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:**	06/11/2012
Ordering Physician:			

CYP2C9, VKORC1, CYP4F2 and Warfarin (Coumadin®) Response

These results were generated in a CLIA-approved laboratory as part of the Coriell Personalized Medicine Collaborative research study. Results take into account 6 genetic variants in the CYP2C9 gene, one genetic variant in the VKORC1 gene, and one genetic variant in the CYP4F2 gene. Variation in these three genes is known to influence the dose of warfarin needed to prevent blood clots without causing dangerous side effects. This report reflects this participant's predicted dosing category (low, intermediate, high) based on their genetic results but does not reflect whether they are currently taking warfarin. In addition, predicted dosing category does not account for other factors known to influence dosing including age, weight, gender, race, diet, other medications and smoking status.

The CPMC has genetic counselors and pharmacists 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 one of our board-certified genetic counselors or pharmacists 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

CPMC tested multiple sites of genetic variation within the CYP2C9, VKORC1, and CYP4F2 genes that affect the way the body responds to warfarin.

Your combination of genetic variant results (listed below in yellow) indicates:

Increased Dose[1] of Warfarin MAY be Needed

VARIANTS TESTED (also known as)	REFERENCE VALUE	YOUR RESULT	YOUR COMBINED GENETIC RESULT[2]
rs1799853 (CYP2C9*2)	C C	CC	
rs1057910 (CYP2C9*3)	A A	AA	
rs28371686 (CYP2C9*5)	C C	CC	
rs9332131 (CYP2C9*6)	A A	AA	CYP2C9*1/*1
rs28371685 (CYP2C9*11)	C C	CC	
rs72558189 (CYP2C9*14)	G G	GG	
rs9923231	G G	GG	VKORC1-GG
rs2108622	G G	GG	CYP4F2-GG

1 Please see the Your Result Interpretation tab for the impact of this result on warfarin dosing and risks.

2 Your personal combination of Variant Results is used to determine your Combined Genetic Result. When your Variant Result for all CYP2C9 variants tested are the same as the reference, the Combined Genetic Result is called CYP2C9 *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.

Interpretation of Your Results

Increased Dose[1] of Warfarin MAY be Needed

Based on Your Combined Genetic Result: CYP2C9*1/*1, VKORC1-GG, CYP4F2-GG

- Your combination of genetic results indicates that you **<u>may not</u> respond adequately to an intermediate[1] therapeutic dose** of warfarin.
- If you require treatment with warfarin, a **higher than intermediate[1] therapeutic dose <u>may be</u> needed**.
- You may be at an increased risk for blood clots if prescribed warfarin using intermediate dosing guidelines.
- INR[2] (clotting time) and clinical features should be used, in combination with your genetic results, to establish warfarin dosing.
- 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.

[1] Based on an intermediate therapeutic dose of 3-4mg/day

[2] INR - International Normalized Ratio is a measurement of clotting time

How Common

The table and picture below show the different dosing categories and how common each is expected to be in the African Ancestry population.

The estimated number of people in each dose category is based on the FDA approved warfarin dosing guidelines[1] only and does not reflect other factors that affect dose such as sex, weight, diet and other medications.

Increased Dose Indicated **88 out of 100 people** An increased dose may be needed to reach the full effect of warfarin. Increased risk for blood clot at an intermediate dose.	
Intermediate Dose Indicated **12 out of 100 people** Expected to benefit from the intermediate dose.	
Lower Dose Indicated **0 out of 100 people** A lower dose of warfarin may be needed. Increased risk for excessive bleeding at an intermediate dose.	

[1] FDA drug label dosing guidelines are based CYP2C9 and VKORC1 genotypes and an intermediate therapeutic daily doses of 3-4mg/day.

What is Warfarin (Coumadin®)?

Warfarin is a blood thinner (anticoagulant).
This medication is used to prevent blood clots from forming or getting bigger.

Uses:

• To prevent or treat blood clots in the veins, lungs, heart, or brain.

Risk Factors Affecting Response to Warfarin

Genetic Risk Factors

Genetic variants, or changes, in three genes called CYP2C9, VKORC1, and CYP4F2 can affect the way your body responds to warfarin.

Some people with certain genetic variants may require a higher or lower dose of warfarin compared to people without these variants.

Non-Genetic Risk Factors

Many factors affect how your body responds to medications.

Non-genetic factors that may influence your response to warfarin include: diet, lifestyle, medical history and interactions between medications.

Genetic Risk Factors

Genetic variants can affect how well a medication works, as well as the risk of side effects.

Genes Affecting Warfarin Response:

CYP2C9, VKORC1, CYP4F2

For information on how CYP2C9, VKORC1 and CYP4F2 affect how the body responds to warfarin click here.

Types of Results

Some genes (CYP2C9) have multiple variants. When a gene has multiple variants a number system is used to name common combinations of variants (example: CYP2C9*2). Some variant combinations have not been assigned a number yet. Other combinations of variants cannot be assigned a number with certainty. Other genes including VKORC1 and CYP4F2 have only one variant that is known to affect the gene function (example: Variant = A, Reference/Normal = G). Because there are multiple genes involved in how your body responds to warfarin you will receive multiple results.

Result Interpretation

Each result is associated with a warfarin dosing recommendation based on your personal result for CYP2C9, VKORC1 and CYP4F2.

Drug-Drug Interactions

In addition to your genes, other medications may affect how your body responds to warfarin.

There are over 100 medications that, when taken with warfarin, can cause an increase in the effect of warfarin and may result in increased risk for bleeding.

There are over 40 medications that, when taken with warfarin, can cause a decrease in the effect of warfarin and may result in an increased risk for blood clots.

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

Other Interactions

In addition to your genes, and other medications, diet and lifestyle may affect how your body responds to warfarin.

The following Foods, Vitamins and Supplements are known to interact with warfarin:

Agrimony	Alfalfa	Aloe Gel	Angelica (Dong Quai)	Aniseed	Arnica	Asafoetida	Aspen
Black Cohosh	Black Haw	Bladder Wrack (Fucus)	Bogbean	Boldo	Bromelains	Buchu	Capsicum
Cassia	Celery	Chamomile (German and Roman)	Clove	Coenzyme Q10	Cranberry	Dandelion	Danshen
Fenugreek	Feverfew	Garlic	German Sarsaparilla	Ginger	Ginkgo Biloba	Ginseng (Panax)	Goldenseal
Horse Chestnut	Horseradish	Inositol Nicotinate	Licorice	Meadowsweet	Mistletoe	Nettle	Onion
Parsley	Passion Flower	Pau d'arco	Policosanol	Poplar	Prickly Ash (Northern)	Quassia	Red Clover
Senega	St. John's wort	Sweet Clover	Sweet Woodruff	Tamarind	Tonka Beans	Wild Carrot	Wild Lettuce
Willow	Wintergreen	Yarrow					

If you are taking warfarin now, or are prescribed it in the future, talk to your healthcare providers about foods, vitamins and supplements that may interact with warfarin.

Result Limitations

- This result alone does **NOT** predict your total response to warfarin.
- Other factors such as body weight, various health conditions, and other medications may impact an individual's response to warfarin.
- There may be other genetic variants within the CYP2C9 gene, VKORC1 gene or CYP4F2 gene which influence response to warfarin but are not included in this test.
- There may be other genetic variants for which response to warfarin has not been documented and/or validated in multiple studies.
- There may be genetic variants in other genes that influence response to warfarin.
- This result reflects published data available at the time this gene-drug pair result was prepared (December 2011). 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. 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: mis-identification 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.

References

- Caldwell MD, et al. Blood. 2008;111(8):4106-12.
- Pérez-Andreu V, et al. Blood. 2009;113(20):4977-9.
- Wadelius M, et al. Pharmacogenomics J. 2005;5(4):262-70.
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- Lindh JD, et al. Clin Pharmacol Ther. 2005;78(5):540-50.
- Sanderson S, et al. Genet Med. 2005;7(2):97-104.
- Dickmann LJ, et al. Mol Pharmacol. 2001;60(2):382-7.
- Cavallari LH, et al. Clin Pharmacol Ther. 2010; 87(4):459-64.
- Ieiri I, et al. Ther Drug Monit. 2000; 22:237-44.
- Zhao F, et al. Clin Pharmacol Ther. 2004; 76:210-9.

Tools guiding warfarin dosing category assignment:

Coumadin Drug label: www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf
www.warfarindosing.org
IWPC et al. N Engl J Med. 2009;360(8):753-64.
Garcia D, et al. Chest. 2005; 127:2049-56.

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.

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 Warfarin Response Genotype Translation Version 1 (January 2012)]

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CYP2C9/VKORC1/CYP4F2 WARFARIN GENE TEST

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:**	06/11/2012

NAME OF GENE: CYP2C9		LOCATION OF GENE: 10q24
Variants tested	**RESULT**	**Reference Genotype**
rs1799853 (CYP2C9*2)	CC	C C
rs1057910 (CYP2C9*3)	AA	A A
rs28371686 (CYP2C9*5)	CC	C C
rs9332131 (CYP2C9*6)	AA	A A
rs28371685 (CYP2C9*11)	CC	C C
rs72558189 (CYP2C9*14)	GG	G G
Combined Result^	**CYP2C9*1/*1**	

^ When the Result for all CYP2C9 variants tested are the same as the reference, the Combined Result is called CYP2C9 *1/*1. In some cases, due to technical limitations, your Combined Result may be CYP2C9*Uncertain. 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).

NAME OF GENE: VKORC1 (-1639G>A)		LOCATION OF GENE: 16p11.2
Variants tested	**RESULT**	**Reference Genotype**
rs9923231	GG	G G

NAME OF GENE: CYP4F2 (433V>M)		LOCATION OF GENE: 19p13
Variants tested	**RESULT**	**Reference Genotype**
rs2108622	GG	G G

Risk interpretation based on Coriell's Warfarin Response Genotype Translation Version 1 (January 2012).

Interpretation

Based on this individual's Combined Genetic Result: CYP2C9*1/*1, VKORC1-GG, CYP4F2-GG an Increased Dose[1] of Warfarin MAY be Needed.

INR[2] (clotting time) and clinical features should be used, in combination with genetic results, to establish warfarin dosing.

This interpretation is based on dosing guidance available in the FDA (Food and Drug Administration) drug label for warfarin (below). Dosing recommendations for individuals with CYP2C9 *5, *6, *11, and *14 are based on functional similarity to CYP2C9*2 (*11, *14), and *3 (*5, *6). CYP4F2 results have been incorporated into the interpretation based on dosing guidance from www.warfarindosing.org using two standard individuals age 50 and 75 with the following characteristics: female, diagnosis of atrial fibrillation, non smoker, BMI in the normal rang, no concomitant medications.

[1] Intermediate therapeutic dose of 3-4mg/day based on FDA approved drug label for warfarin and Garcia et al 2005

[2] INR - International Normalized Ratio is a measurement of clotting time

Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes [1]

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

[1]Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G⟶A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Individuals with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

Test Limitations

DNA-based testing is highly accurate, however there are many sources of potential error including: mis-identification 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 CYP2C9 gene, VKORC1 gene or the CYP4F2 gene that are not included in this test, that influence the response to warfarin. 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.

Test Methodology

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electronically signed by
Marie Hoover, 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. Caldwell MD, et al. Blood. 2008;111(8):4106-12.
2. Pérez-Andreu V, et al. Blood. 2009;113(20):4977-9.
3. Wadelius M, et al. Pharmacogenomics J. 2005;5(4):262-70.
4. Wadelius M, et al. Blood. 2009;113(4):784-92.
5. Lindh JD, et al. Clin Pharmacol Ther. 2005;78(5):540-50.
6. Sanderson S, et al. Genet Med. 2005;7(2):97-104.
7. Dickmann LJ, et al. Mol Pharmacol. 2001;60(2):382-7.
8. Cavallari LH, et al. Clin Pharmacol Ther. 2010; 87(4):459-64.
9. Ieiri I, et al. Ther Drug Monit. 2000; 22:237-44.
10. Zhao F, et al. Clin Pharmacol Ther. 2004; 76:210-9.