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:	STEVE CPMC	**Gender:**	Male
Date of Birth:		**Date Collected:**	
Coriell ID:	DEMOSTEVE	**Date Received:**	
Lab Accessioning Number:	DEMOSTEVE	**Date of Report:**	04/29/2011
Ordering Physician:			

CYP2C19 and clopidogrel (Plavix®) Response

These results were generated in a CLIA-approved laboratory as part of the Coriell Personalized Medicine Collaborative research study. Results take into account 8 genetic variants in the CYP2C19 gene, known to contribute to the metabolism of clopidogrel (Plavix®). This report reflects this participant's metabolism status predicted based on genetic testing but does not reflect whether they are currently taking clopidogrel (Plavix®).

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 CYP2C19 gene that affect the way the body responds to clopidogrel.

Your combination of genetic variant results (listed below in yellow) is commonly referred to as:

CYP2C19*1/*17 (Clopidogrel Ultra-Rapid Metabolizer)

VARIANTS TESTED	YOUR RESULT	REFERENCE VALUE
rs12248560	CT	C C
rs28399504	AA	A A
rs41291556	TT	T T
rs72558184	GG	G G
rs4986893	GG	G G
rs4244285	GG	G G
rs72558186	TT	T T
rs56337013	CC	C C

Other variants, not currently included in this CPMC test may influence this result and interpretation.

Interpretation of Your Results

Clopidogrel Ultra-Rapid Metabolizer

also called CYP2C19*1/*17

- Ultra-Rapid metabolizers have increased CYP2C19 activity.
- Ultra-Rapid metabolizers may process clopidogrel more quickly than people with other variants. Some studies suggest this may result in an increased benefit of the drug. Other studies suggest this result may increase the risk of bleeding.
- Talk to your doctor about treatment options.
- 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.

What is Clopidogrel (Plavix®)?

Clopidogrel is an anti-platelet medication.

This medication is used to prevent platelets, a type of cell found in the blood, from clumping together. When platelets clump together they can form clots which block the flow of blood.

Uses:

- To treat acute coronary syndrome (decreased blood flow to the heart) and peripheral artery disease (poor circulation in the legs)
- To prevent stroke, heart attack, and formation of blood clots after stent placement

Risk Factors Affecting Response to Clopidogrel

Genetic Risk Factors

Genetic variants, or changes, in a gene called CYP2C19 can affect the way your body metabolizes clopidogrel.

Some people with certain genetic variants may not benefit as much from taking clopidogrel compared to people without these variants. These people can be at increased risk for heart attacks or blood clots.

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.

Genes Affecting Clopidogrel Metabolism:

CYP2C19

Types of Variants in CYP2C19

There are many variants in the CYP2C19 gene. A number system has been created to name common combinations of variants. Some variant combinations have not been assigned a number yet. Other combinations of variants cannot be assigned a number with certainty. We all have 2 copies of every gene; when possible, you will have a CYP2C19 result with two numbers.

Example: CYP2C19 *1/*2

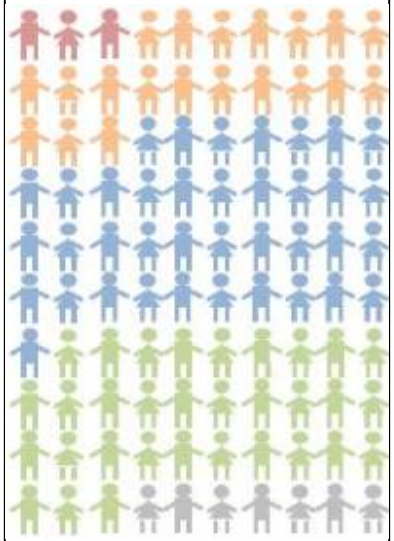
Types of Clopidogrel Metabolizers

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

Example: intermediate metabolizer

How Common

The table and picture below show the different types of clopidogrel metabolizers and how common each is in the Caucasian population.

Reduced CYP2C19 activity	**Poor Metabolizer** **3 out of 100 people** Not likely to receive full benefit of clopidogrel. Increased risk for heart attack and stroke.	
	Intermediate Metabolizer **20 out of 100 people** May not receive full benefit of clopidogrel. Possible increased risk for heart attack and stroke.	
Typical CYP2C19 activity	**Extensive Metabolizer** **38 out of 100 people** Expected to benefit from standard clopidogrel dose.	
Increased CYP2C19 activity	**Ultra-Rapid Metabolizer** **32 out of 100 people** Expected to process medication more quickly. Possible increased benefit. Possible increased risk for bleeding.	
Uncertain CYP2C19 activity	**Metabolizer Status Unknown** **7 out of 100 people** Not enough data to determine clopidogrel response.	

Drug-Drug Interactions

In addition to your genes, other medications may affect how your body metabolizes clopidogrel and may increase the risk of side effects or prevent clopidogrel from working effectively.

The following medications, when taken with clopidogrel, may reduce the benefit of clopidogrel or increase the risk for side effects:

Medication	Also Known As
Omeprazole	Prilosec, Zegerid
Warfarin	Coumadin, Athrombin
Nonsteroidal anti-inflammatory drugs (NSAIDs)	aspirin, ibuprofen, acetaminophen, naproxen

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

Result Limitations

- This result alone does **NOT** predict your total response to clopidogrel.
- Other factors such as body weight, various health conditions, and other medications may impact an individual's response to clopidogrel.
- There may be other genetic variants within the CYP2C19 gene which influence response to clopidogrel but are not included in this test.
- There may be other genetic variants in the CYP2C19 gene for which response to clopidogrel has not been documented and/or validated in multiple studies.
- There may be genetic variants in other genes that influence response to clopidogrel.
- This result reflects published data available at the time this gene-drug pair was approved by the CPMC Informed Cohort Oversight Board (12-8-10). 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 there may be a specific variant on a gene chip that is not able to be read or interpreted. In this case you will not receive a result for that variant. 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

- Chen BL, et al. Clin Exp Pharmacol Physiol.2008;35(8):904-8.
- Collet JP, et al. The Lancet. 2009;373(9660):309-317.
- Ferguson RJ, et al. J Pharmacol Exp Ther. 1998;284(1):356-61.
- Giusti B, et al. Am J Cardiol. 2009; 103(6):806–811.
- Gladding P, et al. JACC Cardiovasc Interv. 2008;1(6):620-7.
- Ibeanu GC, et al. Pharmacogenetics. 1998;8(2):129-35.
- Ibeanu GC, et al. J Pharmacol Exp Ther. 1998;286(3):1490-5.
- Ibeanu GC, et al. J Pharmacol Exp Ther. 1999;290(2):635-40.
- Mega JL, et al. N Engl J Med. 2009;360(4):354-62.
- Mega JL, et al. JAMA. 2010;304; 1821-1830.
- Paré G, et al. NEJM. 2010 Aug 29; online.
- Rogan PK, et al. Pharmacogenetics. 2003;13(4):207-18.
- Shuldiner AR, et al. JAMA. 2009;302(8):849-57.
- Sibbing D, et al. Eur Heart J. 2009;30(8):916-22.
- Sibbing D, et al. Circulation. 2010;121(4):512-8.
- Sim SC, et al. Clin Pharmacol Ther. 2006;79(1):103-13.
- Simon T, et al. N Engl J Med. 2009;360(4):363-75.
- Tiroch KA, et al. Am Heart J. 2010 Sep;160(3):506-12.
- Trenk D, et al. J Am Coll Cardiol. 2008;51(20):1925-34.
- Varenhorst C, et al. Eur Heart J. 2009;30(14):1744-52.
- Wallentin L, et al. Lancet. 2010 Aug 27. [Epub ahead of print]

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 CYP2C19 Clopidogrel Metabolizer Type Genotype Translation Version 1 (March 2011)]

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CYP2C19 Clinical Report

Name:	STEVE CPMC	**Sample Type:**	Saliva
Date of Birth:		**Gender:**	Male
Coriell ID:	DEMOSTEVE	**Date Collected:**	
Lab Accessioning Number:	DEMOSTEVE	**Date Received:**	
Ordering Physician:		**Date of Report:**	04/29/2011

NAME OF GENE: CYP2C19		**LOCATION OF GENE:** 10q24
Variants tested	**RESULT**	**Reference Genotype**
rs12248560	CT	C C
rs28399504	AA	A A
rs41291556	TT	T T
rs72558184	GG	G G
rs4986893	GG	G G
rs4244285	GG	G G
rs72558186	TT	T T
rs56337013	CC	C C
Interpretation	**Ultra-Rapid Metabolizer** also called CYP2C19*1/*17.	

Risk interpretation based on Coriell's CYP2C19 Clopidogrel Metabolizer Type Genotype Translation Version 1 (March 2011)

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 CYP2C19 gene, not included in this test, that influence metabolizer status. 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
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.

Genetic Variant Definitions

- Extensive metabolizers (EM) include those with two normally functioning copies such as CYP2C19*1.
- Intermediate metabolizers (IM) include those with one normally functioning copy of CYP2C19 (CYP2C19*1) and one non-functional variant such as CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7 or CYP2C19*8.
- Reduced Response - Metabolizer Status Uncertain includes those who have at least two non-functional variants in the CYP2C19 gene conferring a reduced response but for whom metabolizer status cannot be definitively determined to be poor or intermediate.
- Poor metabolizers (PM) include those with two non-functional variants such as CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7 or CYP2C19*8.
- Ultra rapid metabolizers (UM) include those with 2 enhanced activity variants such as CYP2C19*17 or one normally functioning copy (CYP2C19*1) and one enhanced activity variant (CYP2C19*17).
- Typical or Increased Response – Metabolizer Status Uncertain includes those with zero non-functional variants, but for whom the presence of one or more enhanced activity variants cannot be determined due to technical limitations.
- Metabolizer Status Uncertain includes those individuals for whom a metabolizer status cannot be assigned either due to technical limitations or due to the lack of clinical data on the effect of the variant combination.

References

1. Mega JL, et al. N Engl J Med 2009; 360:354-62 PMID: 19106084
2. Mega JL, et al. JAMA. 2010; 304; 1821-1830. PMID: 20978260
3. Sibbing D, et al. J. Thromb. Haemost. 2010; 8:1685-1693. PMID:20492469
4. Sibbing D, et al. Circulation. 2010; 121:512-518. PMID:20083681
5. Simon T, et al. N Engl J Med 2009; 360(4):363-75. PMID: 19106083
6. OMIM 124020 (http://www.ncbi.nlm.nih.gov/omim)
7. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/
8. http://www.cypalleles.ki.se/cyp2c19.htm