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:**	11/11/2013
Ordering Physician:			

SLCO1B1 and Simvastatin Response

These results were generated in a CLIA-approved laboratory as part of the Coriell Personalized Medicine Collaborative research study. Results take into account 4 genetic variants in the SLCO1B1 gene, known to contribute to how the liver metabolizes simvastatin (Zocor®). This report reflects this participant's liver uptake status predicted based on genetic testing but does not reflect whether they are currently taking simvastatin (Zocor®).

The CPMC has a genetic counselor who is 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 our 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

CPMC tested multiple sites of genetic variation within the SLCO1B1 gene that affect the way the body responds to simvastatin (Zocor®).

Your combination of genetic variant results is listed below in yellow.
Your SLCO1B1* result is:

SLCO1B1*1/*3
(Intermediate liver uptake activity)

VARIANTS TESTED	YOUR RESULT[1]	REFERENCE VALUE
rs72559745 (SLCO1B1*1)	AG	A A
rs56061388 (SLCO1B1*3)	CT	T T
rs4149056 (SLCO1B1*5)	TT	T T
rs55901008 (SLCO1B1*6)	TT	T T

[1]When your variant result for all SLCO1B1 variants tested are the same as the reference, the combined genetic result is called SLCO1B1*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.

Interpretation of Your Results

Intermediate liver uptake activity

SLCO1B1 Result: SLCO1B1*1/*3

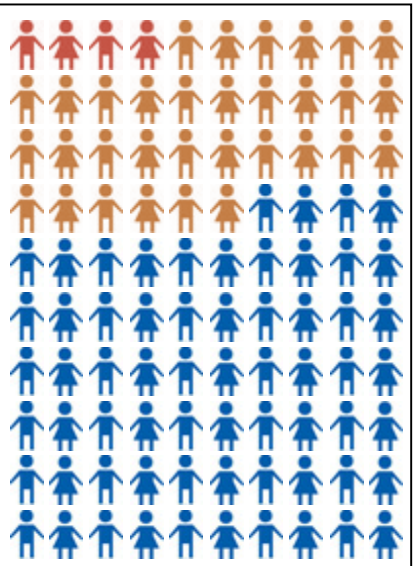
- Your combination of genetic variants indicates that you have intermediate SLCO1B1 liver uptake activity.
- People with intermediate SLCO1B1 liver uptake activity have a moderately increased risk of myopathy (muscle weakness) when taking a 40 mg/day or higher dose of simvastatin.
- If you are currently taking simvastatin, talk to your doctor about appropriate dosing, monitoring, or options for treatment with another type of statin drug.

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 simvastatin (Zocor®) liver uptake activity levels and how common each is in the Caucasian population.

Reduced SLCO1B1 activity	**Reduced Liver Uptake Activity** **4 out of 100 people** High risk of myopathy when taking a 40 mg/day or higher dose of simvastatin (Zocor®).	
	Intermediate Liver Uptake Activity **32 out of 100 people** Moderately increased risk of myopathy when taking a 40 mg/day or higher dose of simvastatin (Zocor®).	
Normal SLCO1B1 activity	**Normal Liver Uptake Activity** **64 out of 100 people** Expected to have a typical response to a standard dose of simvastatin (Zocor®).	

What is Simvastatin (Zocor®)?

Simvastatin (Zocor®) is a statin drug.
This medication is used to lower cholesterol and triglycerides in the blood.

Uses:

- Treatment of high cholesterol
- Treatment of high triglycerides
- To prevent heart attack, stroke and other heart complications in people who have coronary artery disease or diabetes

Risk Factors Affecting Response to Simvastatin (Zocor®)

Genetic Risk Factors

Genetic variants, or changes, in a gene called SLCO1B1 can affect the way your liver metabolizes simvastatin (Zocor®). Some people with certain genetic variants may be at increased risk for myopathy (muscle weakness) when taking a 40 mg/day or higher dose of simvastatin (Zocor®). These individuals may need a lower dose or a different statin drug.

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

All medications are processed by the liver. Variants in the genes that code for liver cell membrane transport proteins may influence how much of a drug is taken into the liver for processing. These variants can affect how well the medication works, as well as the risk of side effects.

Gene Affecting Simvastatin (Zocor®) Metabolism:

SLCO1B1

Types of Variants in SLCO1B1

There are many variants in the SLCO1B1 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 SLCO1B1 result with two numbers.

Example: SLCO1B1*1/*3

Types of Simvastatin Liver Uptake Activity Levels

Each result is associated with a liver uptake activity level which describes how much of the drug is available for the body to use.

Example: intermediate liver uptake activity

Drug-Drug Interactions

In addition to your genes, other medications may affect how your body responds to simvastatin (Zocor®) and may increase the risk of side effects when taking simvastatin (Zocor®).

Medication/Medication Type	Examples
Antifungal medications	Itraconazole/Sporanox®, ketoconazole/Nizoral® , posaconazole/Noxafil®, voriconazole/VFEND®
Macrolide antibiotics	erythromycin/E-mycin®, clarithromycin/Biaxin®, telithromycin/Ketek®
Blood thinners	warfarin/Coumadin®, Athrombin®
HIV protease inhibitors	Atazanavir/Reyataz®, darunavir/Prezista®, fosamprenavir/Lexiva®, indinavir/Crixivan®, nelfinavir/Viracept®, ritonavir/Norvir®, saquinavir/Invirase®, tipranavir/Aptivus®
Hepatitis C medications	boceprevir/Victrelis®, telaprevir/Incivek®
Blood pressure medications	verapamil/Calan®, diltiazem/Cardizem®, amlodipine/Norvasc®
Anti-arrhythmia medications	dronedarone/Multaq®, amiodarone/Cordarone®
gemfibrozil	Lopid®
cyclosporine	Neoral®, Sandimmune®, Gengraf®
danazol	Danocrine®
ranolazine	Ranexa®

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

Other Interactions

In addition to your genes, and other medications, your diet may affect how your body responds to simvastatin (Zocor®) and may increase the risk of side effects when taking simvastatin (Zocor®).

The following foods, vitamins, and supplements are known to interact with simvastatin (Zocor®):

Grapefruit and grapefruit juice

- Avoid eating grapefruit or drinking grapefruit juice while taking simvastatin (Zocor®).
- Drinking grapefruit juice while taking simvastatin (Zocor®) increases the risk of liver damage and a rare but serious condition called rhabdomyolysis that involves the breakdown of skeletal muscle.
- Tell your doctor right away if you have unexplained muscle pain, tenderness, or weakness while taking simvastatin (Zocor®), especially if you also have a fever or dark colored urine.

For a list of foods, vitamins, and supplements that may interact with simvastatin (Zocor®), click here.

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

Result Limitations

- This result alone does **NOT** predict your total response to simvastatin (Zocor®).
- Other factors such as body weight, various health conditions, and other medications may impact an individual's response to simvastatin (Zocor®).
- There may be other genetic variants within the SLCO1B1 gene which influence response to simvastatin (Zocor®) but are not included in this test.
- There may be other genetic variants in the SLCO1B1 gene for which response to simvastatin (Zocor®) has not been documented and/or validated in multiple studies.
- There may be genetic variants in other genes that influence response to simvastatin (Zocor®)
- This result reflects published data available at the time this gene-drug pair was approved by the CPMC Informed Cohort Oversight Board (March 2012). 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: 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.

Methods

References

- Bailey KM, et al. Circ Cardiovasc genet 2010; 3:276-285.
- Donnelly LA, et al. Clin. Pharmacol Ther 2011; 89:210-216.
- Group SC, et al. NEJM 2008; 359:789-799.
- Ho RH, et al. Gastroenterol 2006, 130:1793-1806.
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- Igel M, et al. Clin Pharmacol Ther 2006; 79:419-426.
- Kameyama Y, et al. Pharmacogenet Genomics 2005, 15:513-522.
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- Mwinyi J, et al. Clin Pharmacol Ther 2004; 75:415-421.
- Niemi M, et al. Pharmacogenet 2004; 14:429-440.
- Niemi M, et al. Pharmacogenet Genomics 2005; 15:303-309.
- Niemi M Pharmacogenomics 2007; 8:787-802.
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- Pasanen MK, et al. Pharmacogenet Genomics 2006; 16:873-879.
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- Takane H, et al. J Hum Genet 2006; 51:822-826.
- Thompson JF, et al. Pharmacogenomics J 2005; 5:352-358.
- Tirona RG, et al. J biol chem 2001; 276:35669-35675.
- Voora D, et al. JACC 2009; 54:1609-1616.

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 SLCO1B1/Simvastatin Activity Genotype Version 1 (November 2013)]

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SLCO1B1 GENE TEST FOR SIMVASTATIN RESPONSE

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:**	11/11/2013

NAME OF GENE: SLCO1B1		**LOCATION OF GENE:** 12p12
Variants tested	**RESULT**	**Reference Genotype**
rs72559745 (SLCO1B1*1)	AG	A A
rs56061388 (SLCO1B1*3)	CT	T T
rs4149056 (SLCO1B1*5)	TT	T T
rs55901008 (SLCO1B1*6)	TT	T T
Combined Result^	**SLCO1B1*1/*3**	
^ When the Result for all SLCO1B1 variants tested are the same as the reference, the Combined Result is called SLCO1B1 *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).		

Risk interpretation based on Coriell's SLCO1B1/Simvastatin Response Genotype Translation Version 1 (November 2013).

Interpretation

This individual is expected to have **Intermediate liver uptake activity** based on the Combined Genetic Result: **SLCO1B1*1/*3**

Individuals with intermediate SLCO1B1 liver uptake activity have a moderately increased risk of myopathy when taking a 40 mg/day or higher dose of simvastatin. A reduced dosage or alternate statin drug should be considered.

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 SLCO1B1 gene that are not included in this test, that influence the response to simvastatin (Zocor®). 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.

References

1. Bailey KM, et al. Circ Cardiovasc genet 2010; 3:276-285.
2. Donnelly LA, et al. Clin. Pharmacol Ther 2011; 89:210-216.
3. Group SC, et al. NEJM 2008; 359:789-799.
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20. Tirona RG, et al. J biol chem 2001; 276:35669-35675.
21. Voora D, et al. JACC 2009; 54:1609-1616.