

Overview

Useful For

Detection of individuals with low thiopurine methyltransferase (TPMT) activity who are at risk for excessive myelosuppression or severe hematopoietic toxicity when taking thiopurine drugs

Detection of individuals with hyperactive TPMT activity who have therapeutic resistance to thiopurine drugs and may develop hepatotoxicity if treated with these drugs

Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

Highlights

Individuals who are either homozygous or heterozygous for thiopurine methyltransferase (TPMT) deficiency are at risk of developing life-threatening myelosuppression or severe hematopoietic toxicity when placed on standard doses of azathioprine (Imuran), 6-mercaptopurine (Purinethol), or 6-thioguanine (Thioguanine Tabloid).

Individuals who have TPMT hyperactivity cannot achieve therapeutic levels with thiopurine drugs, and they may develop hepatotoxicity due to treatment with thiopurine drugs.

Determining a patient's TPMT status prior to starting therapy with a thiopurine drug is, therefore, important for purposes of calculating the optimal drug dosage.

Method Name

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Whole blood

Specimen Required

Patient Preparation: Thiopurine methyltransferase (TPMT) enzyme activity can be inhibited by several drugs and may contribute to falsely low results. Patients should abstain from the following drugs for at least 48 hours prior to TPMT testing: naproxen (Aleve), ibuprofen (Advil, Motrin), ketoprofen (Orudis), furosemide (Lasix), sulfasalazine (Azulfidine), mesalamine (Asacol), olsalazine (Dipentum), mefenamic acid (Ponstel), trimethoprim (Proloprim), methotrexate, thiazide diuretics, and benzoic acid inhibitors.

Container/Tube:

Preferred: Lavender top (EDTA)

Acceptable: Green top (sodium or lithium heparin), navy blue top (metal free sodium heparin), or plasma gel tubes

Specimen Volume: 5 mL

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on

file. The following documents are available in Special Instructions:

[-Informed Consent for Genetic Testing \(T576\)](#)

[-Informed Consent for Genetic Testing-Spanish \(T826\)](#)

2. If not ordering electronically, complete, print, and send [Gastroenterology and Hepatology Client Test Request \(T728\)](#) with the specimen

Reject Due To

Gross hemolysis Reject

Specimen Minimum Volume

3 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Refrigerated (preferred)	6 days	
	Ambient	6 days	

Clinical & Interpretive

Clinical Information

Thiopurine methyltransferase (TPMT) deficiency is a condition in which patients treated with standard doses of azathioprine (AZA, Imuran), 6-mercaptopurine (6-MP, Purinethol), or 6-thioguanine (6-TG, Thioguanine Tabloid) may develop life-threatening myelosuppression or severe hematopoietic toxicity. The metabolic conversion of AZA, 6-MP, or 6-TG to purine nucleotides and the subsequent incorporation of these nucleotides into DNA play an important role in both the therapeutic efficacy and the toxicity of these drugs. A competitive catabolic route for the metabolism of thiopurines is catalyzed by the TPMT enzyme, which inactivates them by thiomethylation. A balance must be established between these competing metabolic pathways so that: 1) sufficient amounts of drug are converted to the nucleotide to act as an antimetabolite and 2) the antimetabolite levels do not become so high as to cause potentially lethal bone marrow suppression.

TPMT deficiency is an autosomal recessive condition with an incidence of approximately 1 in 300 individuals homozygous for deleterious variants in the *TPMT* gene; about 10% of the population are heterozygous carriers of *TPMT* variants. Adverse effects of AZA, 6-MP, or 6-TG administration can be observed in individuals who are either homozygous or heterozygous for TPMT deficiency.

TPMT hyperactivity is also a known phenotype. Individuals who are hypermetabolizers have therapeutic resistance to thiopurine drugs and therefore, cannot achieve therapeutic levels. If an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs, they may develop severe hepatotoxicity. Therefore, treatment with alternative medications is recommended for hypermetabolizers.

As such, knowing a patient's TPMT status prior to treatment with AZA, 6-MP, or 6-TG is important for purposes of calculating safe drug dosages for therapy.

Reference Values

3.00-6.66 nmol/mL/hour 6-Methylmercaptopurine (normal)

5.04-9.57 nmol/mL/hour 6-Methylmercaptopurine riboside (normal)

2.70-5.84 nmol/mL/hour 6-Methylthioguanine riboside (normal)

Interpretation

This assay is used to detect individuals with low and intermediate thiopurine methyltransferase (TPMT) activity who may be at risk for myelosuppression when exposed to standard doses of thiopurines, including azathioprine (Imuran), 6-mercaptopurine (Purinethol), or 6-thioguanine (Thioguanine Tabloid). TPMT is the primary metabolic route for inactivation of thiopurine drugs in the bone marrow. When TPMT activity is low, it is predicted that proportionately more 6-mercaptopurine can be converted into the cytotoxic 6-thioguanine nucleotides that accumulate in the bone marrow causing excessive toxicity. This test can also detect TPMT hyperactivity. Individuals who are hypermetabolizers have therapeutic resistance to thiopurine drugs, and therefore they cannot achieve therapeutic levels. If an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs, they may develop severe hepatotoxicity.

The activity of TPMT is measured by 3 different substrates. Reports include the quantitative activity level of TPMT for each of 3 different substrates and an interpretation of these results. When abnormal results are detected, a detailed interpretation is given, including an overview of results and suggestion as to whether patient has TPMT deficiency or hyperactivity, as well as discussion of treatment considerations.

TPMT phenotype testing does not replace the need for clinical monitoring of patients treated with thiopurine drugs. Genotype for TPMT cannot be inferred from TPMT activity (phenotype). Phenotype testing should not be requested for patients currently treated with thiopurine drugs.

TPMT activity is measured in red blood cells. If a patient has had a blood transfusion within 30 to 60 days of testing, the patient's true enzyme activity may not be accurately reflected.

Cautions

Falsely low results may occur as a result of inappropriate specimen handling and hemolysis.

Patients with acute lymphoblastic leukemia may have lower thiopurine methyltransferase activities before treatment and higher activities following treatment.

Clinical Reference

1. Relling MV, Gardner EE, Sandborn WJ, et al: Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther.* 2011 Mar;89(3):387-391
2. Lennard L: Implementation of TPMT testing. *Br J Clin Pharmacol.* 2014 Apr;77(4):704-714
3. Schedel J, Godde A, Schutz E, et al: Impact of thiopurine methyltransferase activity and 6-thioguanine nucleotide concentrations in patients with chronic inflammatory diseases. *Ann N Y Acad Sci.* 2006 Jun;1069:477-491
4. Zhou S: Clinical pharmacogenomics of thiopurine S-methyltransferase. *Curr Clin Pharmacol.* 2006 Jan;1(1):119-128
5. Asadov C, Aliyeva G, Mustafayeva K: Thiopurine S-methyltransferase as a pharmacogenetic biomarker: Significance of testing and review of major methods. *Cardiovasc Hematol Agents Med Chem.* 2017 Nov 8;15(1):23-30

Performance**Method Description**

Red blood cell lysate is incubated in a multi-substrate cocktail. The enzymatically generated thiomethylated products are measured by liquid chromatography tandem mass spectrometry to produce an activity profile for thiopurine methyltransferase.(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

Residual whole blood: 14 days; Processed specimen: 2 months

Performing Laboratory Location

Rochester

Fees & Codes**Test Classification**

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

82657