



## PHARMACOGENETIC ANALYSIS

This genetic analysis includes the following sections:

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

### PATIENT IDENTIFICATION

NFGX00007

**REQUESTING DOCTOR:**

Dr Federico García

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.



## Sample data

Patient identification

NFGX00007

Analysis #

001

Sample Code:

16\_DNA

Entry date:

26/02/2014

### 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		Citalopram	
Clomipramine		Desipramine		Desvenlafaxine	Standard
Duloxetine		Escitalopram	Standard	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	Standard	Clonazepam	Standard
Lamotrigine	Standard	Levetiracetam	Standard	Lithium*	
Lorazepam	Standard	Phenobarbital	Standard	Phenytoin	Standard
Topiramate	Standard	Valproic Acid	Standard	Vigabatrin	Standard

#### Others

Methadone	Standard	Methylphenidate		Naloxone	Standard
Pramipexol	Standard				

Signature of Geneticist Responsible

Date

19/03/2014

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

In this section you will find a list of drugs that, as indicated by the analysis, will cause the patient to react differently to the population average (colour block from previous table), and a series of related recommendations for guidance purposes. When a drug analysis produces results in more than one colour, the summary table will apply the following order of safety: adverse effects (red) > dose monitoring (amber) > greater probability of positive response (green). Final assessment of the analysis is at the doctors discretion.

This report was produced by experts in genetics and is aimed exclusively at doctors that issue prescriptions. It is a tool to facilitate the prescription of drugs for the patient and corresponds exclusively to the doctor issuing the prescription. This genetic analysis is not, and may not be, under any circumstances, a substitute for the doctors prescription or the medical surveillance of any treatment that, according to medical criteria, corresponds to the patient.

## METABOLISER PROFILE OF THE PATIENT

Gene	Genotype	Phenotype
CYP1A2	*1/*1F	Extensive (normal) metaboliser
CYP2B6	*6/*6	Poor metaboliser
CYP2C9	*1/*1	Extensive (normal) metaboliser
CYP2C19	*1/*17	Extensive (normal) metaboliser
CYP2D6	*4/*4	Poor metaboliser

## DRUG

## RECOMMENDATIONS FOR GUIDANCE PURPOSES

### Amitriptyline

**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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

### 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).

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**Bupropion**

**Analysis result:**

- Reduced metabolism of the drug (CYP2B6)

**Recommendation:**

The patient carries a variant that has been associated with reduced metabolism of the drug (CYP2B6), therefore a dose adjustment may be necessary.

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**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).

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**Citalopram**

**Analysis result:**

- Higher likelihood of positive response to treatment (BDNF)
- Increased medical surveillance is necessary (GRIA3)

**Recommendation:**

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF), although, if applicable, increased medical surveillance is recommended (GRIA3).

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**Clomipramine**

**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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

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**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.

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**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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

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**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.

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**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.

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**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.

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**Haloperidol****Analysis result:**

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

**Recommendation:**

The analysis indicates that the patient has a low risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore consider treatment with either a first or second generation antipsychotic as directed on the drug label. 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.

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**Imipramine****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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

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**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.

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**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.

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**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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

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**Paliperidone**

**Analysis result:**

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

**Recommendation:**

The analysis indicates that the patient has a low risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore consider treatment with either a first or second generation antipsychotic as directed on the drug label.

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**Paroxetine**

**Analysis result:**

- Higher likelihood of positive response to treatment (HTR2A)
- Increased risk of drug-related adverse effects (HTR2A)

**Recommendation:**

The analysis indicates there is a higher likelihood of positive response to treatment (HTR2A). However, the analysis indicates an increased risk of developing drug-related adverse effects (HTR2A). Therefore, select an alternative drug or use reduced doses.

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**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.

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**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.

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**Risperidone****Analysis result:**

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

**Recommendation:**

The analysis indicates that the patient has a low risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore consider treatment with either a first or second generation antipsychotic as directed on the drug label. 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.

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**Sertraline****Analysis result:**

- Higher likelihood of positive response to treatment (BDNF)

**Recommendation:**

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

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**Trimipramine****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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

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**Venlafaxine****Analysis result:**

- Poor metabolizer of the drug (CYP2D6)

**Recommendation:**

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Select an alternative drug or adjust dose to clinical response.

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*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: +34 900 102 016 or [info@neurofarmagen.com](mailto:info@neurofarmagen.com)

***Additional genetic information for  
drugs expected to present non-standard activity***

## ADDITIONAL GENETIC INFORMATION

Below you will find a list of drugs that, as indicated by the analysis, will cause the patient to react in a way that is different to the population average.

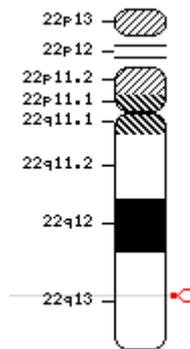
Firstly, it indicates the biological role of the genes where the genetic variants that influence the patients drug response are located. The test results are provided with this information, together with recommendations for guidance purposes.

In order for this information to be of use it must be interpreted by a doctor in the context of the patients clinical history. As in other genetic tests, the information provided by the analysis offers details about a very specific aspect of the patient and under no circumstances can it be used as a substitute for medical surveillance.

## Amitriptyline

### 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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

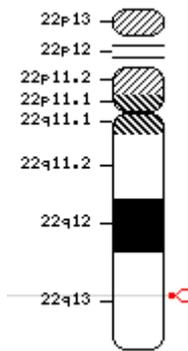
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(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)

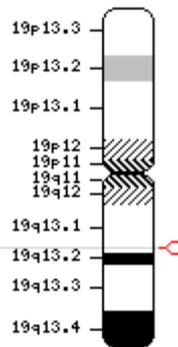
#### Recommendation

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).

## Bupropion

### Description of the genes in which important variations

#### CYP2B6



Gene located on chromosome 19 which encodes a member of the cytochrome P450 superfamily of enzymes (cytochrome P450, family 2, subfamily B, polypeptide 6). The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2B6 is expressed in the liver and the brain and is induced by different drugs and xenobiotics. It has been noted that there is high interindividual variability in CYP2B6 expression levels, which may be due to differences in the transcriptional regulation of the gene and to genetic variations. Different variants of CYP2B6 have been identified, and their frequency varies depending on the population analysed.

CYP2B6 is the main enzyme in the metabolism of drugs such as efavirenz and nevirapine, used in HIV treatment, as well as bupropion, an atypical antidepressant also used as an aid for smoking cessation. Different genetic variations have been identified that reduce the activity of this enzyme and that may alter plasma levels of the drug. Of these, Neuropharmagen® analyses the CYP2B6\*6 allele. CYP2B6 activity can also be modified by concomitant drugs such as efavirenz or rifampicin that act as moderate inducers.

#### Analysis result

- Reduced metabolism of the drug (CYP2B6)

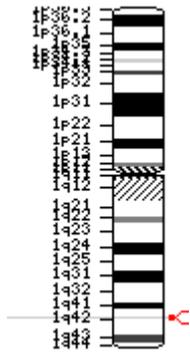
#### Recommendation

The patient carries a variant that has been associated with reduced metabolism of the drug (CYP2B6), therefore a dose adjustment may be necessary.

## 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 metabolite 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)

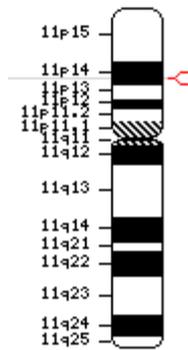
#### Recommendation

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

#### BDNF

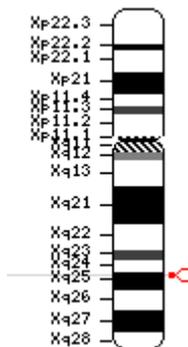


Gene located on chromosome 11 which encodes a protein member of the nerve growth factor family of neurotrophins. BDNF is necessary for survival of neurons in certain areas of the brain and peripheral nervous system, and also promotes the growth and differentiation of new neurons and synapses. It is also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

#### GRIA3



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

Suicidal ideation, or the occurrence of ideas related to suicide is a rare symptom 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 (BDNF)
- Increased medical surveillance is necessary (GRIA3)

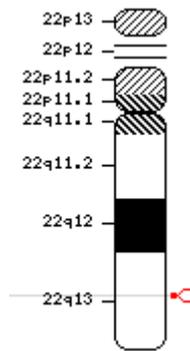
### Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (BDNF), although, if applicable, increased medical surveillance is recommended (GRIA3).

## Clomipramine

### 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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

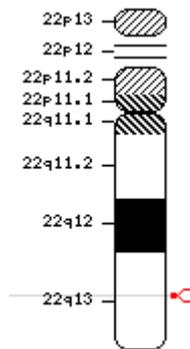
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(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*



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)

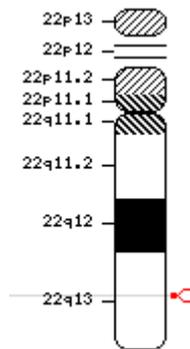
### Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. 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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

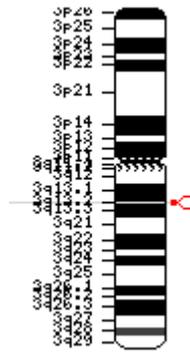
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(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.

## 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)

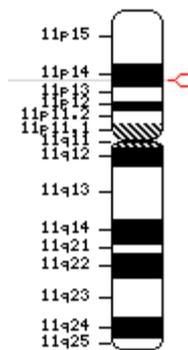
#### Recommendation

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.

## Fluoxetine

### Description of the genes in which important variations

#### *BDNF*

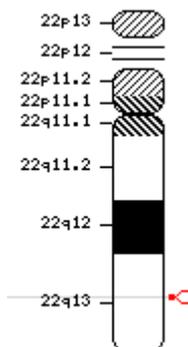


Gene located on chromosome 11 which encodes a protein member of the nerve growth factor family of neurotrophins. BDNF is necessary for survival of neurons in certain areas of the brain and peripheral nervous system, and also promotes the growth and differentiation of new neurons and synapses. It is also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

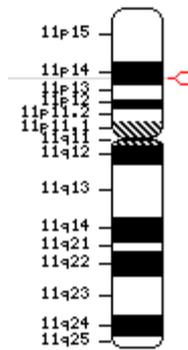
### **Recommendation**

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*

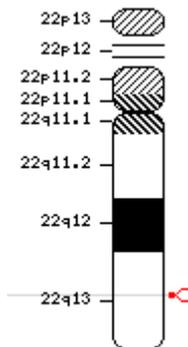


Gene located on chromosome 11 which encodes a protein member of the nerve growth factor family of neurotrophins. BDNF is necessary for survival of neurons in certain areas of the brain and peripheral nervous system, and also promotes the growth and differentiation of new neurons and synapses. It is also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

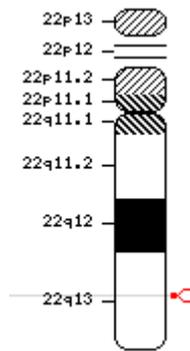
### **Recommendation**

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. If needed, consider monitoring plasma concentrations and dose adjustments.

## Haloperidol

### Description of the genes in which important variations

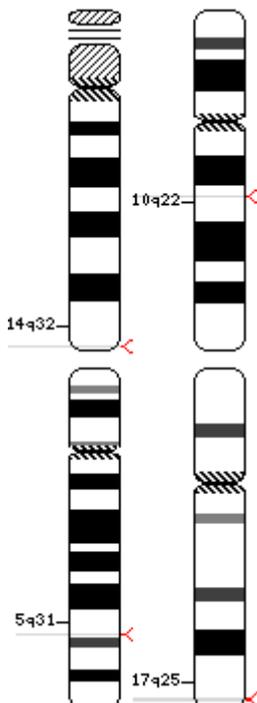
#### CYP2D6



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.

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

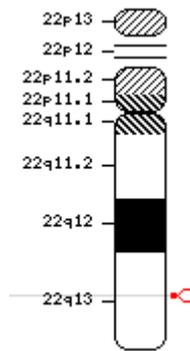
### **Recommendation**

The analysis indicates that the patient has a low risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore consider treatment with either a first or second generation antipsychotic as directed on the drug label. 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

#### 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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

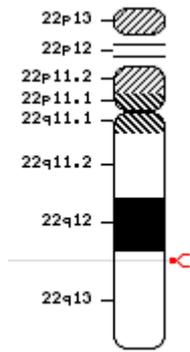
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(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)

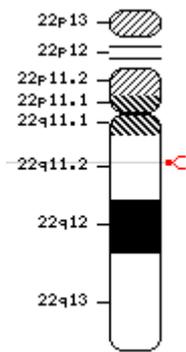
#### Recommendation

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

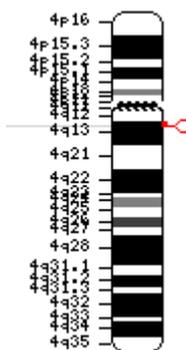


Gene located on chromosome 22, encoding the enzyme catechol-O-methyltransferase (COMT), whose function is to degrade the catecholamines dopamine and norepinephrine, and thus acts modulating the levels of these neurotransmitters in the synaptic space. COMT is expressed primarily in the prefrontal cortex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

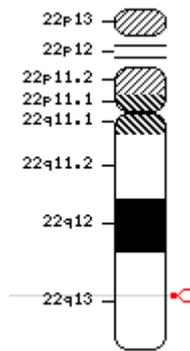
### Recommendation

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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

(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.

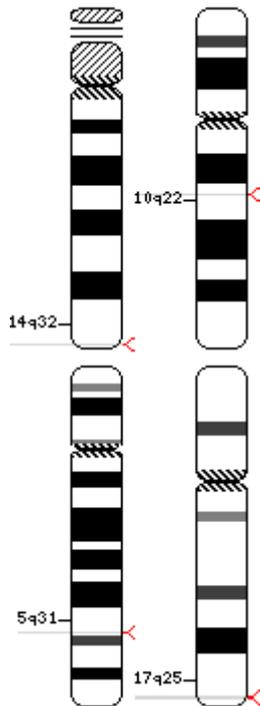
(2) The dosing recommendations apply only to higher initial doses of tricyclics used for treatment of conditions such as depression. For conditions in which lower initial doses are used, such as neuropathic pain, no dose modifications for poor or intermediate metabolizers are recommended, but these patients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

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

### Recommendation

The analysis indicates that the patient has a low risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore consider treatment with either a first or second generation antipsychotic as directed on the drug label.

## Paroxetine

### Description of the genes in which important variations

#### HTR2A



Gene located on chromosome 13 which encodes the 5-hydroxytryptamine (serotonin) 2A receptor. It is the main excitatory receptor subtype among the G protein-coupled receptors for serotonin. Mutations in this gene are associated with susceptibility to schizophrenia and obsessive-compulsive disorder.

Polymorphisms in HTR2A have been associated with different effects, among them the response to selective serotonin reuptake inhibitor (SSRI) antidepressants, the risk of weight gain in the first stages of treatment with olanzapine, or the risk of developing drug-related adverse effects for paroxetine.

#### Analysis result

- Higher likelihood of positive response to treatment (HTR2A)
- Increased risk of drug-related adverse effects (HTR2A)

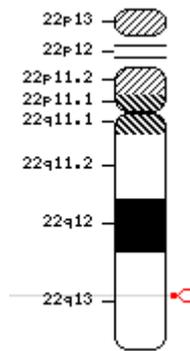
#### Recommendation

The analysis indicates there is a higher likelihood of positive response to treatment (HTR2A). However, the analysis indicates an increased risk of developing drug-related adverse effects (HTR2A). Therefore, select an alternative drug or use reduced doses.

## 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)

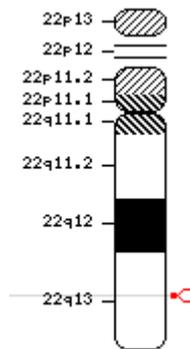
#### Recommendation

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.

## Pimozide

### 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)

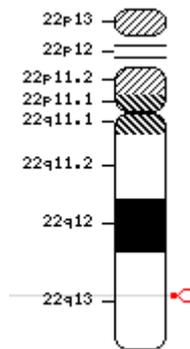
#### Recommendation

The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. 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

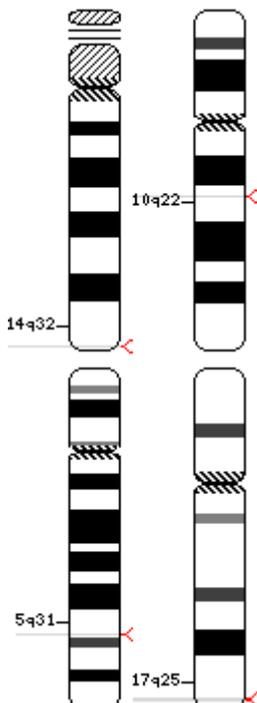
#### CYP2D6



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.

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

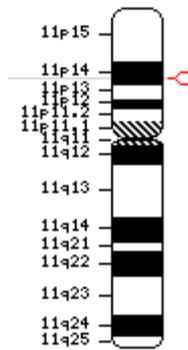
### **Recommendation**

The analysis indicates that the patient has a low risk of developing extrapyramidal symptoms (AKT1-DDIT4-FCHSD1-RPTOR), therefore consider treatment with either a first or second generation antipsychotic as directed on the drug label. 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.

#### Analysis result

- Higher likelihood of positive response to treatment (BDNF)

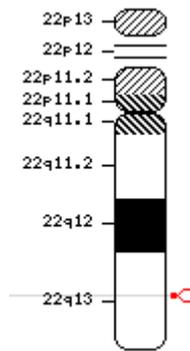
#### Recommendation

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

## Trimipramine

### 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.<sup>1</sup> Use therapeutic drug monitoring to guide dose adjustments<sup>2</sup>.

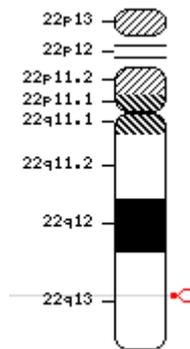
(1) Patients may receive an initial low dose of TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

(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

#### 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. Select an alternative drug or adjust dose to clinical response.

## Annex

*This annex contains information published about possible pharmacological interaction 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 in more than one way, and therefore the clinical impact of changes to the metabolism range should be assessed in overall terms. This information is a reference tool for the clinic and research and, under no circumstances, should replace the doctors judgement.*

*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](http://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		
<b>Amitriptyline</b>	<b>Fluoxetine</b>	<b>Perphenazine</b>
<b>Aripiprazol</b>	<b>Fluvoxamine</b>	<b>Risperidone</b>
<b>Atomoxetine</b>	<b>Haloperidol</b>	<b>Thioridazine</b>
<b>Chlomipramine</b>	<b>Imipramine</b>	<b>Trimipramine</b>
<b>Clozapine</b>	<b>Mianserin</b>	<b>Venlafaxine</b>
<b>Desipramine</b>	<b>Nortriptyline</b>	<b>Zuclopenthixol</b>

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
<b>Bupropion</b>	<b>Cinacalcet</b>
<b>Fluoxetine</b>	<b>Duloxetine</b>
<b>Paroxetine</b>	<b>Terbinafine</b>
<b>Quinidine</b>	

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 cytochrome P450 2C19 inducers

## 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
<b>Moderate inhibitors</b>
<b>Amiodarone</b>
<b>Fluconazole</b>
<b>Miconazole</b>
<b>Oxandrolone</b>

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
<b>Moderate inducers</b>
<b>Carbamazepine</b>
<b>Rifampicin</b>

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)

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**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
<b>Moderate inducers</b>
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.