TPMT and NUDT15

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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] Variants in the *TPMT* and/or *NUDT15* genes are associated with an accumulation of cytotoxic metabolites leading to increased risk of drug-related toxicity with standard doses of thiopurine drugs,[2,3] and the effects on thiopurine catabolism can be additive.

This Test Fact Sheet focuses on genetic testing for *TPMT* and *NUDT15* variants, which can be performed prior to or during thiopurine therapy. The enzyme activity phenotype of TPMT 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. For more information about these tests, refer to the Thiopurine Methyltransferase, RBC and Thiopurine Metabolites in Red Blood Cells Test Fact Sheets.

Featured ARUP Testing

TPMT and NUDT15 3001535

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

Use this genotyping test to assess genetic risk for severe myelosuppression with standard dosing of thiopurine drugs in individuals for whom thiopurine therapy is being considered or who have had an adverse reaction to thiopurine therapy. This test can be performed irrespective of whether thiopurine therapy is currently being administered.

TPMT and *NUDT15* are also available as standalone tests:

TPMT Genotyping 3017372

Method: Polymerase Chain Reaction (PCR)/Flourescence Monitoring

NUDT15 Genotyping 3017373

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

Disease Overview

Thiopurine drugs include azathioprine, mercaptopurine, and thioguanine.[1,2] These are inactive prodrugs that must be metabolized to 6-thioguanine nucleotides (6-TGNs) 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-mercaptopurine (6-MP) may be converted into active (cytotoxic) 6-TGN, which accumulates in the body.[2] Excess 6-TGN 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 activity experience moderate to severe myelosuppression with conventional thiopurine doses.[2,3]

NUDT15 catalyzes the conversion of cytotoxic 6-TG triphosphate metabolites to the less toxic 6-TG monophosphate.[2] *NUDT15* variants (seen with higher frequency among individuals of Asian and Hispanic descent) reduce enzyme activity and contribute to excessive myelosuppression.[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.

Genetics

Genes

TPMT, *NUDT15*

Inheritance

TPMT: Autosomal codominant[2]

NUDT15: Autosomal codominant

Test Interpretation

Variants Tested

TPMT and *NUDT15*: Variants Tested	
Gene (Transcript)	**Allele**
TPMT (NM_000367)	*TPMT*2*: rs1800462, c.238G>C
	*TPMT*3A*: rs1800460, c.460G>A; rs1142345, c.719A>G
	*TPMT*3B*: rs1800460, c.460G>A
	*TPMT*3C*: rs1142345, c.719A>G
	*TPMT*4*: rs1800584, c.626-1G>A
NUDT15 (NM_018283)	*NUDT15*2* or **3*: rs116855232, c.415C>T
	*NUDT15*4*: rs147390019, c.416G>A

Allele frequencies and phenotype predictions are available at www.pharmvar.org or www.pharmgkb.org.

Sensitivity/Specificity

- Clinical sensitivity: 95%[4,5]
- Analytic sensitivity/specificity: 99%

Results

Metabolizer status is reported separately for each gene analyzed.

TPMT and *NUDT15*: Results Interpretation	
***TPMT* Results**	
Number of *TPMT* Variants Detected	**Interpretation**
One	Intermediate metabolizer phenotype predicted Possible susceptibility to dose-related toxicity from standard doses of thiopurine drugs
Two	Poor metabolizer phenotype predicted Probable susceptibility to dose-related toxicity from standard doses of thiopurine drugs
Zero (reported as Negative)	Normal metabolizer phenotype predicted Standard doses of thiopurine drugs are likely appropriate
***NUDT15* Results**	
Number of *NUDT15* Variants Detected[a]	**Interpretation**
One	Intermediate metabolizer phenotype predicted Possible susceptibility to dose-related toxicity from standard doses of thiopurine drugs
Two	Poor metabolizer phenotype predicted Probable susceptibility to dose-related toxicity from standard doses of thiopurine drugs
Zero (reported as Negative)	Normal metabolizer phenotype predicted Standard doses of thiopurine drugs are likely appropriate

TPMT Results	
Number of *TPMT* Variants Detected	Interpretation

[a]The *NUDT15*4* variant is of uncertain function and can result in an indeterminate metabolizer status.

Limitations

- Only targeted *TPMT* and *NUDT15* variants will be detected by this test.
- Diagnostic errors can occur due to rare sequence variations.
- Genotyping in individuals who have received an allogeneic stem cell or bone marrow transplant will reflect donor status and is not recommended.
- Because the complex *TPMT*3A* allele contains the variants found in the **3B* and **3C* alleles, genotyping cannot distinguish the **3A*/negative genotype (intermediate TPMT activity) from the rare **3B*/**3C* genotype (no or low TPMT activity); the **3A*/negative genotype is assumed when both **3B* and **3C* are detected.
- Thiopurine drug metabolism and risk for adverse reactions to thiopurines may be affected by genetic and nongenetic factors that are not evaluated by this test.
- This test does not assess for *TPMT* allele variants associated with ultrahigh enzyme activity.
- Genotyping does not replace the need for therapeutic drug monitoring and clinical observation.

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.

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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.

4. Evans WE. Pharmacogenetics of thiopurine S-methyltransferase and thiopurine therapy. *Ther Drug Monit*. 2004;26(2):186-191.

5. Yates CR, Krynetski EY, Loennechen T, et al. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. *Ann Intern Med*. 1997;126(8):608-614.

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