

## 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

### Testing Algorithm

For more information see:

[-Ulcerative Colitis and Crohn Disease Therapeutic Drug Monitoring Algorithm](#)

[-TPMT Testing in the Treatment of Inflammatory Bowel Disease Algorithm](#)

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Ulcerative Colitis and Crohn Disease Therapeutic Drug Monitoring Algorithm](#)
- [TPMT Testing in the Treatment of Inflammatory Bowel Disease Algorithm](#)

### 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), dark 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:

-[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 Test Request](#) (T728) with the specimen

## Specimen Minimum Volume

3 mL

## Reject Due To

Gross hemolysis	Reject
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## 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 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

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between these competing metabolic pathways so that sufficient amounts of drug are converted to the nucleotide to act as an antimetabolite and 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**

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

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

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

**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 cannot achieve therapeutic levels as they have therapeutic resistance to thiopurine drugs. Severe hepatotoxicity may develop if an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs.

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 60 days of testing, the

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patient's true enzyme activity may not be accurately reflected.

**Cautions**

Falsely low results may occur due to inappropriate specimen handling or 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;89(3):387-391
2. Lennard L. Implementation of TPMT testing. *Br J Clin Pharmacol.* 2014;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;1069:477-491
4. Zhou S. Clinical pharmacogenomics of thiopurine S-methyltransferase. *Curr Clin Pharmacol.* 2006;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;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

**Day(s) Performed**

Monday, Wednesday, Friday

**Report Available**

4 to 7 days

**Specimen Retention Time**

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

**Performing Laboratory Location**

Rochester

**Fees & Codes**

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**Fees**

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

**Test Classification**

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

**CPT Code Information**

84433

**LOINC® Information**

Test ID	Test Order Name	Order LOINC® Value
TPMT3	TPMT Activity Profile, RBC	91139-6

Result ID	Test Result Name	Result LOINC® Value
48038	Interpretation	59462-2
48034	6-Methylmercaptopurine	91141-2
48035	6-Methylmercaptopurine riboside	91142-0
48036	6-Methylthioguanine riboside	91143-8
48037	Reviewed By	18771-6