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:**	02/07/2013
Ordering Physician:			

TPMT and Thiopurine 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 common genetic variants in the TPMT gene. Variants in the TPMT gene are known to affect the metabolism of thiopurine drugs such as azathioprine (Imuran®), mercaptopurine (Purinethol®), thioguanine (6-TG, Tabloid® or Lanvis®). People with certain genetic variants may require a lower dose or may be at risk for severe, life threatening, side-effects including bone marrow suppression. This report reflects the participant's predicted TPMT activity level (low/absent, intermediate/reduced, or typical) based on their genetic results but does not reflect whether or not they are currently taking a thiopurine drug. In addition, predicted TPMT activity level does not account for other factors that may influence dosing including age, weight, gender, race, diet and other medications.

The CPMC has genetic counselors 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 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 TPMT gene that affect the way the body responds to thiopurine drugs.

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

TPMT*1/*3C
(TPMT Intermediate (Reduced) Activity)

VARIANTS TESTED	YOUR RESULT	REFERENCE VALUE
rs1142345 (TPMT*3C)	AA	A A
rs1800584 (TPMT*4)	GG	G G
rs1800460 (TPMT*3B)	GG	G G
rs1800462 (TPMT*2)	GG	G G

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

TPMT Intermediate (Reduced) Activity

TPMT * Result: TPMT*1/*3C

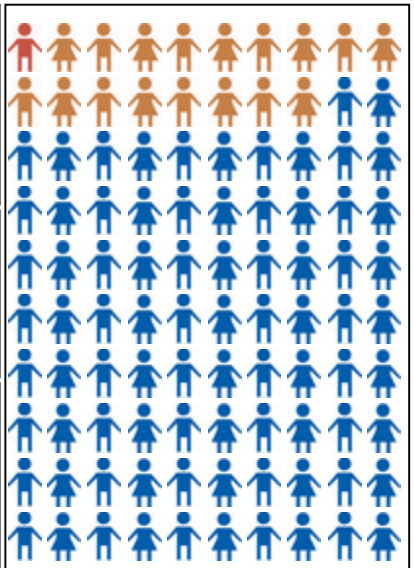
- Your combination of genetic variants is associated with intermediate (reduced) TPMT activity.
- People with intermediate TPMT activity may require a lower dose of a thiopurine drug and may be at an increased risk of bone marrow suppression at a standard dose of a thiopurine drug. Bone marrow suppression is a severe decrease in cells responsible for providing immunity, carrying oxygen, and those responsible for normal blood clotting.
- Talk to your doctor about appropriate monitoring and whether alternative medications are needed.

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 thiopurine activity levels and how common each is in the African Ancestry population.

TPMT Low/Absent Activity **1 out of 100 people** Thiopurine drugs may be toxic. Increased risk of developing severe, life threatening side effects (bone marrow suppression) if prescribed a standard dose.	
TPMT Intermediate (Reduced) Activity **17 out of 100 people** May be at an increased risk for toxicity at a standard dose of a thiopurine drug.	
TPMT Typical Activity **82 out of 100 people** Expected to respond to a standard dose of a thiopurine drug. No increased risk of side effects due to gene status.	

What are Thiopurines?

(examples include: azathioprine (Imuran®), mercaptopurine (Purinethol®), thioguanine (6-TG, Tabloid® or Lanvis®)

Thiopurines are drugs that suppress the normal activity of the body's immune system.

Uses:

- Treatment of lymphoblastic leukemia
- Treatment of autoimmune disorders (including Crohn's disease and rheumatoid arthritis)
- To prevent organ transplant rejection

Risk Factors Affecting Response to Thiopurines

Genetic Risk Factors

Genetic variants, or changes, in a gene called TPMT can affect the way your body processes thiopurine drugs.

Some people with certain genetic variants may require a lower dose or may be at risk for severe, life threatening, side-effects including bone marrow suppression, compared to people without these variants.

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 Thiopurine Activity:

TPMT

Types of Results

There are four common variants in the TPMT gene that are known to affect the gene function. A number system has been created to name combinations of these variants. We all have 2 copies of every gene; when possible, you will have a TPMT result with two numbers.

Example: TPMT *1/*2

TPMT Activity

Each result is associated with an activity level which describes how well the enzyme is working.

Example: intermediate (reduced) activity

Drug-Drug Interactions

In addition to your genes, other medications may affect how your body responds to thiopurine drugs and may increase the risk of side effects when taking thiopurine drugs.

The following medications, when taken with a thiopurine drug, may increase the risk for side effects:

Medication	Also Known As
Allopurinol	Lopurin, Zyloprim
Warfarin	Coumadin, Jantoven
ACE inhibitors	Lotensin, Capoten, Vasotec
Ribavirin	Copegus, Rebetol, RibaTab, RibaSphere
Aminosalicylates	Colazal, Asacol, Dipentum, Azulfidine

- thioguanine (Tabloid®), click here
- azathioprine (Imuran®), click here
- mercaptopurine (Purinethol®), click here

If you are taking a thiopurine drug now, or are prescribed one in the future, talk to your healthcare providers about other medications you are taking that may interact with thiopurine drugs.

Result Limitations

- This result alone does **NOT** predict your response to thiopurine drugs.
- Other factors such as body weight, various health conditions, and other medications may impact an individual's response to thiopurine drugs.
- There may be other genetic variants within the TPMT gene which influence response to thiopurine drugs but are not included in this test.
- There may be other genetic variants in the TPMT gene for which response to thiopurine drugs has not been documented and/or validated in multiple studies.
- There may be genetic variants in other genes that influence response to thiopurine drugs.
- This result reflects published data available at the time this gene-drug pair was approved by the CPMC Informed Cohort Oversight Board (December 2010). 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).

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

- Ansari A, et al. Aliment Pharmacol Ther. 2008; 28(8): 973-83.
- Ansari A, et al. Aliment Pharmacol Ther. 2002; 16(10): 1743-50.
- Anstey A V, et al. Br J Dermatol. 2004; 151(6): 1123-32.
- Black A J, et al. Ann Intern Med. 1998; 129(9): 716-8.
- Dong X W, et al. World J Gastroenterol. 2010; 16(25): 3187-95.
- Higgs J E, et al. Pharmacogenomics. 2010; 11(2): 177-88.
- Kaskas BA, et al. Gut. 2003; 52(1): 140-2.
- Lennard L, et al. Lancet 1990; 336(8709): 225-9.
- Oselin K and Anier K. Drug Metab Dispos. 2007; 35(9): 1452-4.
- Sanderson J, et al. Ann Clin Biochem 2004; 41(Pt 4): 294-302.
- Weinshilboum R M. and Sladek SL. Am J Hum Genet 1980; 32(5): 651-62.

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 TPMT Activity Genotype Translation Version 1 (December 2010)]

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TPMT GENE TEST FOR THIOPURINE 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:**	02/07/2013

NAME OF GENE: TPMT		**LOCATION OF GENE:** 6p22.3
Variants tested	**RESULT**	**Reference Genotype**
rs1142345 (TPMT*3C)	AA	A A
rs1800584 (TPMT*4)	GG	G G
rs1800460 (TPMT*3B)	GG	G G
rs1800462 (TPMT*2)	GG	G G
Combined Result^	**TPMT*1/*3C**	
^ When the Result for all TPMT variants tested are the same as the reference, the Combined Result is called TPMT *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 TPMT Activity Genotype Translation Version 1 (December 2010).

Interpretation

Based on this individual's Combined Genetic Result TPMT*1/*3C, intermediate TPMT activity is expected.

Individuals with intermediate TPMT activity may require a lower dose of a thiopurine drug and may be at an increased risk of bone marrow suppression at a standard dose of a thiopurine drug. A reduced dosage or alternate immunosuppressant therapy 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 TPMT gene that are not included in this test, that influence the response to thiopurine drugs. 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. Ansari A, et al. Aliment Pharmacol Ther. 2008; 28(8): 973-83.
2. Ansari A, et al. Aliment Pharmacol Ther. 2002; 16(10): 1743-50.
3. Anstey A V, et al. Br J Dermatol. 2004; 151(6): 1123-32.
4. Black A J, et al. Ann Intern Med. 1998; 129(9): 716-8.
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