GeneAccount

SYNLAB

You were tested for 27 genes, out of which 6 may affect the efficacy or safety of your medication: **CYP2C19, CYP2C9, CYP2D6, IFNL3, SLCO1B1, VKORC1**

Your genetic factors may affect the efficacy or safety of 115 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

boceprevir, eliglustat, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, simvastatin, siponimod, telaprevir, tetrabenazine, thioridazine

DRUGS WITH GENETIC VARIATION OF SOME CLINICAL RELEVANCE

amitriptyline, atomoxetine, atorvastatin, citalopram, clomipramine, clopidogrel, desipramine, doxepin, escitalopram, imipramine, metoprolol, nortriptyline, primaquine, tamoxifen, trimipramine, venlafaxine, voriconazole, warfarin

DRUGS WITH GENETIC VARIATION OF MINOR CLINICAL RELEVANCE

acenocoumarol, amoxapine, amphetamine, aripiprazole, brexpiprazole, brivaracetam, bupropion, carisoprodol, carvedilol, cevimeline, clobazam, codeine, dapsone, darifenacin, desflurane, desvenlafaxine, deutetrabenazine, dexlansoprazole, dextromethorphan, diazepam, digoxin, donepezil, enflurane, fesoterodine, flecainide, flibanserin, flupenthixol, fluvoxamine, gefitinib, haloperidol, halothane, hydrocodone, iloperidone, isoflurane, isoniazid, lacosamide, lansoprazole, lofexidine, lovastatin, meclizine, methotrexate, methoxyflurane, methylthioninium, metoclopramide, mirtazapine, mivacurium, moclobemide, modafinil, nebivolol, nitrofurantoin, omeprazole, ondansetron, oxycodone, pantoprazole, paroxetine, pegloticase, perphenazine, phenprocoumon, phenytoin, pimozide, pitolisant, pravastatin, propafenone, protriptyline, quinidine, quinine, ranolazine, rasburicase, risperidone, rosuvastatin, sertindole, sevoflurane, simeprevir, sofosbuvir, sulfadiazine, suxamethonium, tafenoquine, tamsulosin, terbinafine, tetracaine, tolterodine, tramadol, tropisetron, valbenazine, vincristine, vortioxetine, zuclopenthixol

DRUGS WITH NO CLINICALLY RELEVANT GENETIC VARIATION

alcohol, amifampridine, amifampridine phosphate, arformoterol, aripiprazole lauroxil, articaine, ascorbic acid, atazanavir, avatrombopag, azathioprine, belinostat, binimetinib , caffeine, capecitabine, cariprazine, celecoxib, chloroprocaine, chloroquine, chlorpropamide, ciprofloxacin, cisplatin, clozapine, dabrafenib, daclatasvir, diclofenac, dolutegravir, dronabinol, duloxetine, efavirenz, elagolix, eltrombopag, erdafitinib, erlotinib, esomeprazole, estradiol, estriol, ethinylestradiol, flucytosine, fluorouracil, fluoxetine, flurbiprofen, flutamide, fluvastatin, fosphenytoin, galantamine, glibenclamide, glimepiride, glipizide, glyceryl trinitrate, govitecan, hydralazine, hydroxychloroquine, ibuprofen, indacaterol, irbesartan, irinotecan, lesinurad, levofloxacin, lidocaine, lornoxicam, losartan, lusutrombopag, mafenide, meloxicam, mepivacaine, mercaptopurine, methadone, mirabegron, moxifloxacin, nalidixic acid, nefazodone, nevirapine, nilotinib, norfloxacin, olanzapine, paliperidone, palonosetron, pazopanib, pioglitazone, piroxicam, prasugrel, prilocaine, probenecid, propranolol, rabeprazole, raltegravir, rimegepant, romiplostim, ropivacaine, rosiglitazone, rucaparib, sertraline, sodium nitrite, sulfamethoxazole, sulfasalazine, sulfisoxazole, tacrolimus, tegafur, tenoxicam, thioguanine, tibolone, ticagrelor, tolazamide, tolbutamide, umeclidinium, upadacitinib

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.

CUT AWAY THIS INFORMATION AND STORE IT IN A SAFE PLACE FOR LATER REFERENCE.

THE LATEST GENETIC INFORMATION IS FOUND ONLINE

We update our service periodically since pharmacogenetic knowledge is constantly evolving and getting more accurate by new research discoveries.

Login to the GeneAccount web service with your mobile or desktop device to see your test results and up-to-date report. Via the service, you can print or send your test results to your doctor.

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YOUR PIN CODE

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In order to protect your privacy, share this information only after serious consideration and only to trusted persons, e.g. your doctor.

HIGHLY AFFECTED MEDICATIONS ORDERED BY THERAPEUTIC AREA

Therapeutic area		Active ingredient	Phenotype	Classification
Alimentary Tract And Metabolism	Other Alimentary Tract And Metabolism Products	eliglustat	CYP2D6 IM Intermediate Metabolizer	D
Blood And Blood Forming Organs	Antithrombotic Agents	clopidogrel	CYP2C19 IM Intermediate Metabolizer	C
		warfarin	CYP2C9 NM Normal Metabolizer (Activity score 2)	C
		warfarin	VKORC1 Remarkably reduced expression of the enzyme	C
Cardiovascular System	Beta Blocking Agents, Plain	metoprolol	CYP2D6 IM Intermediate Metabolizer	C
	Beta Blocking Agents And Other Antihypertensives	metoprolol	CYP2D6 IM Intermediate Metabolizer	C
	Lipid Modifying Agents, Plain	atorvastatin	SLCO1B1 Decreased function	C
		simvastatin	SLCO1B1 Decreased function	D
	Lipid Modifying Agents, Combinations	atorvastatin	SLCO1B1 Decreased function	C
General Antiinfectives For Systemic Use	Antimycotics For Systemic Use	voriconazole	CYP2C19 IM Intermediate Metabolizer	C
Antineoplastic And Immunomodulating Agents	Hormone Antagonists And Related Agents	tamoxifen	CYP2D6 IM Intermediate Metabolizer	C
	Immunostimulating Agents	peginterferon alfa-2a	IFNL3 Unfavorable response genotype	D
Nervous System	Antidepressants	amitriptyline	CYP2D6 IM Intermediate Metabolizer	C
		citalopram	CYP2C19 IM Intermediate Metabolizer	C
		clomipramine	CYP2D6 IM Intermediate Metabolizer	C
		doxepin	CYP2D6 IM Intermediate Metabolizer	C
		escitalopram	CYP2C19 IM Intermediate Metabolizer	C
		nortriptyline	CYP2D6 IM Intermediate Metabolizer	C
		trimipramine	CYP2D6 IM Intermediate Metabolizer	C
		venlafaxine	CYP2D6 IM Intermediate Metabolizer	C
	Psychostimulants	atomoxetine	CYP2D6 IM Intermediate Metabolizer	C
	Psycholeptics And Psychoanaleptics In Combination	amitriptyline	CYP2D6 IM Intermediate Metabolizer	C
	Other Nervous System Drugs	tetrabenazine	CYP2D6 IM Intermediate Metabolizer	D

SUMMARY OF TESTED GENES AND THEIR PREDICTED PHENOTYPES

Gene	Diplotype	Phenotype
ABCB1	WT/WT	Possibly low expression of P-GP
ALDH2	*1/*1	Normal enzyme activity
BCHE	WT/F2	Decreased enzyme activity
CACNA1S	WT/WT	Uncertain susceptibility to malignant hyperthermia
CYP1A2	*1/*1	Normal metabolism
CYP2B6	*1/*4	RM Rapid Metabolizer
CYP2C19	*1/*2	IM Intermediate Metabolizer
CYP2C8	*1/*1	Normal metabolism
CYP2C9	*1/*1	NM Normal Metabolizer (Activity score 2), activity score 2
CYP2C_rs12777823	G/A	Decreased warfarin dose requirement
CYP2D6	*4/*41	IM Intermediate Metabolizer, activity score 0.5
CYP3A4	*1/*1	Normal metabolism
CYP3A5	*3/*3	PM Poor metabolizer
CYP4F2	*1/*1	Normal metabolizer
DPYD	WT/c.85T>C	NM Normal metabolizer, activity score 2
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	C/C	High responder
IFNL3	WT/var	Unfavorable response genotype
MTHFR	WT/A1298C	Decreased enzyme activity
NAT2	*4/*4	Rapid acetylator
NUDT15	*1/*1	Normal metabolizer
SLCO1B1	*1/*15	Decreased function
TPMT	*1/*1	NM Normal metabolizer
UGT1A1	*1 or *36/*1 or *36	NM Normal Metabolizer
VKORC1	*2/*2	Remarkably 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): The genetic variation increases the sensitivity to acenocoumarol. Recommend to use 50% of the standard initial dose. Recommend more frequent monitoring of the INR.

VKORC1: Remarkably reduced expression of the enzyme

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

alcohol

A Minor or no flushing reaction to alcohol.

ALDH2: Normal enzyme activity

amifampridine

A Label-recommended dosing and administration.

NAT2: Rapid acetylator

amifampridine phosphate

A Label-recommended dosing and administration.

NAT2: Rapid acetylator

amitriptyline

C Exposure to amitriptyline and thus risk of adverse effects may be increased with this genotype. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Consider 25% reduction of recommended starting dose. 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). This recommendation is classified as optional for those with CYP2D6 activity score of 1.

CYP2D6: IM Intermediate Metabolizer

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

CYP2C19: IM Intermediate Metabolizer

amoxapine

B Label-recommended dosage and administration. As for other tricyclic antidepressants, the exposure to the drug is potentially increased with this genotype.

CYP2D6: IM Intermediate 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: IM Intermediate Metabolizer

arformoterol

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

A Label-recommended dosing and administration.

UGT1A1: NM Normal Metabolizer

aripiprazole

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

CYP2D6: IM Intermediate Metabolizer

aripiprazole lauroxil

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate 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

A With this genotype the risk of jaundice caused by atazanavir is not 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).

atomoxetine

C Metabolism of the drug is variable on different allelic combinations which fall under the phenotype of intermediate metabolizer. Check the exact CYP2D6 star allele genotype and/or activity score (AS) from the pharmacogenetic report and choose the appropriate dosing guideline by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC) according to the AS of the CYP2D6 enzyme: PATIENTS WITH AS 1.0 (or no *10 allele present): Possibly higher atomoxetine concentrations as compared to normal metabolizers but questionable clinical significance. Possibly increased risk of discontinuation as compared to poor

UGT1A1: NM Normal Metabolizer

metabolizers. 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 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. PATIENTS WITH AS < 1.0 (or *10 allele present): Decreased metabolism of the drug and higher drug concentrations as compared with normal metabolizers. Possibly increased risk of discontinuation as compared with poor metabolizers. FOR ADULTS: Initiate with a dose of 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day. If response is inadequate after 2 weeks consider obtaining a plasma concentration 2-4 hours after dosing. If concentration is < 200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml. If unacceptable side effects are present at any time, consider a reduction in dose. FOR CHILDREN: Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 2-4 hours after dosing. If response is inadequate and concentration is < 200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml. If unacceptable side effects are present at any time, consider a reduction in dose.

CYP2D6: IM Intermediate Metabolizer

atorvastatin

C In patients with SLCO1B1 521 T/C genotype (i.e. rs4149056-TC or *1/*5) the risk of myopathy may be increased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): If patient has additional significant risk factors for statin-induced myopathy, choose an alternative. Do not choose simvastatin as this is also affected by SLCO1B1 gene variation. Rosuvastatin and pravastatin are influenced to a similar extent by SLCO1B1 polymorphisms, but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not influenced significantly by SLCO1B1 gene variation or CYP3A4 inhibitors. If an alternative is not an option: Advise the patient to contact their doctor in the event of muscle symptoms. If patient has no additional significant risk factors for statin myopathy, initiate the drug and advise patient to contact their doctor in the event of muscle symptoms.

SLCO1B1: Decreased function

A Label-recommended dosing and administration.

CYP3A4: Normal metabolism

avatrombopag

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

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 Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Start with normal starting dose (e.g. 2-3 mg/kg/day) and adjust dosing based on disease-specific guidelines. Allow 2 weeks to reach steady-state after each dose adjustment. Note that also TPMT genotype affects the risk for thiopurine-induced adverse reactions. See if TPMT test result is available and treat according to the recommendation for more severe phenotype for either TPMT or NUDT15 gene (e.g. if NUDT15 phenotype is normal and TPMT phenotype is poor metabolizer, treat according to the TPMT poor metabolizer guideline).

NUDT15: Normal metabolizer

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. Note that also NUDT15 genotype affects the risk for thiopurine-induced adverse reactions. See if NUDT15 test result is available and treat according to the recommendation for more severe phenotype for either TPMT or NUDT15 gene (e.g. if TPMT phenotype is normal and NUDT15 phenotype is poor metabolizer, treat according to the NUDT15 poor metabolizer guideline).

TPMT: NM Normal metabolizer

belinostat

A Label-recommended dosing and administration.

UGT1A1: NM Normal Metabolizer

binimetinib

A Label-recommended dosing and administration.

UGT1A1: NM Normal 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. With this genotype the exposure to brexpiprazole is potentially increased.

CYP2D6: IM Intermediate 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

bupropion

caffeine

B Label-recommended dosing and administration. This genotype is likely associated with increased formation of hydroxybupropion, active metabolite of bupropion. One study showed 1.66-fold higher total clearance of bupropion in carriers of increased-function (*4) allele compared to wild-type. Clinical significance of this increase is currently unknown.

CYP2B6: RM Rapid Metabolizer

capecitabine

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

DPYD: NM Normal metabolizer

carisoprodol

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

CYP2C19: IM Intermediate Metabolizer

celecoxib

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

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

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

cisplatin

A Label-recommended dosing and administration.

TPMT: NM Normal metabolizer

clobazam

B Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

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

CYP1A2: Normal metabolism

cariprazine

A Label-recommended dosing and administration.

CYP2D6: 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 elevated. This does not, however, result in an increase in side effects.

CYP2D6: IM Intermediate Metabolizer

cevimeline

B With this genotype the exposure to cevimeline and thus the risk for adverse reactions are increased. According to the label approved by the U.S. Food and Drug Administration (FDA) the drug should be used with caution.

CYP2D6: IM Intermediate Metabolizer

chloroquine

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: 1. Adults up to 65 years: 30 mg as tablets or 22 mg as drops. 2. Adults 65 years or older: 15 mg as tablets or 10 mg as drops.

CYP2C19: IM Intermediate Metabolizer

B Label-recommended dosage. With this genotype the metabolism of citalopram is potentially slower but there is no coherent scientific evidence on its clinical significance.

CYP2D6: IM Intermediate Metabolizer

A Label-recommended dosage. Patients with this genotype may be more likely to respond to antidepressant treatment as compared to other genotypes.

GRIK4: High responder

clomipramine

C Exposure to clomipramine and thus risk of adverse effects may be increased with this genotype. 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: Consider 25% reduction of recommended starting dose. 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). This recommendation is classified as optional for those with CYP2D6 activity score of 1.

CYP2D6: IM Intermediate Metabolizer

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

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 (Activity score 2)

clozapine

A Label-recommended dosing and administration.

CYP1A2: Normal metabolism

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

codeine

B With this genotype the metabolism of codeine to morphine is decreased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Use codeine label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider a non-tramadol opioid.

CYP2D6: IM Intermediate 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

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

dapsone

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

A Label-recommended dosing and administration.

NAT2: Rapid acetylator

darifenacin

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

CYP2D6: IM Intermediate Metabolizer

desflurane

B No malignant hyperthermia (MH)-causative variants were detected. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown. Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants. It should be noted that individuals with muscle diseases caused by, or associated with, genetic abnormalities in RYR1 receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

CACNA1S: Uncertain susceptibility to malignant hyperthermia

desipramine

C Exposure to desipramine and thus risk of adverse effects may be increased with this genotype. 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: Consider 25% reduction of recommended starting dose. 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). This recommendation is classified as optional for those with CYP2D6 activity score of 1.

CYP2D6: IM Intermediate Metabolizer

desvenlafaxine

B Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

deutetrabenazine

dexlansoprazole

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: IM Intermediate Metabolizer

dextromethorphan

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

CYP2D6: IM Intermediate Metabolizer

diclofenac

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

dolutegravir

A Label-recommended dosing and administration.

UGT1A1: NM Normal Metabolizer

doxepin

C Exposure to doxepin and thus risk of adverse effects may be increased with this genotype. 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: Consider 25% reduction of recommended starting dose. 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). This recommendation is classified as optional for those with CYP2D6 activity score of 1.

CYP2D6: IM Intermediate Metabolizer

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

CYP2C19: IM Intermediate Metabolizer

duloxetine

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

elagolix

A Label-recommended dosing and administration.

SLCO1B1: Decreased function

eltrombopag

A Label-recommended dosing and administration.

F2 (prothrombin): No increased risk of venous thromboembolism

A Label-recommended dosing and administration.

B With this genotype the exposure to dexlansoprazole is potentially increased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Initiate standard starting daily dose. For chronic therapy (>12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy.

CYP2C19: IM Intermediate 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 low expression of P-GP

donepezil

B Label-recommended dosage. With this genotype the metabolism of donepezil is potentially reduced, which may improve the drug response, but the scientific evidence for its clinical significance is inconsistent.

CYP2D6: IM Intermediate Metabolizer

dronabinol

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

efavirenz

A Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC) for adults and children who weigh more than 40 kg: Initiate efavirenz with standard dose of 600 mg/day.

CYP2B6: RM Rapid Metabolizer

eliglustat

D According to the summary of product characteristics provided by the manufacturer: For intermediate CYP2D6 metabolizers the dose is 84 mg twice daily. See drug label or summary of product characteristics for specific dosing or contraindications when used concomitantly with strong or moderate CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, duloxetine, terbinafine) or strong or moderate CYP3A inhibitors (e.g. clarithromycin, ketoconazole, erythromycin, ciprofloxacin, fluconazole).

CYP2D6: IM Intermediate Metabolizer

enflurane

B No malignant hyperthermia (MH)-causative variants were detected. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown. Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants. It should be noted that individuals with muscle diseases caused by, or associated with, genetic abnormalities in RYR1

F5: No increased risk of venous thromboembolism

receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

CACNA1S: Uncertain susceptibility to malignant hyperthermia

erdafitinib

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

erlotinib

A Label-recommended dosing and administration.

UGT1A1: NM Normal 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 dosage. With this genotype the metabolism of escitalopram is potentially slower but there is no coherent scientific evidence on its clinical significance.

CYP2D6: IM Intermediate Metabolizer

A Label-recommended dosage. Patients with this genotype may be more likely to respond to antidepressant treatment as compared to other genotypes.

GRIK4: High responder

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. With this genotype the exposure to active metabolite of fesoterodine is potentially increased, especially if there is a CYP3A4 inhibitor in use concomitantly.

CYP2D6: IM Intermediate Metabolizer

flecainide

B With this genotype the exposure to flecainide is potentially increased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The genetic variation reduces conversion of flecainide to inactive metabolites. This may increase the risk of side effects. Indications other than diagnosis of Brugada syndrome: Reduce the dose to 75% of the standard dose and record an ECG and monitor the plasma concentration. Provocation test for diagnosis of Brugada syndrome: No action required. At a dose of 2.0 mg/kg body weight to a maximum of 150 mg, the response is better for patients with alleles that result in reduced activity.

CYP2D6: IM Intermediate 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 (Activity score 2)

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

CYP2D6: IM Intermediate Metabolizer

flucytosine

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

DPYD: NM Normal 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 increases as a result of the reduced 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: IM Intermediate Metabolizer

flurbiprofen

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

fluvastatin

A Label-recommended dosage. Variations in SLCO1B1 gene do not significantly affect on pharmacokinetics of fluvastatin.

SLCO1B1: Decreased function

fosphenytoin

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

gefitinib

B Label-recommended dosage. With this genotype the metabolism of gefitinib is potentially reduced. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is needed for this gene-drug interaction. Side effects can occur more frequently, as the gene variation increases the gefitinib plasma concentration. However, the side effects are reversible and manageable, to an extent that adjustment of the therapy in advance is not necessary.

CYP2D6: IM Intermediate Metabolizer

glimepiride

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

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

B Label-recommended dosing and administration.

CYP2D6: IM Intermediate 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: IM Intermediate 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

fluvoxamine

B Label-recommended dosage. With this genotype the exposure to fluvoxamine is potentially increased which may predispose to adverse effects.

CYP2D6: IM Intermediate Metabolizer

galantamine

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

glibenclamide

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

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

govitecan

A Label-recommended dosing and administration.

UGT1A1: NM Normal Metabolizer

halothane

B No malignant hyperthermia (MH)-causative variants were detected. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown. Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants. It should be noted that individuals with muscle diseases caused by, or associated with, genetic abnormalities in RYR1 receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

CACNA1S: Uncertain susceptibility to malignant hyperthermia

hydralazine

A Label-recommended dosing and administration.

NAT2: Rapid acetylator

hydrocodone

B Evidence for effects on metabolism or efficacy of this drug regarding this genotype is minimal. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Use hydrocodone label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider non-codeine or non-tramadol opioid

CYP2D6: IM Intermediate Metabolizer

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

ibuprofen

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

iloperidone

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

CYP2D6: IM Intermediate Metabolizer

imipramine

C Exposure to imipramine and thus risk of adverse effects may be increased with this genotype. 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: Consider 25% reduction of recommended starting dose. 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). This recommendation is classified as optional for those with CYP2D6 activity score of 1.

CYP2D6: IM Intermediate 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: NM Normal Metabolizer

irbesartan

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

irinotecan

A Label-recommended dosing and administration.

UGT1A1: NM Normal Metabolizer

isoflurane

B No malignant hyperthermia (MH)-causative variants were detected. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown. Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants. It should be noted that individuals with muscle diseases caused by, or associated with, genetic abnormalities in RYR1 receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

CACNA1S: Uncertain susceptibility to malignant hyperthermia

isoniazid

B Label-recommended dosing and administration. With this genotype the drug exposure is potentially decreased as compared to slower acetylation speed genotypes. This predisposes to treatment failure. In one study it has been shown that increased dosing (7.5 mg/kg) reduces the risk of treatment failure.

NAT2: Rapid acetylator

lacosamide

B Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

lansoprazole

B With this genotype the exposure to lansoprazole is potentially increased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Initiate standard starting daily dose. For chronic therapy (>12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy.

CYP2C19: IM Intermediate Metabolizer

lesinurad

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

levofloxacin

lidocaine

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

lofexidine

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

CYP2D6: IM Intermediate Metabolizer

losartan

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

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

meclizine

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

CYP2D6: IM Intermediate Metabolizer

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: RM Rapid Metabolizer

methoxyflurane

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

lornoxicam

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

lovastatin

B Label-recommended dosage. With this genotype the risk for statin-induced myopathy may be increased but less for other statins than simvastatin.

SLCO1B1: Decreased function

mafenide

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

meloxicam

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

mercaptopurine

A Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Start with normal starting dose (e.g. 75 mg/m2/day or 1.5 mg/kg/day) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents. Allow at least 2 weeks to reach steady state after each dose adjustment. Note that also TPMT genotype affects the risk for thiopurine-induced adverse reactions. See if TPMT test result is available and treat according to the recommendation for more severe phenotype for either TPMT or NUDT15 gene (e.g. if NUDT15 phenotype is normal and TPMT phenotype is poor metabolizer, treat according to the TPMT poor metabolizer guideline).

NUDT15: Normal metabolizer

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. Note that also NUDT15 genotype affects the risk for thiopurine-induced adverse reactions. See if NUDT15 test result is available and treat according to the recommendation for more severe phenotype for either TPMT or NUDT15 gene (e.g. if TPMT phenotype is normal and NUDT15 phenotype is poor metabolizer, treat according to the NUDT15 poor metabolizer guideline).

TPMT: NM Normal metabolizer

methotrexate

B With this genotype the risk for methotrexate toxicity is potentially increased. However, the scientific evidence about this is limited and partly controversial.

MTHFR: Decreased enzyme activity

B Label-recommended dosing and administration. Patients with this genotype might have decreased clearance of methotrexate durnig high-dose methotexate treatment. Risk for gastrointestinal side-effects might be decreased.

SLCO1B1: Decreased function

methylthioninium

B No malignant hyperthermia (MH)-causative variants were detected. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown. Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants. It should be noted that individuals with muscle diseases caused by, or associated with, genetic abnormalities in RYR1 receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

CACNA1S: Uncertain susceptibility to malignant hyperthermia

metoclopramide

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

CYP2D6: IM Intermediate Metabolizer

metoprolol

C With this genotype the exposure to metoprolol is potentially increased but evidence of its significance in relation to efficacy or adverse drug effects (ADEs) is controversial. If adverse drug effects occur, dosage recommendation by a Dutch group of experts (Dutch Pharmacogenetics Working Group) may be beneficial: The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia. Recommendation: If a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia: Increase the dose in smaller steps and/or prescribe no more than 50% of the standard dose. Other cases: No action required.

CYP2D6: IM Intermediate Metabolizer

mirabegron

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

CYP2D6: IM Intermediate Metabolizer

mirtazapine

B Label-recommended dosage. With this genotype the metabolism of mirtazapine is reduced. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): No action is required for this gene-drug interaction. The higher plasma concentration of mirtazapine does not result in an increase in the side effects.

CYP2D6: IM Intermediate Metabolizer

mivacurium

B Label-recommended dosage and administration. With this phenotype the duration of neuromuscular blockade may be slightly longer than in patients with normal pseudocholinesterase activity. Neuromuscular blockade and recovery should be monitored appropriately.

BCHE: Decreased enzyme activity

moclobemide

B 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

modafinil

B Label-recommended dosing and administration.

CYP2D6: 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

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 dosage and administration. With this genotype the exposure to nebivolol is potentially increased.

CYP2D6: IM Intermediate Metabolizer

nefazodone

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

nevirapine

A Label-recommended dosing and administration.

CYP2B6: RM Rapid Metabolizer

nilotinib

A Label-recommended dosing and administration.

UGT1A1: NM Normal 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

olanzapine

A Label-recommended dosing and administration.

CYP1A2: Normal metabolism

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

ondansetron

B Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

A Label-recommended dosage. With this genotype, the anti-emetic efficacy of ondansetron is potentially better as compared to other genotypes. This considers especially chemotherapy-induced and post-operational nausea and vomiting in the early phase.

ABCB1: Possibly low expression of P-GP

paliperidone

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

pantoprazole

B With this genotype the exposure to pantoprazole is potentially increased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Initiate standard starting daily dose. For chronic therapy (>12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy.

CYP2C19: IM Intermediate Metabolizer

pazopanib

A Label-recommended dosing and administration.

UGT1A1: NM Normal Metabolizer

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.

nortriptyline

C Exposure to nortriptyline and thus risk of adverse effects may be increased with this genotype. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Consider 25% reduction of recommended starting dose. 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). This recommendation is classified as optional for those with CYP2D6 activity score of 1.

CYP2D6: IM Intermediate Metabolizer

omeprazole

B With this genotype the exposure to omeprazole is potentially increased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Initiate standard starting daily dose. For chronic therapy (>12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy.

CYP2C19: IM Intermediate Metabolizer

oxycodone

B With this genotype the speed of metabolism of oxycodone is decreased but evidence of its significance in relation to efficacy or adverse drug effects is controversial. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): No recommendation for oxycodone therapy because of weak evidence regarding adverse events or analgesia.

CYP2D6: IM Intermediate Metabolizer

palonosetron

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

paroxetine

B Label-recommended dosage. With this genotype the exposure to paroxetine is potentially increased which may predispose to adverse effects.

CYP2D6: IM Intermediate Metabolizer

A Label-recommended dosing and administration.

CYP1A2: Normal metabolism

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

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

IFNL3: Unfavorable response genotype

perphenazine

B Label-recommended dosage. With this genotype the exposure to perphenazine is potentially increased.

CYP2D6: IM Intermediate 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): The genetic variation increases the sensitivity to phenprocoumon. Recommend to use 50% of the standard initial dose. Recommend more frequent monitoring of the INR.

VKORC1: Remarkably reduced expression of the enzyme

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

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 (Activity score 2)

pimozide

B Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The risk of QT-prolongation – and thereby also the risk of torsade de points – is theoretically increased, because the genetic variation results in an increase in the plasma concentration of pimozide. The risk of an excessively high plasma concentration can be negated by following the dose recommendations provided below. Recommendation: Use no more than the following doses (80% of the standard maximum dose): adults 16 mg/day, children 0.08 mg/kg per day to a maximum of 3 mg/day.

CYP2D6: IM Intermediate Metabolizer

pioglitazone

A Label-recommended dosing and administration.

CYP2C8: Normal metabolism

piroxicam

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

pitolisant

B Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

prasugrel

A Label-recommended dosing and administration.

CYP2B6: RM Rapid Metabolizer

A Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

A Label-recommended dosing and administration.

CYP3A5: PM Poor metabolizer

pravastatin

B Label-recommended dosage. With this genotype the risk for statin-induced myopathy may be increased but less for other statins than simvastatin.

SLCO1B1: Decreased function

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

C With this genotype the metabolism of primaquine to its active metabolites is potentially decreased which may lead to ineffective treatment and malarial relapses.

CYP2D6: IM Intermediate 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

B With this genotype the exposure to propafenone is potentially increased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This may increase the risk of side effects. Recommendation: It is not possible to offer adequately substantiated recommendations for dose adjustment based on the literature. Either guide the dose by therapeutic drug monitoring, perform an ECG and be alert to side effects, or choose an alternative. Antiarrhythmic drugs that are hardly if at all metabolised by CYP2D6 include, for example, sotalol, disopyramide, quinidine and amiodarone.

CYP2D6: IM Intermediate Metabolizer

propranolol

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

protriptyline

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

CYP2D6: IM Intermediate 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: IM Intermediate 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

A Label-recommended dosing and administration.

UGT1A1: NM Normal Metabolizer

ranolazine

B Label-recommended dosing and administration. With this genotype the exposure to ranolazine is potentially increased. Be aware of adverse drug effects.

CYP2D6: IM Intermediate 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.

IFNL3: Unfavorable response genotype

rimegepant

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

risperidone

B 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. Reduction of the dose or 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. There is little evidence to support an increase in side effects caused by the genetic variation. The genetic variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.

CYP2D6: IM Intermediate Metabolizer

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

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

rosiglitazone

A Label-recommended dosing and administration.

CYP2C8: Normal metabolism

rucaparib

A Label-recommended dosing and administration.

CYP1A2: Normal metabolism

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

sertraline

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

CYP2C19: IM Intermediate 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 summary of product characteristics or drug label, after treatment titration, with this genotype the recommended maintenance dosage is 2 mg taken orally once daily starting on day 6. Note also the potential effect of inducers and inhibitors of CYP3A4 and/or CYP2C9 (see drug label or summary of product characteristics for details).

CYP2C9: NM Normal Metabolizer (Activity score 2)

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

A Label-recommended dosing and administration.

NAT2: Rapid acetylator

rosuvastatin

B Label-recommended dosage. With this genotype the risk for statin-induced myopathy may be increased but less for other statins than simvastatin.

SLCO1B1: Decreased function

sertindole

B With this genotype the metabolism of sertindole is potentially reduced as compared to normal metabolizers. However, according to the summary of product characteristics, sertindole concentration is not predictive of therapeutic effect for an individual patient; thus, dosing individualisation is best achieved by assessment of therapeutic effect and tolerability.

CYP2D6: IM Intermediate Metabolizer

sevoflurane

B No malignant hyperthermia (MH)-causative variants were detected. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown. Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants. It should be noted that individuals with muscle diseases caused by, or associated with, genetic abnormalities in RYR1 receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

CACNA1S: Uncertain susceptibility to malignant hyperthermia

simvastatin

D With this genotype the risk for simvastatin-induced myopathy is increased. Prescribe a lower dose or consider an alternative statin (e.g. pravastatin or rosuvastatin); consider routine creatine kinase surveillance.

SLCO1B1: Decreased function

A Label-recommended dosing and administration.

CYP3A4: Normal metabolism

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

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

A Label-recommended dosing and administration.

NAT2: Rapid acetylator

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

B Label-recommended dosage and administration. With this phenotype the duration of neuromuscular blockade may be slightly longer than in patients with normal pseudocholinesterase activity. Neuromuscular blockade and recovery should be monitored appropriately.

BCHE: Decreased enzyme activity

B No malignant hyperthermia (MH)-causative variants were detected. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown. Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants. It should be noted that individuals with muscle diseases caused by, or associated with, genetic abnormalities in RYR1 receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

CACNA1S: Uncertain susceptibility to malignant hyperthermia

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

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

tamoxifen

C With this genotype the endoxifen concentrations (an active tamoxifen metabolite) are potentially lower compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of CYP2D6 genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Avoid CYP2D6 strong to weak inhibitors. This recommendation is graded by CPIC as 'moderate' for CYP2D6 activity score (AS) < 1.0 (or with allele combinations including *10 allele) and 'optional' for AS 1.0 (or with allele combinations without *10 allele (data extrapolated from evidence considering *10 allele)).

CYP2D6: IM Intermediate 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

tamsulosin

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

CYP2D6: IM Intermediate Metabolizer

tegafur

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

DPYD: NM Normal 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

tenoxicam

A Label-recommended dosing and administration.

CYP2C9: NM Normal Metabolizer (Activity score 2)

terbinafine

B Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

tetrabenazine

D According to the U.S. Food and Drug Administration (FDA), with this genotype the dosing is as follows: At doses under 50 mg per day: The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given as 12.5 mg twice a day. The dose should be titrated up slowly at weekly intervals by 12.5 mg, to allow the identification of a dose that reduces chorea and is well tolerated. If a dose of 37.5 to 50 mg per day is needed, it should be given in a three times a day regimen. The maximum recommended single dose is 25 mg. At doses above 50 mg per day: The dose should be titrated up slowly at weekly intervals by 12.5 mg, to allow the identification of a dose that reduces chorea and is well tolerated. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg.

CYP2D6: IM Intermediate Metabolizer

tetracaine

B Label-recommended dosage and administration. According to FDA-approved summary of product characteristics patients with this phenotype are at increased risk for toxic plasma concentrations of the drug compared to patients with normal pseudocholinesterase activity. Monitor patients with pseudocholinesterase deficiency for signs of local anesthetic toxicity.

BCHE: Decreased enzyme activity

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

thioguanine

A Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Start with normal starting dose (40-60 mg/m2/day). Adjust dosing every two weeks without any special emphasis on thioguanine. Allow 2 weeks to reach steady-state after each dose adjustment. Note that also TPMT genotype affects the risk for thiopurine-induced adverse reactions. See if TPMT test result is available and treat according to the recommendation for more severe phenotype for either TPMT or NUDT15 gene (e.g. if NUDT15 phenotype is normal and TPMT phenotype is poor metabolizer, treat according to the TPMT poor metabolizer guideline).

NUDT15: Normal metabolizer

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. Note that also NUDT15 genotype affects the risk for thiopurine-induced adverse reactions. See if NUDT15 test result is available and treat according to the recommendation for more severe phenotype for either TPMT or NUDT15 gene (e.g. if TPMT phenotype is normal and NUDT15 phenotype is poor metabolizer, treat according to the NUDT15 poor metabolizer guideline).

TPMT: NM Normal metabolizer

thioridazine

D Exposure to thioridazine and thus the risk of Torsades de pointes arrhythmia (due to prolongation of QTc) are increased. Thioridazine is contraindicated in patients who are known to have a genetic defect leading to reduced levels of activity of CYP2D6.

CYP2D6: IM Intermediate Metabolizer

tibolone

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

ticagrelor

A Label-recommended dosing and administration.

CYP2C19: IM Intermediate Metabolizer

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 (Activity score 2)

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 dosage and administration. With this genotype the exposure to the drug is potentially increased.

CYP2D6: IM Intermediate Metabolizer

tramadol

B With this genotype metabolism of tramadol to an active metabolite is decreased, which may lead to insufficient pain relief. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Use tramadol label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider a non-codeine opioid.

CYP2D6: IM Intermediate Metabolizer

trimipramine

C Exposure to trimipramine and thus risk of adverse effects may be increased with this genotype. 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: Consider 25% reduction of recommended starting dose. 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). This recommendation is classified as optional for those with CYP2D6 activity score of 1.

tropisetron

B Label-recommended dosage. With this genotype the metabolism of tropisetron is potentially reduced.

CYP2D6: IM Intermediate Metabolizer

CYP2D6: IM Intermediate Metabolizer

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

CYP2C19: IM Intermediate Metabolizer

umeclidinium

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate Metabolizer

upadacitinib

A Label-recommended dosing and administration.

CYP2D6: IM Intermediate 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: IM Intermediate Metabolizer

venlafaxine

C Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found. It is not possible to offer adequately substantiated advice for dose reduction based on the literature. Avoid venlafaxine. Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline. If it is not possible to avoid venlafaxine and side effects occur: 1) Reduce the dose. 2) Monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.

CYP2D6: IM Intermediate Metabolizer

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

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

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

vortioxetine

B Label-recommended dosage and administration. With this genotype the exposure to vortioxetine is potentially increased.

CYP2D6: 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 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 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 (Activity score 2)

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: Remarkably 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, VKORC1 and CYP4F2 genes. In African American patients with this CYP2C rs12777823 genotype, decrease the calculated dose by 10 - 25%.

CYP2C rs12777823: Decreased warfarin dose requirement

A 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, there's no need for further changes in warfarin dosing.

CYP4F2: Normal metabolizer

zuclopenthixol

B With this genotype the exposure to zuclopenthixol is potentially increased. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased zuclopenthixol plasma concentrations. Recommendation: Start with 75% of the standard dose or to choose an alternative 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: IM Intermediate 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 low expression of P-GP

WT/WT

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.

Decreased enzyme activity

WT/F2

Analyzed 3 of 3 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CACNA1S)

CACNA1S is a gene which encodes the alpha1 S subunit of the dihydropyridine receptor, expressed in the sarcoplasmic reticulum membrane of muscle cells. It activates the RYR1 calcium channel during membrane depolarization in contracting myocytes. Genetic variants of CACNA1S predispose to malignant hyperthermia, a potentially life-threatening state caused by halogenated volatile anesthetics (e.g. sevoflurane, enflurane, halothane) and depolarizing muscle relaxant suxamethonium (or succinylcholine). Symptoms of malignant hyperthermia include e.g. muscle rigidity, masseter spasm, tachycardia, arrhythmias, acidosis and hyperthermia. These agents used in anesthesia should be avoided in patients known to carry these variants. Prevalence of the genetic trait predisposing to malignant hyperthemia is approximately 1/2,000-1/3,000 and the state occurs in 1/10,000-1/250,000 anesthesias. It is good to notice that also variants in RYR1 gene predispose to malignant hyperthermia.

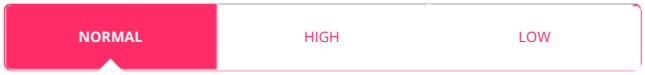
Uncertain susceptibility to malignant hyperthermia

WT/WT

Analyzed 2 of 2 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.



Normal metabolism

*1/*1

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.

RM Rapid Metabolizer

*1/*4

Analyzed 5 of 5 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP2C rs12777823)

CYP2C rs12777823 G>A is a genetic variant which is associated with lower warfarin doses in the African American population (approximately 10 - 25% lower doses than in non-carriers). The variant is located in the CYP2C gene cluster in chromosome 10.

Decreased warfarin dose requirement

G/A

Analyzed 1 of 1 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

*1/*2

Analyzed 7 of 7 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.

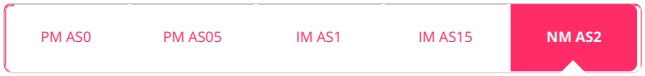
Normal metabolism

*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 (Activity score 2)
Activity score: **2**

*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.

IM Intermediate Metabolizer
Activity score: **0.5**

*4/*41

Analyzed 15 of 15 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.

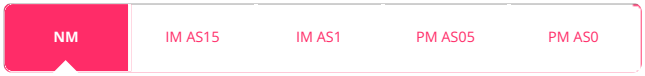
Normal metabolizer

*1/*1

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
Activity score: **2**

WT/c.85T>C

Analyzed 5 of 5 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.

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.

High responder

C/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.

Unfavorable response genotype

WT/var

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (MTHFR)

MTHFR gene encodes the methylenetetrahydrofolate reductase enzyme which is critical for folate metabolism. It affects methylation and DNA synthesis pathways by reducing 5,10-methylenetetrahydrofolate (MTHF) to 5-methyltetrahydrofolate. 5-MTHF is used as a substrate for conversion of homocysteine to methionine which is subsequently used in methylation reactions. 5,10-MTHF is used in de novo purine synthesis. Several common genetic variants in the gene are characterized. Certain genetic variants decrease the enzyme activity of MTHFR which potentially affects outcome or adverse effects of e.g. antirheumatic and antineoplastic drugs, such as methotrexate, which target the DNA synthesis pathways. Associations between genetic variants of MTHFR and risk for cardiovascular diseases, Alzheimer disease, neural tube defects and cancer have been described but their scientific validity and reproducibility is low so far.

Decreased enzyme activity

WT/A1298C

Analyzed 2 of 2 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (NAT2)

Arylamine N-acetyltransferase 2 (NAT2) is an enzyme which acetylates and thus often detoxifies several foreign compounds. Partly, it also activates and generates certain carcinogens and its activity may thus have association to cancer risk (e.g. prostate or colorectal cancer). Evidence for these associations is however inconsistent. NAT2 is most prominently expressed in the liver and intestines. Several genetic variants in NAT2 gene have been described and their effect on the acetylation activity of the enzyme are varying. Acetylation and subsequent excretion of certain medications, e.g. isoniazide and hydralazine, are affected by the genetic variations of NAT2. Dose alterations may be warranted in patients carrying variants which slow down the NAT2 acetylation.

Rapid acetylator

*4/*4

Analyzed 4 of 4 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (NUDT15)

NUDT15 encodes nucleoside diphosphatase enzyme which converts metabolites which converts thiopurine drug metabolites to less cytotoxic form. The R139C variant (rs116855232; c.415C>T) was the first variant which was linked to increased thiopurine toxicity, leading to increased risk for thiopurine-induced bone marrow failure. Since then, additional variants from NUDT15 gene have been identified, some of which have resulted in decreased enzyme activity in vitro. Currently, the evidence from other variants than R139C is too weak to give treatment recommendations. Based on gnomAD data, the frequency of R139C variant allele in Europeans is 0.7% and in Eastern Asians 9%. Thiopurine drug metabolism is also affected by TPMT gene.

Normal metabolizer

*1/*1

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.

Decreased function

*1/*15

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.

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.

NM Normal Metabolizer

*1 or *36/*1 or *36

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.

Remarkably reduced expression of the enzyme

*2/*2

Analyzed 1 of 1 single nucleotide polymorphisms (SNP).

RAW DATA

Gene	RS	Genotype
ABCB1	rs1045642	T/T
ALDH2	rs671	G/G
BCHE	rs1799807	T/T
BCHE	rs1803274	C/C
BCHE	rs28933390	C/A
CACNA1S	rs1800559	C/C
CACNA1S	rs772226819	G/G
CYP1A2	rs12720461	C/C
CYP1A2	rs2069514	G/G
CYP1A2	rs35694136	T/T
CYP1A2	rs762551	C/C
CYP2B6	rs2279343	A/G
CYP2B6	rs28399499	T/T
CYP2B6	rs34223104	T/T
CYP2B6	rs36060847	G/G
CYP2B6	rs3745274	G/G
CYP2C19	rs12248560	C/C
CYP2C19	rs12769205	A/G
CYP2C19	rs17878459	G/G
CYP2C19	rs28399504	A/A
CYP2C19	rs41291556	T/T
CYP2C19	rs4244285	G/A
CYP2C19	rs4986893	G/G
CYP2C8	rs10509681	T/T
CYP2C8	rs11572080	C/C
CYP2C8	rs11572103	T/T
CYP2C9	rs1057910	A/A
CYP2C9	rs1799853	C/C
CYP2C9	rs28371685	C/C
CYP2C9	rs28371686	C/C
CYP2C9	rs7900194	G/G
CYP2C9	rs9332131	A/A
CYP2C_rs12777823	rs12777823	G/A
CYP2D6	CNV	2
CYP2D6	rs1065852	G/A
CYP2D6	rs1135840	G/G
CYP2D6	rs16947	G/A
CYP2D6	rs267608319	C/C
CYP2D6	rs28371706	G/G
CYP2D6	rs28371725	C/T
CYP2D6	rs35742686	T/T

CYP2D6	rs3892097	C/T
CYP2D6	rs5030655	A/A
CYP2D6	rs5030656	TCT/TCT
CYP2D6	rs5030865	C/C
CYP2D6	rs5030867	T/T
CYP2D6	rs59421388	C/C
CYP2D6	rs769258	C/C
CYP3A4	rs2740574	T/T
CYP3A4	rs35599367	G/G
CYP3A5	rs10264272	C/C
CYP3A5	rs41303343	-/-
CYP3A5	rs55817950	G/G
CYP3A5	rs776746	C/C
CYP4F2	rs2108622	C/C
DPYD	rs1801265	A/G
DPYD	rs3918290	C/C
DPYD	rs55886062	A/A
DPYD	rs56038477	C/C
DPYD	rs67376798	T/T
F2	rs1799963	G/G
F5	rs6025	C/C
G6PD	rs1050828	C/C
G6PD	rs1050829	T/T
G6PD	rs137852339	C/C
G6PD	rs5030868	G/G
G6PD	rs5030869	C/C
G6PD	rs72554665	C/C
G6PD	rs78478128	G/G
GRIK4	rs1954787	C/C
IFNL3	rs12979860	C/T
MTHFR	rs1801131	T/G
MTHFR	rs1801133	G/G
NAT2	rs1799930	G/G
NAT2	rs1799931	G/G
NAT2	rs1801279	G/G
NAT2	rs1801280	T/T
NUDT15	rs116855232	C/C
SLCO1B1	rs2306283	A/G
SLCO1B1	rs4149056	T/C
TPMT	rs1142345	T/T
TPMT	rs1800460	C/C
TPMT	rs1800462	C/C
TPMT	rs1800584	C/C
UGT1A1	rs4148323	G/G

UGT1A1	rs887829	C/C
VKORC1	rs9923231	T/T