGT1A1 metabolizer phenotype. Evolving jaundice may cause early discontinuation of the causing drug.

IM Intermediate Metabolizer

*1 or *36/*28 or *37

Analyzed 2 of 2 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (VKORC1)

Warfarin treatment is used to prevent thrombotic disorders. In addition to numerous other factors, genetic factors have their role in individual determination of warfarin dose. VKORC1 enzyme (vitamin K epoxide reductase complex subunit 1), which takes part in activation of coagulation factors, has inherited variant forms that affect the required dose of warfarin. Taking this into consideration (together with variants of CYP2C9 enzyme) may help in finding the optimal warfarin dose.

Reduced expression of the enzyme

*1/*2

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

RAW DATA

Gene	RS	Genotype
ABCB1		
ALDH2		
BCHE		
BCHE		
BCHE		
CYP1A2		
CYP1A2		
CYP1A2		
CYP1A2		
CYP2B6		
CYP2B6		
CYP2B6		
CYP2B6		
CYP2C19		
CYP2C19		
CYP2C19		
CYP2C19		
CYP2C19		
CYP2C8		
CYP2C8		
CYP2C8		
CYP2C9		
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