PHARMACOGENETIC ANALYSIS

This genetic analysis includes the following sections:

- **Results Report**
- **Additional genetic information**
- **Annex**

PATIENT IDENTIFICATION

NFGI00001

REQUESTING DOCTOR:	Dr Facultativo prueba
Hospital/Clinic:	

Results Report

Genetic analysis carried out at AB-BIOTICS S.A.
Parc Científic i Tecnològic de la UdG - c/Pic de Peguera 11 - 17003 Girona.
Healthcare authorization registration code E17867643.

Our laboratory has a Quality Management System certified by IQNet
which fullfills the requirements of the ISO 9001:2008 standard (ER-0788/2013).

Sample data

Patient identification	NFGI00001	**Analysis #**	999
Sample Code:	ABC_DNA	**Entry date:**	04/22/2014

SUMMARY TABLE

An initial interpretation of the results obtained from the patients genetic profile is displayed in a table below. For each drug examined, the result is indicated according to the following code:

- Standard: No genetic variants relevant to the treatment have been found. Use as directed.
- Need for drug dose monitoring and/or less likelihood of positive response.
- Increased likelihood of positive response and/or lower risk of adverse drug reactions.
- Increased risk of adverse drug reactions.

Antidepressants					
Amitriptyline		**Bupropion**	Standard	**Citalopram**	
Clomipramine		**Desipramine**		**Desvenlafaxine**	
Duloxetine		**Escitalopram**		**Fluoxetine**	
Fluvoxamine		**Imipramine**		**Mirtazapine**	Standard
Nortriptyline		**Paroxetine**		**Sertraline**	
Trimipramine		**Venlafaxine**			

Antipsychotics					
Aripiprazole		**Clozapine**		**Haloperidol**	
Olanzapine	Standard	**Paliperidone**		**Perphenazine**	
Pimozide		**Quetiapine**	Standard	**Risperidone**	
Ziprasidone	Standard				

Stabilizers and anticonvulsants					
Carbamazepine		**Clobazam**		**Clonazepam**	Standard
Lamotrigine	Standard	**Levetiracetam**	Standard	**Lithium***	
Lorazepam	Standard	**Phenobarbital**	Standard	**Phenytoin**	
Topiramate	Standard	**Valproic Acid**	Standard	**Vigabatrin**	Standard

Others					
Methadone	Standard	**Methylphenidate**		**Naloxone**	Standard
Pramipexol	Standard				

Report reviewed and verified by AB·BIOTICS **Date** 04/23/2014

Dr Miquel Tuson

** According to the ATC code, Lithium is considered an antipsychotic (N05AN01). By request of the physicians the classification of lithium in the table has been modified and it is shown in the mood stabilizers section.*

RESULTS REPORT

This section lists the drugs for which the genetic analysis suggests that the patient will behave differently from the average population (colour box from the previous table), as well as a series of recommendations for guidance purposes. When different genetic results indicated in different colours coexist for a given drug, the resulting colour in the summary table will follow this safety priority rule: risk of adverse drug reactions (red) > dose monitoring and/or less likelihood of positive response (amber) > increased likelihood of positive response (green) and/or lower risk of adverse drug reactions. The final evaluation of the analysis is at the physician´s discretion.

METABOLISER PROFILE OF THE PATIENT

Gene	Genotype	Phenotype
CYP1A2	*1/*1F	Extensive (normal) metaboliser
CYP2B6	*1/*6	Extensive (normal) metaboliser
CYP2C9	*1/*3	Intermediate metaboliser
CYP2C19	*2/*2	Poor metaboliser
CYP2D6	*4/*4	Poor metaboliser

DRUG — RECOMMENDATIONS FOR GUIDANCE PURPOSES

Amitriptyline

Analysis result:

- Higher likelihood of positive response to treatment (ABCB1)
- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1). Moreover, the analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metaboliser of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

Aripiprazole

Analysis result:

- Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Consider reducing the starting dose to 50%, and proceed to titrate dose in response to efficacy (do not exceed the maximum dose of 10mg/day).

Carbamazepine

Analysis result:

- Faster detoxification of the drug (EPHX1)

Recommendation:

The analysis indicates that a higher dose than standard may be necessary to achieve therapeutic effects (EPHX1).

Citalopram

Analysis result:

- Higher likelihood of positive response to treatment (ABCB1, BDNF)
- Poor metabolizer of the drug (CYP2C19)
- Increased medical surveillance is necessary (GRIA3)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1, BDNF). Moreover, the analysis indicates that the patient is a CYP2C19 poor metabolizer of this drug. Do not exceed a daily dose of 20mg (risk of QTc prolongation). In addition, increased medical surveillance is also recommended (GRIA3).

Clobazam

Analysis result:

- Poor metabolizer of the drug (CYP2C19)

Recommendation:

The analysis indicates that the patient is a CYP2C19 poor metabolizer of this drug. Consider a starting dose of 5mg/day and dose titration should proceed slowly according to weight, but to half the recommended total daily dose, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose, depending on the weight group, may be started on day 21.

Clomipramine

Analysis result:

- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

Clozapine

Analysis result:

- Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. However, there is no evidence suggesting a clinical effect of this phenotype; therefore use as directed and titrate dose in response to efficacy and adverse drug events.

Desipramine

Analysis result:

- Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

Desvenlafaxine

Analysis result:

- Higher likelihood of positive response to treatment (ABCB1)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Duloxetine

Analysis result:

- Decreased likelihood of positive response to treatment (DRD3)

Recommendation:

The analysis indicates there is a decreased likelihood of positive response to treatment for general anxiety disorder (DRD3). Therefore, if applicable, consider the use of an alternative drug.

Escitalopram

Analysis result:

- Poor metabolizer of the drug (CYP2C19)

Recommendation:

The analysis indicates that the patient is a CYP2C19 poor metabolizer of this drug. However, there is no evidence suggesting a clinical effect of this phenotype; therefore use as directed and titrate dose in response to efficacy and adverse drug events.

Fluoxetine

Analysis result:

- Higher likelihood of positive response to treatment (BDNF)
- Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF). Moreover, the analysis indicates the patient is a CYP2D6 poor metabolizer of this drug. However, there is no evidence suggesting a clinical effect of this phenotype; therefore use as directed and titrate dose in response to efficacy and adverse drug events.

Fluvoxamine

Analysis result:

- Higher likelihood of positive response to treatment (BDNF)
- Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF). Moreover, the analysis indicates the patient is a CYP2D6 poor metabolizer of this drug. If needed, consider monitoring plasma concentrations and dose adjustments.

Haloperidol

Analysis result:

- Poor metabolizer of the drug (CYP2D6)
- High risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR)

Recommendation:

The analysis indicates that the patient has a high risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore treatment with a low EPS-risk second generation antipsychotic is recommended. If this drug is warranted, consider the additional use of an anticholinergic. In addition, the analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Reduce dose by 50% or select an alternative drug.

Imipramine

Analysis result:

- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

Lithium

Analysis result:

- Higher likelihood of positive response to treatment (CACNG2)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (CACNG2), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Methylphenidate

Analysis result:

- Higher likelihood of positive response to treatment (COMT, LPHN3)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (COMT, LPHN3), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Nortriptyline

Analysis result:

Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

Paliperidone

Analysis result:

High risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR)

Recommendation:

The analysis indicates that the patient has a high risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore treatment with a low EPS-risk second generation antipsychotic is recommended. If this drug is warranted, consider the additional use of an anticholinergic.

Paroxetine

Analysis result:

Higher likelihood of positive response to treatment (ABCB1)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Perphenazine

Analysis result:

Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Therefore, there is a higher risk of adverse drug events. Consider dose adjustments in response to efficacy and ADE.

Phenytoin

Analysis result:

Intermediate metabolizer of the drug (CYP2C9)

Recommendation:

The analysis indicates that the patient is a CYP2C9 intermediate metabolizer of this drug. Consider using a standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days. Be alert to adverse drug events such as ataxia, nystagmus, dysarthria or sedation.

Pimozide

Analysis result:

Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Doses should not exceed 4 mg/day, and should not be increased earlier than 14 days.

Risperidone

Analysis result:

- Poor metabolizer of the drug (CYP2D6)
- High risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR)
- Higher likelihood of positive response to treatment (RGS4)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (RGS4). However, the analysis indicates that the patient has a high risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore treatment with a low EPS-risk second generation antipsychotic is recommended. If this drug is warranted, consider the additional use of an anticholinergic. In addition, the analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Select an alternative drug or be extra alert to adverse drug events and adjust dose to clinical response.

Sertraline

Analysis result:

- Higher likelihood of positive response to treatment (BDNF)
- Poor metabolizer of the drug (CYP2C19)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF). Moreover, the analysis indicates that the patient is a CYP2C19 poor metaboliser of this drug. Be extra alert to adverse drug events and, if needed, consider an up to 50% dose reduction.

Trimipramine

Analysis result:

- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation:

The analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

Venlafaxine

Analysis result:

- Higher likelihood of positive response to treatment (ABCB1)
- Poor metabolizer of the drug (CYP2D6)

Recommendation:

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1). Moreover, the analysis indicates the patient is a CYP2D6 poor metabolizer of this drug. Select an alternative drug or adjust dose to clinical response.

The following information applies only to tricyclic antidepressants, and as long as they are referenced in the text of the recommendation:

(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients should be monitored closely for side effects.

(3) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, CYP2D6 ultrarapid metabolizers are at risk of failing TCA therapy, thus alternative agents should be considered.

For any further information about the analysis, please do not hesitate to contact us at: info@neuropharmagen.co.il

Additional genetic information for drugs indicated as non-standard in the report

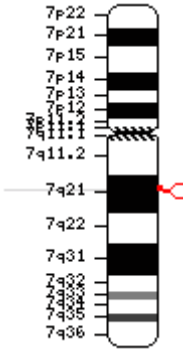
ADDITIONAL GENETIC INFORMATION

This section includes additional information about the biological role of the genes and genetic variants found in the analysis that may influence the patient´s response to drugs. This information is provided alongside with the test results and suggested recommendations for each particular drug displayed as non-standard in the report.

Amitriptyline

Description of the genes in which important variations

ABCB1



Gene located on chromosome 7 which encodes a membrane-associated protein, member of the superfamily of ATP-binding cassette (ABC) transporters and of the MDR/TAP subfamily (involved in multidrug resistance). This protein is also known as P-glycoprotein (P-gp) or multidrug resistance protein (MDR1). It is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. The ABCB1 protein also functions as a transporter in the blood-brain barrier.

The clinical efficacy of drugs that act on the central nervous system and are administered systemically depends in part on the capacity of these compounds to cross the blood-brain barrier, regulated by transporter proteins such as ABCB1.

Genetic variations in ABCB1 have been linked to drug resistance, and also to drug efficacy, in particular of antidepressant drugs that are substrates of this protein.

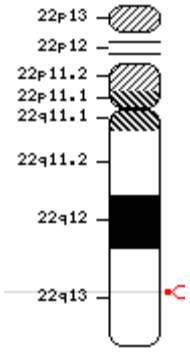
CYP2C19

Gene located on chromosome 10 which encodes a member of the cytochrome P450 superfamily of enzymes (cytochrome P450, family 2, subfamily C, polypeptide 19). The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2C19 is known to metabolize many xenobiotics, including omeprazole, diazepam and some barbiturates.

Individuals are classified into different groups according to their CYP2C19 activity level. The most frequent variation of CYP2C19 leads to what are known as ultrarapid metabolisers of drugs metabolised by this cytochrome. There are also less common variants that create poor metabolisers of drugs metabolised by CYP2C19.

When assessing the impact of a patient´s genotype, it is important to take into account the fact that this enzyme´s activity is affected by inducer and inhibitor substances. The presence of inducers increases the enzyme transcription levels and therefore increases the impact of the ultrarapid metaboliser genotype. In contrast, inhibitors will make the patient behave like a poor metaboliser, regardless of their genotype.

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

CYP2D6 is an extremely important gene in pharmacogenetics, because the different polymorphisms found in this gene substantially alter the enzyme activity. There are several variants that result in a loss of function of CYP2D6 (such as variants CYP2D6*4 and *5). Individuals homozygous for these variants are called poor metabolizers, and for a given dose of the drug show higher than normal plasma levels. Given the correlation between plasma drug levels and toxicity, it is important to detect the CYP2D6 genotype of the patient in order to guide drug dose adjustments. On the other hand, there are variants associated with increased metabolism of drugs (such as variants CYP2D6*1xN, *2xN and *35x2). Individuals carrying such variants are called ultrarapid metabolizers, and for the same dose of drug may show lower than normal plasma levels.

Analysis result

- Higher likelihood of positive response to treatment (ABCB1)
- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1). Moreover, the analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metaboliser of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

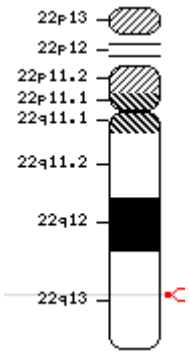
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients should be monitored closely for side effects.

Aripiprazole

Description of the genes in which important variations

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

CYP2D6 is an extremely important gene in pharmacogenetics, because the different polymorphisms found in this gene substantially alter the enzyme activity. There are several variants that result in a loss of function of CYP2D6 (such as variants CYP2D6*4 and *5). Individuals homozygous for these variants are called poor metabolizers, and for a given dose of the drug show higher than normal plasma levels. Given the correlation between plasma drug levels and toxicity, it is important to detect the CYP2D6 genotype of the patient in order to guide drug dose adjustments. On the other hand, there are variants associated with increased metabolism of drugs (such as variants CYP2D6*1xN, *2xN and *35x2). Individuals carrying such variants are called ultrarapid metabolizers, and for the same dose of drug may show lower than normal plasma levels.

Analysis result

- Poor metabolizer of the drug (CYP2D6)

Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Consider reducing the starting dose to 50%, and proceed to titrate dose in response to efficacy (do not exceed the maximum dose of 10mg/day).

Carbamazepine

Description of the genes in which important variations

EPHX1

Gene located on chromosome 1 which encodes epoxide hydrolase, a critical biotransformation enzyme that converts epoxides from the degradation of aromatic compounds to trans-dihydrodiols which can be conjugated and excreted from the body. Epoxide hydrolase functions in both the activation and detoxification of epoxides.

EPHX1 is involved in the degradation of the active metabolyte of carbamazepine (carbamazepine-10,11-epoxide), regulating the amount of active carbamazepine present in blood. Polymorphisms that alter EPHX1 activity have been identified.

Analysis result

- Faster detoxification of the drug (EPHX1)

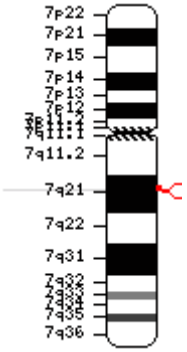
Recommendation

The analysis indicates that a higher dose than standard may be necessary to achieve therapeutic effects (EPHX1).

Citalopram

Description of the genes in which important variations

ABCB1

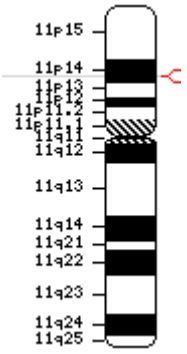


Gene located on chromosome 7 which encodes a membrane-associated protein, member of the superfamily of ATP-binding cassette (ABC) transporters and of the MDR/TAP subfamily (involved in multidrug resistance). This protein is also known as P-glycoprotein (P-gp) or multidrug resistance protein (MDR1). It is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. The ABCB1 protein also functions as a transporter in the blood-brain barrier.

The clinical efficacy of drugs that act on the central nervous system and are administered systemically depends in part on the capacity of these compounds to cross the blood-brain barrier, regulated by transporter proteins such as ABCB1.

Genetic variations in ABCB1 have been linked to drug resistance, and also to drug efficacy, in particular of antidepressant drugs that are substrates of this protein.

BDNF

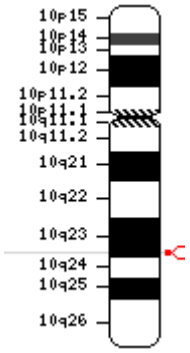


Gene located on chromosome 11 which encodes a protein member of the nerve growth factor family of neurotrophins. BDNF is necessary for survival of neurons in certain areas of the brain and peripheral nervous system, and also promotes the growth and differentiation of new neurons and synapses. It is also important for long-term memory.

A study of animal models suggested that knockdown of BDNF in specific brain areas could elicit behaviors associated with depression. Other studies found correlation between low BDNF levels and untreated depressed patients. In addition, BDNF has been considered in several studies as a predictor of antidepressant effectiveness.

Neurofarmagen analyses a BDNF gene polymorphism to evaluate response to selective serotonin reuptake inhibitors (SSRI) antidepressants.

CYP2C19



Gene located on chromosome 10 which encodes a member of the cytochrome P450 superfamily of enzymes (cytochrome P450, family 2, subfamily C, polypeptide 19). The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2C19 is known to metabolize many xenobiotics, including omeprazole, diazepam and some barbiturates.

Individuals are classified into different groups according to their CYP2C19 activity level. The most frequent variation of CYP2C19 leads to what are known as ultrarapid metabolisers of drugs metabolised by this cytochrome. There are also less common variants that create poor metabolisers of drugs metabolised by CYP2C19.

When assessing the impact of a patient´s genotype, it is important to take into account the fact that this enzyme´s activity is affected by inducer and inhibitor substances. The presence of inducers increases the enzyme transcription levels and therefore increases the impact of the ultrarapid metaboliser genotype. In contrast, inhibitors will make the patient behave like a poor metaboliser, regardless of their genotype.

GRIA3

Gene located on chromosome X which encodes subunit GluA3 of the AMPA-sensitive glutamate receptors.

Suicidal ideation, or the occurence of ideas related to suicide is a rare sympton associated with antidepressants treatment. It usually occurs within weeks of starting treatment and most commonly in teenagers or young adults undergoing treatment. Since 2004, the FDA has advised printing information about the risk of suicidal ideation on the label of antidepressant drugs.

A polymorphism in this gene has been associated with the risk of suicidal ideation in patients treated with citalopram.

Analysis result

- Higher likelihood of positive response to treatment (ABCB1, BDNF)
- Poor metabolizer of the drug (CYP2C19)
- Increased medical surveillance is necessary (GRIA3)

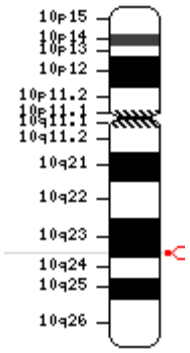
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1, BDNF). Moreover, the analysis indicates that the patient is a CYP2C19 poor metabolizer of this drug. Do not exceed a daily dose of 20mg (risk of QTc prolongation). In addition, increased medical surveillance is also recommended (GRIA3).

Clobazam

Description of the genes in which important variations

CYP2C19



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Analysis result

- Poor metabolizer of the drug (CYP2C19)

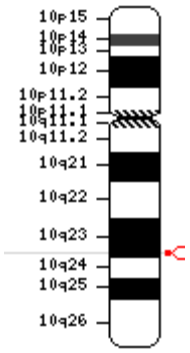
Recommendation

The analysis indicates that the patient is a CYP2C19 poor metabolizer of this drug. Consider a starting dose of 5mg/day and dose titration should proceed slowly according to weight, but to half the recommended total daily dose, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose, depending on the weight group, may be started on day 21.

Clomipramine

Description of the genes in which important variations

CYP2C19



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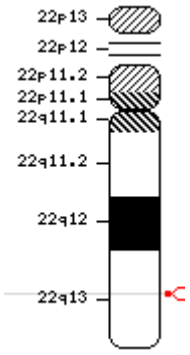
Individuals are classified into different groups according to their CYP2C19 activity level. The most frequent variation of CYP2C19 leads to what are known as ultrarapid metabolisers of drugs metabolised by this cytochrome. There are also less common variants that create poor metabolisers of drugs metabolised by CYP2C19.

When assessing the impact of a patient´s genotype, it is important to take into account the fact that this enzyme´s activity is affected by inducer and inhibitor substances. The presence of inducers increases the enzyme transcription levels and therefore increases the impact of the ultrarapid metaboliser genotype. In contrast, inhibitors will make the patient behave like a poor metaboliser, regardless of their genotype.

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

CYP2D6 is an extremely important gene in pharmacogenetics, because the different polymorphisms found in this gene substantially alter the enzyme activity. There are several variants that result in a loss of function of CYP2D6 (such as variants CYP2D6*4 and *5). Individuals homozygous for these variants are called poor metabolizers, and for a given dose of the drug show higher than normal plasma levels. Given the correlation between plasma drug levels and toxicity, it is important to detect the CYP2D6 genotype of the patient in order to guide drug dose adjustments. On the other hand, there are variants associated with increased metabolism of drugs (such as variants CYP2D6*1xN, *2xN and *35x2). Individuals carrying such variants are called ultrarapid metabolizers, and for the same dose of drug may show lower than normal plasma levels.

Analysis result

- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation

The analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

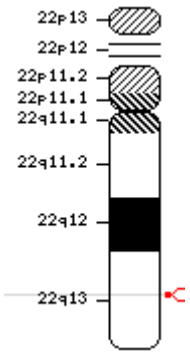
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients should be monitored closely for side effects.

Clozapine

Description of the genes in which important variations

CYP2D6



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Analysis result

- Poor metabolizer of the drug (CYP2D6)

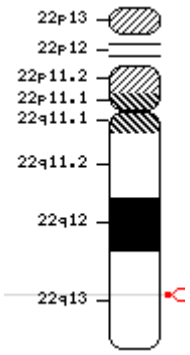
Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. However, there is no evidence suggesting a clinical effect of this phenotype; therefore use as directed and titrate dose in response to efficacy and adverse drug events.

Desipramine

Description of the genes in which important variations

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

CYP2D6 is an extremely important gene in pharmacogenetics, because the different polymorphisms found in this gene substantially alter the enzyme activity. There are several variants that result in a loss of function of CYP2D6 (such as variants CYP2D6*4 and *5). Individuals homozygous for these variants are called poor metabolizers, and for a given dose of the drug show higher than normal plasma levels. Given the correlation between plasma drug levels and toxicity, it is important to detect the CYP2D6 genotype of the patient in order to guide drug dose adjustments. On the other hand, there are variants associated with increased metabolism of drugs (such as variants CYP2D6*1xN, *2xN and *35x2). Individuals carrying such variants are called ultrarapid metabolizers, and for the same dose of drug may show lower than normal plasma levels.

Analysis result

- Poor metabolizer of the drug (CYP2D6)

Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

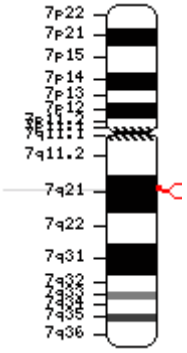
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients should be monitored closely for side effects.

Desvenlafaxine

Description of the genes in which important variations

ABCB1



Gene located on chromosome 7 which encodes a membrane-associated protein, member of the superfamily of ATP-binding cassette (ABC) transporters and of the MDR/TAP subfamily (involved in multidrug resistance). This protein is also known as P-glycoprotein (P-gp) or multidrug resistance protein (MDR1). It is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. The ABCB1 protein also functions as a transporter in the blood-brain barrier.

The clinical efficacy of drugs that act on the central nervous system and are administered systemically depends in part on the capacity of these compounds to cross the blood-brain barrier, regulated by transporter proteins such as ABCB1.

Genetic variations in ABCB1 have been linked to drug resistance, and also to drug efficacy, in particular of antidepressant drugs that are substrates of this protein.

Analysis result

- Higher likelihood of positive response to treatment (ABCB1)

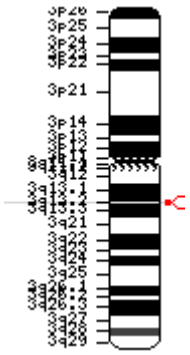
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Duloxetine

Description of the genes in which important variations

DRD3



Gene located on chromosome 3 which encodes the dopamine receptor D3. DRD3 is a G-protein coupled receptor that inhibits adenylyl cyclase activity. This receptor is localized to the limbic areas of the brain, which are associated with cognitive, emotional, and endocrine functions. DRD3 is the molecular target for drugs used in the treatment of schizophrenia, anti-addiction medications and drugs for the treatment of Parkinson´s disease.

Several studies have linked the presence of genetic variants in DRD3 to different aspects of psychoactive drugs response. Among these polymorphisms, a variant has been identified that is related to a higher likelihood of positive response to treatment with pramipexol. Genetic variants of DRD3 have also been identified that are related to the response to treatment with duloxetine in generalised anxiety disorder. The same variants were not associated with response to duloxetine treatment in major depressive disorder.

Analysis result

- Decreased likelihood of positive response to treatment (DRD3)

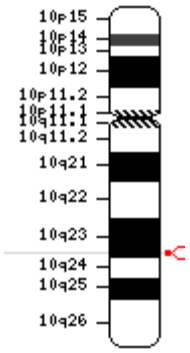
Recommendation

The analysis indicates there is a decreased likelihood of positive response to treatment for general anxiety disorder (DRD3). Therefore, if applicable, consider the use of an alternative drug.

Escitalopram

Description of the genes in which important variations

CYP2C19



Gene located on chromosome 10 which encodes a member of the cytochrome P450 superfamily of enzymes (cytochrome P450, family 2, subfamily C, polypeptide 19). The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2C19 is known to metabolize many xenobiotics, including omeprazole, diazepam and some barbiturates.

Individuals are classified into different groups according to their CYP2C19 activity level. The most frequent variation of CYP2C19 leads to what are known as ultrarapid metabolisers of drugs metabolised by this cytochrome. There are also less common variants that create poor metabolisers of drugs metabolised by CYP2C19.

When assessing the impact of a patient´s genotype, it is important to take into account the fact that this enzyme´s activity is affected by inducer and inhibitor substances. The presence of inducers increases the enzyme transcription levels and therefore increases the impact of the ultrarapid metaboliser genotype. In contrast, inhibitors will make the patient behave like a poor metaboliser, regardless of their genotype.

Analysis result

- Poor metabolizer of the drug (CYP2C19)

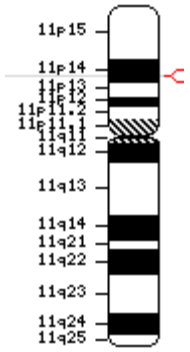
Recommendation

The analysis indicates that the patient is a CYP2C19 poor metabolizer of this drug. However, there is no evidence suggesting a clinical effect of this phenotype; therefore use as directed and titrate dose in response to efficacy and adverse drug events.

Fluoxetine

Description of the genes in which important variations

BDNF

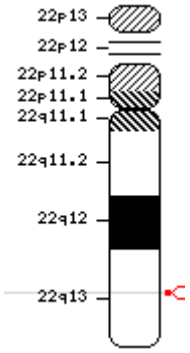


Gene located on chromosome 11 which encodes a protein member of the nerve growth factor family of neurotrophins. BDNF is necessary for survival of neurons in certain areas of the brain and peripheral nervous system, and also promotes the growth and differentiation of new neurons and synapses. It is also important for long-term memory.

A study of animal models suggested that knockdown of BDNF in specific brain areas could elicit behaviors associated with depression. Other studies found correlation between low BDNF levels and untreated depressed patients. In addition, BDNF has been considered in several studies as a predictor of antidepressant effectiveness.

Neurofarmagen analyses a BDNF gene polymorphism to evaluate response to selective serotonin reuptake inhibitors (SSRI) antidepressants.

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

CYP2D6 is an extremely important gene in pharmacogenetics, because the different polymorphisms found in this gene substantially alter the enzyme activity. There are several variants that result in a loss of function of CYP2D6 (such as variants CYP2D6*4 and *5). Individuals homozygous for these variants are called poor metabolizers, and for a given dose of the drug show higher than normal plasma levels. Given the correlation between plasma drug levels and toxicity, it is important to detect the CYP2D6 genotype of the patient in order to guide drug dose adjustments. On the other hand, there are variants associated with increased metabolism of drugs (such as variants CYP2D6*1xN, *2xN and *35x2). Individuals carrying such variants are called ultrarapid metabolizers, and for the same dose of drug may show lower than normal plasma levels.

Analysis result

- Higher likelihood of positive response to treatment (BDNF)
- Poor metabolizer of the drug (CYP2D6)

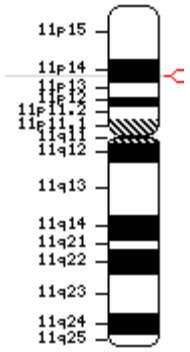
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF). Moreover, the analysis indicates the patient is a CYP2D6 poor metabolizer of this drug. However, there is no evidence suggesting a clinical effect of this phenotype; therefore use as directed and titrate dose in response to efficacy and adverse drug events.

Fluvoxamine

Description of the genes in which important variations

BDNF



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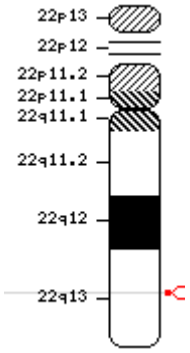
Neurofarmagen analyses a BDNF gene polymorphism to evaluate response to selective serotonin reuptake inhibitors (SSRI) antidepressants.

CYP2D6



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Analysis result

- Higher likelihood of positive response to treatment (BDNF)
- Poor metabolizer of the drug (CYP2D6)

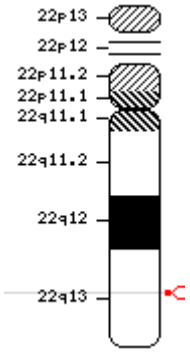
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF). Moreover, the analysis indicates the patient is a CYP2D6 poor metabolizer of this drug. If needed, consider monitoring plasma concentrations and dose adjustments.

Haloperidol

Description of the genes in which important variations

CYP2D6



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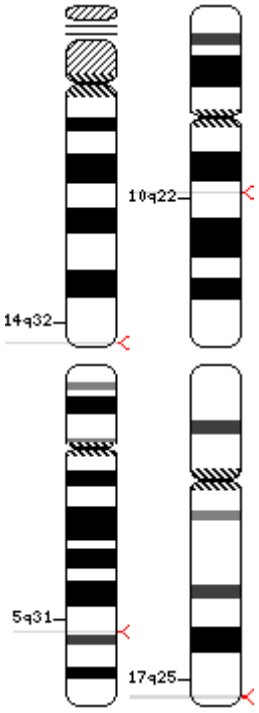
AKT1-DDIT4-FCHSD1-RPTOR



Extrapyramidal symptoms (EPS) are frequent and serious acute adverse reactions of antipsychotic drugs, including several recognized syndromes such as parkinsonism, akathisia, acute dystonia and tardive dyskinesia. Not all antipsychotic drugs induce EPS to the same extent: the risk of EPS is higher in patients receiving first generation antipsychotic drugs (50-70%) than newer compounds (15%). Although the underlying mechanism for EPS is not clear, striatal dopamine D2 receptor (DRD2) blockade is believed to be the main cause.

Research studies have tried to characterize potential risk factors associated to the onset of EPS, such as psychiatric diagnosis, younger age or male gender, and specific genetic markers have also been examined, including CYP2D6, DRD2, DRD3 and RGS2 polymorphisms.

Neurofarmagen includes a method that allows to predict the onset of EPS induced by an antipsychotic treatment based on a four gene-interaction model.

Analysis result

- Poor metabolizer of the drug (CYP2D6)
- High risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR)

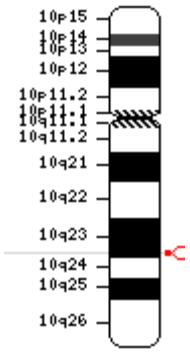
Recommendation

The analysis indicates that the patient has a high risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore treatment with a low EPS-risk second generation antipsychotic is recommended. If this drug is warranted, consider the additional use of an anticholinergic. In addition, the analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Reduce dose by 50% or select an alternative drug.

Imipramine

Description of the genes in which important variations

CYP2C19

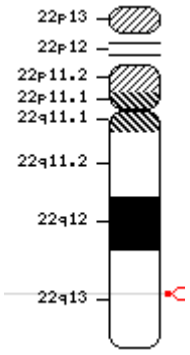


Gene located on chromosome 10 which encodes a member of the cytochrome P450 superfamily of enzymes (cytochrome P450, family 2, subfamily C, polypeptide 19). The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2C19 is known to metabolize many xenobiotics, including omeprazole, diazepam and some barbiturates.

Individuals are classified into different groups according to their CYP2C19 activity level. The most frequent variation of CYP2C19 leads to what are known as ultrarapid metabolisers of drugs metabolised by this cytochrome. There are also less common variants that create poor metabolisers of drugs metabolised by CYP2C19.

When assessing the impact of a patient´s genotype, it is important to take into account the fact that this enzyme´s activity is affected by inducer and inhibitor substances. The presence of inducers increases the enzyme transcription levels and therefore increases the impact of the ultrarapid metaboliser genotype. In contrast, inhibitors will make the patient behave like a poor metaboliser, regardless of their genotype.

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

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Analysis result

- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation

The analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

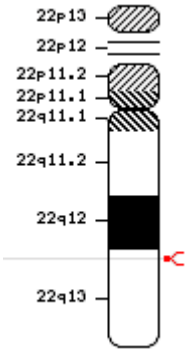
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients should be monitored closely for side effects.

Lithium

Description of the genes in which important variations

CACNG2



Gene located on chromosome 22 which encodes a protein homologous to the mouse protein Stargazin, which is part of voltage-dependent calcium channels. In humans, however, CACNG2 works as an auxiliary protein for AMPA-type glutamate receptors, regulating both trafficking and channel gating.

Lithium was one of the first drugs used in neuropsychiatry. The activity mechanism of lithium when used to treat bipolar disorder is not understood in detail, although it is known that at least part of its effect is due to the drug acting on glutamate receptors. A polymorphism in this gene has been associated to a higher likelihood of positive response to lithium.

Analysis result

- Higher likelihood of positive response to treatment (CACNG2)

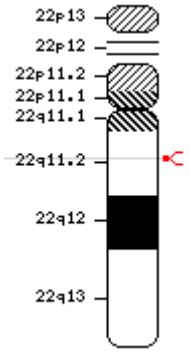
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (CACNG2), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Methylphenidate

Description of the genes in which important variations

COMT

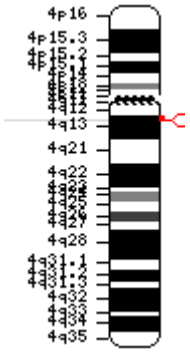


Gene located on chromosome 22, encoding the enzyme catechol-O-methyltransferase (COMT), whose function is to degrade the catecholamines dopamine and norepinephrine, and thus acts modulating the levels of these neurotransmitters in the synaptic space. COMT is expressed primarily in the prefrontal cortex and amygdala (both related to ADHD).

There is a COMT polymorphism called Val158Met that has been shown to affect the enzyme activity and has been implicated in various aspects of ADHD and other psychiatric disorders. Val/Val homozygotes show high COMT activity, Val/Met heterozygotes show intermediate activity, and Met/Met homozygotes show 4-fold lower activity.

An association has been reported between Val158Met polymorphism in this gene and reponse to the treatment with methylphenidate.

LPHN3



Gene located on chromosome 4 that encodes the G-protein coupled receptor (GPCR) latrophilin 3. Gene LPHN3 is mainly expressed in brain areas associated with ADHD such as the amygdala, the caudate nucleus, the cerebellum and the cerebral cortex. Latrophilins may function in both cell adhesion and signal transduction.

Several LPHN3 variations have been observed to be more frequently transmitted in patients with ADHD. One of these variations has also been associated with the response to the treatment with psychostimulants, such as Methylphenidate.

Analysis result

- Higher likelihood of positive response to treatment (COMT, LPHN3)

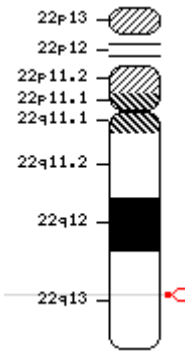
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (COMT, LPHN3), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Nortriptyline

Description of the genes in which important variations

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

CYP2D6 is an extremely important gene in pharmacogenetics, because the different polymorphisms found in this gene substantially alter the enzyme activity. There are several variants that result in a loss of function of CYP2D6 (such as variants CYP2D6*4 and *5). Individuals homozygous for these variants are called poor metabolizers, and for a given dose of the drug show higher than normal plasma levels. Given the correlation between plasma drug levels and toxicity, it is important to detect the CYP2D6 genotype of the patient in order to guide drug dose adjustments. On the other hand, there are variants associated with increased metabolism of drugs (such as variants CYP2D6*1xN, *2xN and *35x2). Individuals carrying such variants are called ultrarapid metabolizers, and for the same dose of drug may show lower than normal plasma levels.

Analysis result

- Poor metabolizer of the drug (CYP2D6)

Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

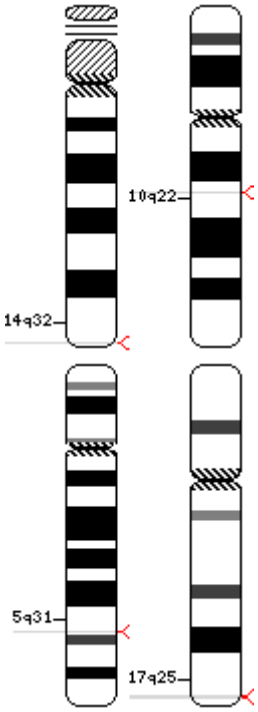
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients should be monitored closely for side effects.

Paliperidone

Description of the genes in which important variations

AKT1-DDIT4-FCHSD1-RPTOR



Extrapyramidal symptoms (EPS) are frequent and serious acute adverse reactions of antipsychotic drugs, including several recognized syndromes such as parkinsonism, akathisia, acute dystonia and tardive dyskinesia. Not all antipsychotic drugs induce EPS to the same extent: the risk of EPS is higher in patients receiving first generation antipsychotic drugs (50-70%) than newer compounds (15%). Although the underlying mechanism for EPS is not clear, striatal dopamine D2 receptor (DRD2) blockade is believed to be the main cause.

Research studies have tried to characterize potential risk factors associated to the onset of EPS, such as psychiatric diagnosis, younger age or male gender, and specific genetic markers have also been examined, including CYP2D6, DRD2, DRD3 and RGS2 polymorphisms.

Neurofarmagen includes a method that allows to predict the onset of EPS induced by an antipsychotic treatment based on a four gene-interaction model.

Analysis result

- High risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR)

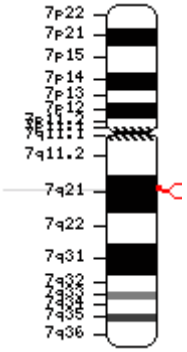
Recommendation

The analysis indicates that the patient has a high risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore treatment with a low EPS-risk second generation antipsychotic is recommended. If this drug is warranted, consider the additional use of an anticholinergic.

Paroxetine

Description of the genes in which important variations

ABCB1



Gene located on chromosome 7 which encodes a membrane-associated protein, member of the superfamily of ATP-binding cassette (ABC) transporters and of the MDR/TAP subfamily (involved in multidrug resistance). This protein is also known as P-glycoprotein (P-gp) or multidrug resistance protein (MDR1). It is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. The ABCB1 protein also functions as a transporter in the blood-brain barrier.

The clinical efficacy of drugs that act on the central nervous system and are administered systemically depends in part on the capacity of these compounds to cross the blood-brain barrier, regulated by transporter proteins such as ABCB1.

Genetic variations in ABCB1 have been linked to drug resistance, and also to drug efficacy, in particular of antidepressant drugs that are substrates of this protein.

Analysis result

- Higher likelihood of positive response to treatment (ABCB1)

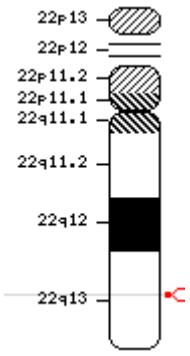
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1), and therefore, if applicable, use of this drug is recommended in preference to other similar alternatives.

Perphenazine

Description of the genes in which important variations

CYP2D6



Gene located on chromosome 22 which encodes a member of the superfamily of cytochrome P450 (cytochrome P450, family 2, subfamily D, polypeptide 6). The proteins of the cytochrome P450 superfamily are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Ultimately, the action of these enzymes will control drug levels in blood and within cells, so they are critical for determining the most appropriate dose for each patient. It is estimated that CYP2D6 is responsible for the metabolism of approximately 25% of the prescribed drugs.

CYP2D6 is an extremely important gene in pharmacogenetics, because the different polymorphisms found in this gene substantially alter the enzyme activity. There are several variants that result in a loss of function of CYP2D6 (such as variants CYP2D6*4 and *5). Individuals homozygous for these variants are called poor metabolizers, and for a given dose of the drug show higher than normal plasma levels. Given the correlation between plasma drug levels and toxicity, it is important to detect the CYP2D6 genotype of the patient in order to guide drug dose adjustments. On the other hand, there are variants associated with increased metabolism of drugs (such as variants CYP2D6*1xN, *2xN and *35x2). Individuals carrying such variants are called ultrarapid metabolizers, and for the same dose of drug may show lower than normal plasma levels.

Analysis result

- Poor metabolizer of the drug (CYP2D6)

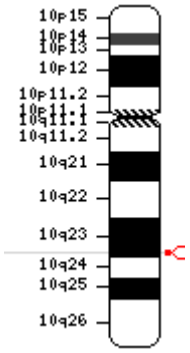
Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Therefore, there is a higher risk of adverse drug events. Consider dose adjustments in response to efficacy and ADE.

Phenytoin

Description of the genes in which important variations

CYP2C9



Gene located on chromosome 10 which encodes a member of the cytochrome P450 superfamily of enzymes (cytochrome P450, family 2, subfamily C, polypeptide 9). The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2C9 is mainly expressed in the liver and is responsible for the metabolism of several drugs, including the anticoagulant warfarin. The role of this enzyme is of special interest in neurology with regard to the metabolism of phenytoin, a drug commonly prescribed for the treatment of epilepsy that has a very narrow therapeutic index.

Neuropharmagen® analyzes variations in the CYP2C9 gene that modify the enzyme activity and therefore can impact the dosage of drug to the patient.

Analysis result

- Intermediate metabolizer of the drug (CYP2C9)

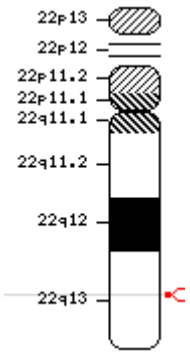
Recommendation

The analysis indicates that the patient is a CYP2C9 intermediate metabolizer of this drug. Consider using a standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days. Be alert to adverse drug events such as ataxia, nystagmus, dysarthria or sedation.

Pimozide

Description of the genes in which important variations

CYP2D6



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Analysis result

- Poor metabolizer of the drug (CYP2D6)

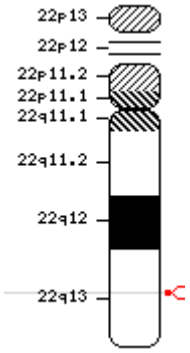
Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Doses should not exceed 4 mg/day, and should not be increased earlier than 14 days.

Risperidone

Description of the genes in which important variations

CYP2D6



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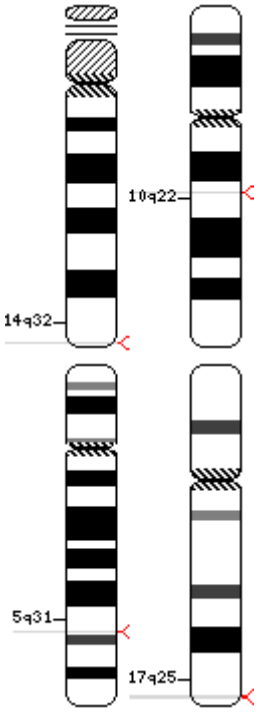
AKT1-DDIT4-FCHSD1-RPTOR

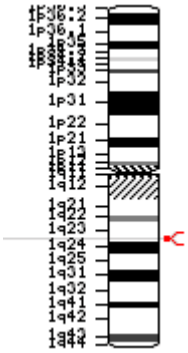


Extrapyramidal symptoms (EPS) are frequent and serious acute adverse reactions of antipsychotic drugs, including several recognized syndromes such as parkinsonism, akathisia, acute dystonia and tardive dyskinesia. Not all antipsychotic drugs induce EPS to the same extent: the risk of EPS is higher in patients receiving first generation antipsychotic drugs (50-70%) than newer compounds (15%). Although the underlying mechanism for EPS is not clear, striatal dopamine D2 receptor (DRD2) blockade is believed to be the main cause.

Research studies have tried to characterize potential risk factors associated to the onset of EPS, such as psychiatric diagnosis, younger age or male gender, and specific genetic markers have also been examined, including CYP2D6, DRD2, DRD3 and RGS2 polymorphisms.

Neurofarmagen includes a method that allows to predict the onset of EPS induced by an antipsychotic treatment based on a four gene-interaction model.

RGS4



Gene located on chromosome 1 which encodes the regulator of G-protein signaling 4. RGS family members are regulatory molecules that act as GTPase activating proteins (GAPs) for G alpha subunits of heterotrimeric G proteins, favoring breakdown of the phosphodiester bond of GTP to GDP, whereby G protein is inactivated. RGS4 is involved in controlling the duration of the signal of G-protein coupled receptors.

G proteins control dopamine, serotonin and glutamate signaling, therefore the link between RGS4 and neuropsychiatric disorders has been studied. Several studies have associated a decrease in RGS4 levels with susceptibility to schizophrenia, although the effects are small and still controversial. However, it has been described an association between certain RGS4 polymorphisms and response to antipsychotic treatment.

Analysis result

- Poor metabolizer of the drug (CYP2D6)
- High risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR)
- Higher likelihood of positive response to treatment (RGS4)

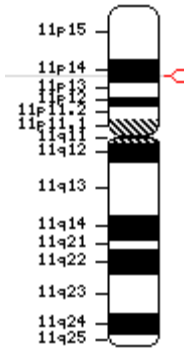
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (RGS4). However, the analysis indicates that the patient has a high risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore treatment with a low EPS-risk second generation antipsychotic is recommended. If this drug is warranted, consider the additional use of an anticholinergic. In addition, the analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Select an alternative drug or be extra alert to adverse drug events and adjust dose to clinical response.

Sertraline

Description of the genes in which important variations

BDNF

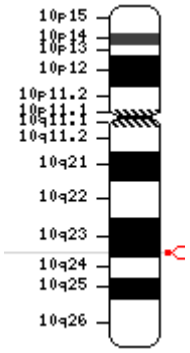


Gene located on chromosome 11 which encodes a protein member of the nerve growth factor family of neurotrophins. BDNF is necessary for survival of neurons in certain areas of the brain and peripheral nervous system, and also promotes the growth and differentiation of new neurons and synapses. It is also important for long-term memory.

A study of animal models suggested that knockdown of BDNF in specific brain areas could elicit behaviors associated with depression. Other studies found correlation between low BDNF levels and untreated depressed patients. In addition, BDNF has been considered in several studies as a predictor of antidepressant effectiveness.

Neurofarmagen analyses a BDNF gene polymorphism to evaluate response to selective serotonin reuptake inhibitors (SSRI) antidepressants.

CYP2C19



Gene located on chromosome 10 which encodes a member of the cytochrome P450 superfamily of enzymes (cytochrome P450, family 2, subfamily C, polypeptide 19). The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2C19 is known to metabolize many xenobiotics, including omeprazole, diazepam and some barbiturates.

Individuals are classified into different groups according to their CYP2C19 activity level. The most frequent variation of CYP2C19 leads to what are known as ultrarapid metabolisers of drugs metabolised by this cytochrome. There are also less common variants that create poor metabolisers of drugs metabolised by CYP2C19.

When assessing the impact of a patient´s genotype, it is important to take into account the fact that this enzyme´s activity is affected by inducer and inhibitor substances. The presence of inducers increases the enzyme transcription levels and therefore increases the impact of the ultrarapid metaboliser genotype. In contrast, inhibitors will make the patient behave like a poor metaboliser, regardless of their genotype.

Analysis result

- Higher likelihood of positive response to treatment (BDNF)
- Poor metabolizer of the drug (CYP2C19)

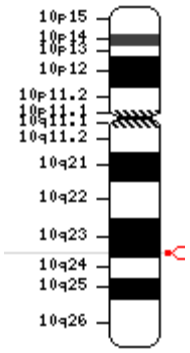
Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF). Moreover, the analysis indicates that the patient is a CYP2C19 poor metaboliser of this drug. Be extra alert to adverse drug events and, if needed, consider an up to 50% dose reduction.

Trimipramine

Description of the genes in which important variations

CYP2C19



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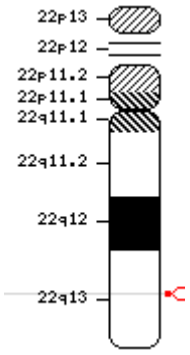
CYP2D6



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Analysis result

- Poor metabolizer of the drug (CYP2C19, CYP2D6)

Recommendation

The analysis indicates that the patient is a CYP2C19 poor and a CYP2D6 poor metabolizer of this drug. Consider an alternative drug not metabolized by this pathway. If this drug is warranted, consider a 50% reduction of the recommended starting dose.[1] Use therapeutic drug monitoring to guide dose adjustments[2].

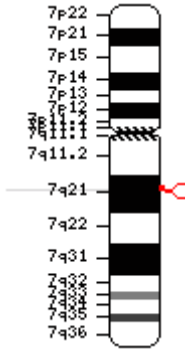
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients should be monitored closely for side effects.

Venlafaxine

Description of the genes in which important variations

ABCB1

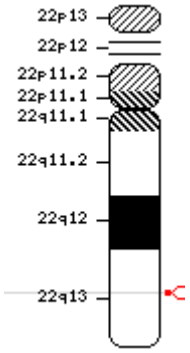


Gene located on chromosome 7 which encodes a membrane-associated protein, member of the superfamily of ATP-binding cassette (ABC) transporters and of the MDR/TAP subfamily (involved in multidrug resistance). This protein is also known as P-glycoprotein (P-gp) or multidrug resistance protein (MDR1). It is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. The ABCB1 protein also functions as a transporter in the blood-brain barrier.

The clinical efficacy of drugs that act on the central nervous system and are administered systemically depends in part on the capacity of these compounds to cross the blood-brain barrier, regulated by transporter proteins such as ABCB1.

Genetic variations in ABCB1 have been linked to drug resistance, and also to drug efficacy, in particular of antidepressant drugs that are substrates of this protein.

CYP2D6



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Analysis result

- Higher likelihood of positive response to treatment (ABCB1)
- Poor metabolizer of the drug (CYP2D6)

Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (ABCB1). Moreover, the analysis indicates the patient is a CYP2D6 poor metabolizer of this drug. Select an alternative drug or adjust dose to clinical response.

Annex

This annex summarizes published information about pharmacological interactions related to cytochrome P450 metabolism. The annex tables list relevant drugs that are fully or partially metabolised by the most important isoforms of cytochrome P450 (CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP2B6). Some drugs are metabolised by more than one enzyme and, therefore, in these cases the clinical impact of changes in the metabolism must be assessed globally. This information is a reference tool for doctors and investigators and, under no circumstances, should replace medical surveillance.

Reference:

U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Interaction with cytochrome 2D6 (CYP2D6)

In psychiatry, many drugs are metabolised by the cytochrome P450 2D6 (CYP2D6) enzyme, so therefore the plasma levels of these drugs are conditioned by the activity of this enzyme. CYP2D6 activity can be impaired by genetic factors (analysed by NEUROPHARMAGEN®) and by concomitant drugs.

The table below lists the drugs analysed by NEUROPHARMAGEN® with a metabolism that depends on CYP2D6. It may be necessary to adjust the dose of these drugs in accordance with concomitant medication.

CYP2D6 substrates		
Amitriptyline	**Fluoxetine**	**Perphenazine**
Aripiprazol	**Fluvoxamine**	**Risperidone**
Atomoxetine	**Haloperidol**	**Thioridazine**
Chlomipramine	**Imipramine**	**Trimipramine**
Clozapine	**Mianserin**	**Venlafaxine**
Desipramine	**Nortriptyline**	**Zuclopenthixol**

Table 1: List of drugs metabolised by the cytochrome P450 2D6 enzyme

The combination of CYP2D6 substrates with enzyme **inhibitors** (see Table 2) may increase its plasma levels and therefore the adverse effects they cause. In this case, the patient will behave like a **poor metaboliser**, regardless of their genotype, and as a result it may be necessary to **reduce the dose** of both the main and concomitant drugs.

CYP2D6 inhibitors	
Strong inhibitors	**Moderate inhibitors**
Bupropion	**Cinacalcet**
Fluoxetine	**Duloxetine**
Paroxetine	**Terbinafine**
Quinidine	

Table 2: List of cytochrome P450 2D6 inhibitors

Interaction with cytochrome 2C19 (CYP2C19)

In psychiatry, some important drugs depend on the CYP2C19 enzyme activity for their metabolism in such a way that the plasma levels of these drugs are conditioned by the activity of this enzyme. CYP2C19 activity can be impaired by genetic factors (analysed by NEUROPHARMAGEN®) and by concomitant drugs.

The table below lists the drugs analysed by NEUROPHARMAGEN® with a metabolism that is dependent on CYP2C19. It may be necessary to adjust the dose of these drugs in accordance with concomitant medication.

CYP2C19 substrates
Amitriptyline
Citalopram
Chlomipramine
Escitalopram
Imipramine
Sertraline

Table 3: List of drugs metabolised by the cytochrome P450 2C19 enzyme

The combination of CYP2C19 substrates with enzyme **inhibitors** (see Table 4) may increase its plasma levels and therefore the adverse effects they cause. In these cases, the patient will behave like a **poor metaboliser**, regardless of their genotype, and as a result it may be necessary to **reduce the dose** of both the main and concomitant drugs.

CYP2C19 inhibitors	
Strong inhibitors	**Moderate inhibitors**
Fluconazole	**Esomeprazole**
Fluvoxamine	**Fluoxetine**
Ticlopidine	**Moclobemide**
	Omeprazole
	Voriconazole

Table 4: List of cytochrome P450 2C19 inhibitors

The combination of CYP2C19 substrates with enzyme **inducers** (see Table 5) may reduce its plasma levels and therefore the efficacy of the treatment. Use of concomitant medication of this type may make it necessary to **increase the dose** of the drug.

CYP2C19 inducers
Moderate inducers
Rifampicin

Table 5: List of drugs metabolised by the cytochrome P450 2C19 enzyme

Interaction with cytochrome 2C9 (CYP2C9)

Phenytoin metabolism requires activity by cytochrome P450 2C9 (CYP2C9), so therefore plasma levels of this drug are conditioned by the enzymes activity. CYP2C9 activity can be impaired by genetic factors (analysed by NEUROPHARMAGEN®) and by concomitant drugs.

The combination of Phenytoin with enzyme **inhibitors** (see Table 6) may increase its plasma levels and therefore the adverse effects of the drug. In these cases, the patient will behave like a **poor metaboliser**, regardless of their genotype, and as a result it may be necessary to **reduce the dose** of Phenytoin and concomitant drugs.

CYP2C9 inhibitors
Moderate inhibitors
Amiodarone
Fluconazole
Miconazole
Oxandrolone

Table 6: List of cytochrome P450 2C9 inhibitors

The combination of Phenytoin with enzyme **inducers** (see Table 7) may reduce its plasma levels and therefore the efficacy of the treatment. The use of concomitant medication of this type may make it necessary to **increase the dose** of the drug.

CYP2C9 inducers
Moderate inducers
Carbamazepine
Rifampicin

Table 7: List of cytochrome P450 2C9 inducers

Interaction with cytochrome 1A2 (CYP1A2)

Olanzapine metabolism requires activity by cytochrome P450 1A2 (CYP1A2), so therefore plasma levels of this drug are conditioned by the enzymes activity. CYP1A2 activity can be impaired by genetic factors (analysed by NEUROPHARMAGEN®) and by concomitant drugs.

To tailor the treatment to the patient it would be recommended to take into account the patient´s genetic variations as well as information regarding concomitant medication indicated in the following tables.

The combination of Olanzapine with enzyme **inhibitors** (see Table 8) may increase its plasma levels and therefore the adverse effects of the drug. In these cases, the patient will behave like a **poor metaboliser**, regardless of its genotype, and as a result it may be necessary to **reduce the dose** of Olanzapine and concomitant drugs.

CYP1A2 Inhibitors	
Strong inhibitors	**Moderate inhibitors**
Ciprofloxacin and other fluoroquinolones	**Methoxalen**
Fluvoxamine	**Mexiletine**
	Oral contraceptives
	Phenylpropanolamine
	Zileuton

Table 8: List of cytochrome P450 1A2 inhibitors

The combination of Phenytoin with enzyme **inducers** (see Table 9) may reduce its plasma levels and therefore the efficacy of the treatment. The use of concomitant medication of this type may make it necessary to **increase the dose** of the drug.

CYP1A2 Inducers
Moderate inducers
Tobacco
Montelukast
Phenytoin

Table 9: List of cytochrome P450 1A2 inducers

Interaction with cytochrome 2B6 (CYP2B6)

Bupropion metabolism requires the activity of cytochrome P450 2B6 (CYP2B6) such that plasma levels of this drug may be influenced by the activity of the enzyme. CYP2B6 activity may be altered by genetic factors (analysed by Neurofarmagen®), and by concomitant medication.

Bupropion combination with CYP2B6 **inducers** (see Table 10) may decrease Bupropion plasma levels and, therefore, reduce the effectiveness of the treatment. Thus, the use of concomitant medication of this type may require **monitoring the efficacy** of Bupropion treatment.

CYP2B6 inducers
Moderate inducers
Efavirenz
Rifampicin

Table 10: List of cytochrome P450 2B6 inducers

Legal notice

This report is intended for physicians only. The Neurofarmagen genetic analysis cannot be considered in any case by the prescribing physician as a substitute for his or her prescriptive activity or for the required medical surveillance in any treatment to their patients. It is the sole responsibility of the prescribing physician to make treatment decisions based on the individual characteristics of the patient, of the drug prescribed and a comprehensive interpretation of the report.

The results are derived from genetic information and research-based association studies published to date, highlighting therefore the probability that there are additional genetic factors not included in the analysis or even other factors currently undescribed not covered by this report. Also, it is possible that the information related to the medications currently listed can be modified or extended by reason of developments arising from scientific research in this field.

For information purposes, it is noteworthy that the response to drugs can be affected by non-genetic factors such as age, sex, weight, height, treatments and concomitant diseases, among others. Also, the information contained in this report should be considered by the prescribing physician as part of a whole evaluation, integrating and contextualizing the pharmacogenetic information provided by the analysis with potential drug interactions and the medical history and drug history of the patient.