Thiopurine Methyltransferase, RBC

Thiopurine drug therapy is used to treat autoimmune diseases, inflammatory bowel disease, acute lymphoblastic leukemia, and to prevent rejection after solid organ transplant.[1] The inactivation of thiopurine drugs is catalyzed in part by thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15).[1,2,3]

This test fact sheet focuses on enzyme activity phenotype testing for TPMT, which can be measured directly prior to drug administration. After the initiation of therapy, concentrations of thiopurines and metabolites can be measured to optimize thiopurine therapy dosing. Genetic testing for *TPMT* and *NUDT15* variants can be performed prior to or during thiopurine therapy. For more information on thiopurine metabolite and genetic testing, refer to the Thiopurine Metabolites in Red Blood Cells and *TPMT* and *NUDT15* Test Fact Sheets.

Featured ARUP Testing

Thiopurine Methyltransferase, RBC 0092066

Method: Enzymatic Assay/Quantitative Liquid Chromatography-Tandem Mass Spectrometry

Use this phenotypic test to assess risk for severe myelosuppression with standard dosing of thiopurine drugs in individuals for whom thiopurine therapy is being considered. This test must be performed prior to the initiation of thiopurine therapy. This test may also be used to detect the rapid thiopurine metabolizer phenotype.

Disease Overview

Thiopurine drugs include azathioprine, mercaptopurine, and thioguanine.[1,2] These are inactive prodrugs that must be metabolized to 6-thioguanine nucleotides (6-TGN) to function.[1,2] The primary metabolic route for inactivation of thiopurine drugs is catalyzed by TPMT.[2] TPMT can be inhibited by common drugs, including NSAIDs, diuretics, and ulcerative colitis treatments such as mesalamine.

When TPMT activity is low, more 6-MP may be converted into active (cytotoxic) 6-TGN, which accumulates in the body.[2] Excess 6-TG in bone marrow (BM) inhibits purine synthesis, which in turn inhibits cell proliferation and contributes to excessive myelosuppression.[2] Specific TPMT variants (seen with higher frequency among individuals of African and European descent) have been associated with TPMT deficiency of varying severity.[2,3] In individuals with no or very low TPMT activity, severe myelosuppression occurs with conventional thiopurine doses.[2,3] Thirty to sixty percent of individuals with intermediate TPMT experience moderate to severe myelosuppression with conventional thiopurine doses.[2,3]

Thiopurine dosing should rely on disease-specific guidelines and the degree of myelosuppression; refer to the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for thiopurine dosing based on TPMT and NUDT15 genotypes.

Test Interpretation

Results

TPMT Activity With Standard Dosing of Thiopurine Drugs			
Activity	**Range**	**Predicted Risk of Bone Marrow Toxicity (Myelosuppression)**	**Recommended Thiopurine Dose Adjustments**
Normal	24.0-44.0 U/mL	Low	None
Low	<17.0 U/mL	High	Do not use thiopurine drugs
Intermediate	17-23.9 U/mL	Intermediate	Consider dose reduction Manage carefully
High	>44.0 U/mL	None	Consider dose increase Manage carefully

Limitations

- This test does not replace the need for therapeutic drug monitoring and clinical observation.
- TPMT inhibitors may contribute to falsely low phenotype test results.
- TPMT phenotype should be assessed prior to treatment with thiopurine drugs.
- Blood transfusion within 30 days may reflect donor status.

References

1. Bayoumy AB, Crouwel F, Chanda N, et al. Advances in thiopurine drug delivery: the current state-of-the-art. *Eur J Drug Metab Pharmacokinet*. 2021;46(6):743-758.

2. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther*. 2019;105(5):1095-1105.

3. Pratt VM, Cavallari LH, Fulmer ML, et al. TPMT and NUDT15 genotyping recommendations: a joint consensus recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. *J Mol Diagn*. 2022;24(10):1051-1063.

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