Report Contents

1. Coriell Personalized Medicine Collaborative Research Study Report. This report includes all data included in the clinical report as well as supplemental drug specific interpretations and educational material.
2. Clinical Report. This report was generated and approved by Coriell's CLIA certified genotyping laboratory.

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CPMC Research Study Report

Name:	NATALIE DEMO	**Gender:**	Female
Date of Birth:		**Date Collected:**	
Coriell ID:	DEMONAT	**Date Received:**	
Lab Accessioning Number:	DEMONAT	**Date of Report:**	12/19/2017
Ordering Physician:			

CYP2D6 and Paroxetine (Paxil®) Response

These results were generated in a CLIA-approved laboratory as part of the Coriell Personalized Medicine Collaborative research study. Results take into account 20 genetic variants in the CYP2D6 gene and the total number of gene copies that are present, all of which are known to contribute to the metabolism of paroxetine (Paxil®). This report reflects this participant's predicted metabolism status based on genetic testing but does not reflect whether they are currently taking paroxetine (Paxil®).

The CPMC has a genetic counselor available to assist with report interpretation at no charge. For questions please contact us at cpmcgc@coriell.org or by phone at 888-580-8028. Participants may schedule an appointment with a board certified genetic counselor by logging into their web portal account and clicking on "request an appointment". For general information about the CPMC please visit our website cpmc.coriell.org.

This research report includes all data included in the clinical report as well as supplemental drug specific interpretations and educational material. Please see the report that follows for the official clinical report.

Your Genetic Result

The CPMC tested multiple sites of genetic variation within the CYP2D6 gene and checked the number of copies of CYP2D6 that you carry, all of which affect the way the body responds to paroxetine (Paxil®).

Your combination of genetic variant results is listed below in yellow.
Your CYP2D6* result is:

CYP2D6*1/*1 (x4)
(Paroxetine Ultra-Rapid Metabolizer)

VARIANTS TESTED	YOUR RESULT[1]	REFERENCE VALUE
rs35742686 (CYP2D6*3)	A/A	A/A
rs3892097 (CYP2D6*4M, CYP2D6*4)	G/G	G/G
rs5030655 (CYP2D6*6)	T/T	T/T
rs5030867 (CYP2D6*7)	A/A	A/A
rs28371720 (CYP2D6*9)	AGA/AGA	AGA/AGA
rs1065852 (CYP2D6*10, CYP2D6*4, CYP2D6*14A, CYP2D6*36, CYP2D6*56B, CYP2D6*64, CYP2D6*69)	C/C	C/C
rs5030863 (CYP2D6*11)	G/G	G/G
rs5030862 (CYP2D6*12)	G/G	G/G
rs5030865 (CYP2D6*14B, CYP2D6*14A)	G/G	G/G
rs72549357 (CYP2D6*15)	T/T	T/T
rs28371706 (CYP2D6*17, CYP2D6*40, CYP2D6*64)	C/C	C/C
rs72549353 (CYP2D6*19)	AACT/AACT	AACT/AACT
rs72549354 (CYP2D6*20)	-/-	-/-
rs72549352 (CYP2D6*21)	-/-	-/-
rs72549351 (CYP2D6*38)	GACT/GACT	GACT/GACT
rs72549356 (CYP2D6*40)	-/-	-/-
rs28371725 (CYP2D6*41, CYP2D6*69)	G/G	G/G
rs72549346 (CYP2D6*42)	-/-	-/-
rs72549349 (CYP2D6*44)	G/G	G/G
rs72549347 (CYP2D6*56, CYP2D6*56B)	C/C	C/C
EXON 9 GENE CONVERSION COPIES (CYP2D6*36)	0	0
CYP2D6 GENE COPY NUMBER[2]	4	2

[1]When your variant result for all CYP2D6 variants tested are the same as the reference, the combined genetic result is called CYP2D6*1/*1. In some cases your combined genetic result may be uncertain. Other variants, not currently included in this CPMC test may influence this result and interpretation.

[2]When a CYP2D6 copy number of greater than two copies is detected, the CPMC test cannot determine which of the two CYP2D6*numbered genes has multiple copies and both possibilities are considered in the interpretation of your metabolizer type.

Interpretation of Your Results

Paroxetine Ultra-Rapid Metabolizer

CYP2D6 Result: CYP2D6*1/*1 (x4)

- Your combination of genetic variants indicates that you have increased CYP2D6 activity.
- Ultra-rapid metabolizers process paroxetine (Paxil®) at a fast rate and might not benefit from paroxetine (Paxil®).
- An alternative antidepressant should be considered.
- If you are currently taking paroxetine (Paxil®) and are not experiencing an improvement in your symptoms, talk to your doctor about an alternative antidepressant medication.
- This result may also affect your response to other medications.

Share this information with your healthcare providers.

Do not make any changes to any medication without talking to your healthcare provider.

How Common

The table and picture below show the different types of paroxetine metabolizers and how common each is in the African Ancestry population.

Reduced CYP2D6 activity	**Poor Metabolizer** **3 out of 100 people** Expected to respond to paroxetine (Paxil®), yet may be at an increased risk of an adverse reaction.	
	Intermediate Metabolizer **26 out of 100 people** Expected to respond to paroxetine (Paxil®).	
Typical CYP2D6 activity	**Extensive Metabolizer** **69 out of 100 people** Expected to respond to paroxetine (Paxil®).	
Increased CYP2D6 activity	**Ultra-Rapid Metabolizer** **2 out of 100 people** Less likely to respond to paroxetine (Paxil®).	

What is Paroxetine (Paxil®)?

Paroxetine (Paxil®) is a type of antidepressant drug known as a selective serotonin reuptake inhibitor (SSRI).

Used to Treat:

- Major Depressive Disorder (MDD)
- Obsessive-Compulsive Disorder (OCD)
- Panic Disorder
- Social Anxiety Disorder
- Posttraumatic Stress Disorder (PTSD)
- Generalized Anxiety Disorder (GAD)
- Premenstrual Dysphoric Disorder (PMDD)
- Menopausal vasomotor symptoms (e.g. hot flashes and night sweats)

Risk Factors Affecting Response to Paroxetine (Paxil®)

Genetic Risk Factors

Genetic variants, or changes, in a gene called CYP2D6 can affect the way your body metabolizes paroxetine (Paxil®). Some people with certain genetic variants may not benefit as much from taking paroxetine (Paxil®), while some people with another type of genetic variation may be at an increased risk of having an adverse reaction to paroxetine (Paxil®).

Non-Genetic Risk Factors

Many factors affect how your body responds to medications.

Non-genetic factors include: diet, lifestyle, medical history and interactions between medications.

Genetic Risk Factors

Some medications are metabolized (broken down or activated) by enzymes. Variants in the genes coding for these enzymes may cause your body to metabolize a medication more quickly or more slowly than normal. This change can affect how well the medication works, as well as the risk of side effects.

Gene Affecting Paroxetine (Paxil®) Metabolism:

CYP2D6

Types of Variants in CYP2D6

There are many variants in the CYP2D6 gene. Some variants are changes in the DNA sequence and others are changes in the number of copies of the entire gene. A number system has been created to name common combinations of variants and to name the number of gene copies. Some variant combinations have not been assigned a number yet. Other combinations of variants cannot be assigned a number with certainty. When possible, you will have a CYP2D6 result with two numbers. If a copy number variation is present, this will be shown by a multiplication sign followed by the number of copies of the gene.

Example: CYP2D6 *1/*4 (× 3)

Types of Paroxetine Metabolizers

Each result is associated with a metabolizer status which describes how the enzyme is working.

Example: poor metabolizer

Drug-Drug Interactions

In addition to your genes, other medications that you take may affect how your body responds to paroxetine (Paxil®) and may increase the risk of side effects associated with both paroxetine (Paxil®) and the other medications.

There are over 800 drugs that are known to interact with paroxetine (Paxil®). The following are some examples of medications, that when taken with paroxetine (Paxil®), may not work as well, may reduce the benefit of taking paroxetine (Paxil®), or may increase the risk for side effects:

- Anticoagulants ('blood thinners') such as warfarin (Coumadin®)
- Antidepressants such as amitriptyline (Elavil®), amoxapine (Asendin®), clomipramine (Anafranil®), desipramine (Norpramin®), doxepin (Adapin®, Sinequan®), imipramine (Tofranil®), nortriptyline (Aventyl®, Pamelor®), protriptyline (Vivactil®), and trimipramine (Surmontil®)
- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil®, Motrin®), and naproxen (Aleve®, Naprosyn®)
- Atazanavir (Reyataz®)
- Bromocriptine (Parlodel®)
- Bupropion (Wellbutrin®)
- Celecoxib (Celebrex®)
- Chlorpromazine (Thorazine®)
- Cimetidine (Tagamet®)
- Clopidogrel (Plavix®)
- Codeine (found in many cough and pain medications)
- Dexamethasone (Decadron®)

If you are taking paroxetine (Paxil®) now, or are prescribed it in the future, talk to your healthcare providers about other medications you are taking that may interact with paroxetine (Paxil®).

Result Limitations

- This result alone does **NOT** predict your total response to paroxetine (Paxil®).
- Other factors such as body weight, various health conditions, and other medications may impact an individual's response to paroxetine (Paxil®).
- There may be other genetic variants within the CYP2D6 gene which influence response to paroxetine (Paxil®) but are not included in this test.
- There may be other genetic variants or combinations of known genetic variants in the CYP2D6 gene for which response to paroxetine (Paxil®) has not been documented and/or validated in multiple studies.
- There may be genetic variants in other genes that influence response to paroxetine (Paxil®).
- This result reflects published data available at the time this gene-drug pair was approved by the CPMC Informed Cohort Oversight Board (September, 2013). The information provided may change as new scientific information becomes available.
- Although rare, it is possible that you may receive an incorrect result; 100% accuracy of reported results cannot be guaranteed.
- Occasionally, we will be unable to interpret one or more gene variants. In this case you will not receive a result for those variants and in some cases your drug response cannot be interpreted. It is expected that you will receive results for about 95% of variants approved by the Pharmacogenetics Advisory Group (PAG) and Informed Cohort Oversight Board (ICOB).
- Every effort will be made to provide you with risk information based on your reported race/ethnicity. However, data may not be available for all races/ethnicities. Please see your individual results to determine which race/ethnicity the data is based on.

Test Limitations

DNA-based testing is highly accurate, however there are many sources of potential error including: misidentification of samples, rare technical errors, trace contamination of PCR reactions, and rare genetic variants that interfere with analysis. This test or one or more of its components was developed and its performance characteristics determined by the Coriell Institute for Medical Research. It has not been approved by the Food and Drug Administration (FDA). The FDA has determined that such approval is not necessary. The Coriell Institute is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high-complexity testing.

Methods

References

- Berle JO, et al. *The Journal of Clinical Psychiatry.* 2004; 65:1228-1234.
- Charlier C, et al. *Therapeutic Drug Monitoring.* 2003; 25:738-742.
- Guzey C & Spigset O. *Journal of Clinical Psychopharmacology.* 2006; 26:211-212.
- Hicks JK, et al. *Clinical Pharmacology and Therapeutics.* 2015; 98 (2): 127-134.
- Laine K, et al. *Therapeutic Drug Monitoring.* 2004; 26:685-687.
- Swen JJ, et al. *Clinical Pharmacology and Therapeutics.* 2008; 83:781-787.
- Swen JJ, et al. *Clinical Pharmacology and Therapeutics.* 2011; 89:662-673.
- Zourkova A & Hadasova E. *General Physiology and Biophysics.* 2003; 22:103-113.
- Zourkova A, et al. *Journal of Sex & Marital Therapy.* 2007; 33:343-355.

Test Methodology

Saliva samples were collected using Oragene DNA Collection Kits (DNA Genotek) and DNA was extracted manually according to the manufacturer's instructions or automatically using a DNAdvance Kit (Agencourt). Purified DNA was quantified using UV absorbance at 260 nm. One microgram of the resulting DNA from each sample was used as template in the Affymetrix DMET Plus GeneChip assay. Data analysis was performed using Affymetrix DMET Console software. Ten nanogram of DNA from each sample was used in the CYP2D6 copy number assay (Taqman Copy Number Assay, ThermoFisher, Hs00010001). Data analysis was performed using CopyCaller V2.1 software (ThermoFisher). Risk interpretation was based on Coriell's CYP2D6/Paroxetine (Paxil®) Response Genotype Translation Version 1.

To view your clinical report, click here. The clinical report contains the lab generated testing information and does not include all the content in the research study report.

[Risk interpretation based on Coriell's CYP2D6/Paroxetine (Paxil®) Activity Genotype Translation Version 1 (January, 2015)]

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CYP2D6 GENE TEST FOR PAROXETINE (PAXIL®) RESPONSE

Name:	NATALIE DEMO	**Sample Type:**	Saliva
Date of Birth:		**Gender:**	Female
Coriell ID:	DEMONAT	**Date Collected:**	
Lab Accessioning Number:	DEMONAT	**Date Received:**	
Ordering Physician:		**Date of Report:**	12/19/2017

NAME OF GENE: CYP2D6		**LOCATION OF GENE:** 22q13
Variants tested	**RESULT**	**Reference Genotype**
rs35742686 (CYP2D6*3)	A/A	A/A
rs3892097 (CYP2D6*4M, CYP2D6*4)	G/G	G/G
rs5030655 (CYP2D6*6)	T/T	T/T
rs5030867 (CYP2D6*7)	A/A	A/A
rs28371720 (CYP2D6*9)	AGA/AGA	AGA/AGA
rs1065852 (CYP2D6*10, CYP2D6*4, CYP2D6*14A, CYP2D6*36, CYP2D6*56B, CYP2D6*64, CYP2D6*69)	C/C	C/C
rs5030863 (CYP2D6*11)	G/G	G/G
rs5030862 (CYP2D6*12)	G/G	G/G
rs5030865 (CYP2D6*14B, CYP2D6*14A)	G/G	G/G
rs72549357 (CYP2D6*15)	T/T	T/T
rs28371706 (CYP2D6*17, CYP2D6*40, CYP2D6*64)	C/C	C/C
rs72549353 (CYP2D6*19)	AACT/AACT	AACT/AACT
rs72549354 (CYP2D6*20)	-/-	-/-
rs72549352 (CYP2D6*21)	-/-	-/-
rs72549351 (CYP2D6*38)	GACT/GACT	GACT/GACT
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rs72549346 (CYP2D6*42)	-/-	-/-
rs72549349 (CYP2D6*44)	G/G	G/G
rs72549347 (CYP2D6*56, CYP2D6*56B)	C/C	C/C
EXON 9 GENE CONVERSION COPIES (CYP2D6*36)	0	0
CYP2D6 GENE COPY NUMBER[2]	4	2
Combined Result^	**CYP2D6*1/*1 (x4)**	

^ When the Result for all CYP2D6 variants tested are the same as the reference, the Combined Result is called CYP2D6 *1/*1. In some cases, due to technical limitations, your Combined Result may not be able to be determined. It may still be possible to provide an interpretation for such a result based on possible genetic outcomes (for example in rare combinations of non-reference results at more than one variant, or the presence of a “result not available” at one or more variants).

[2]When a CYP2D6 copy number of greater than two copies is detected, the CPMC test cannot determine which of the two CYP2D6*numbered genes has multiple copies and both possibilities are considered in the interpretation of metabolizer type.

Risk interpretation based on Coriell's CYP2D6/Paroxetine (Paxil®) Response Genotype Translation Version 1 (January, 2015).

Interpretation

This individual is expected to be a **Paroxetine Ultra-Rapid Metabolizer** based on the Combined Genetic Result: **CYP2D6*1/*1 (x4)**

Individuals who are ultra-rapid metabolizers have increased CYP2D6 enzymatic function and may not respond to paroxetine (Paxil®). An alternative antidepressant medication (not primarily metabolized by CYP2D6; e.g. sertraline, citalopram, and escitalopram) should be considered.

Test Limitations

DNA-based testing is highly accurate, however there are many sources of potential error including: misidentification of samples, rare technical errors, trace contamination of PCR reactions, and rare genetic variants that interfere with analysis. There may be other variants in the CYP2D6 gene that are not included in this test that influence the response to paroxetine (Paxil®). This test or one or more of its components was developed and its performance characteristics determined by the Coriell Institute for Medical Research. It has not been approved by the Food and Drug Administration (FDA). The FDA has determined that such approval is not necessary. The Coriell Institute is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high-complexity testing.

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Electronically signed by

Owatha L. Tatum, PhD, Laboratory Director

This clinical report only includes data generated in the CLIA approved genotyping laboratory, for additional information please see the research report.

References

1. Berle JO, et al. *The Journal of Clinical Psychiatry.* 2004; 65:1228-1234.
2. Charlier C, et al. *Therapeutic Drug Monitoring.* 2003; 25:738-742.
3. Guzey C & Spigset O. *Journal of Clinical Psychopharmacology.* 2006; 26:211-212.
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