

TPMT Mutation Analysis

For rapid identification of poor thiopurine metabolizers

Overview

Variability in Drug Metabolism

Drug metabolism can vary significantly between individuals. Patients given similar dosages can have widely divergent results due to **genetic polymorphisms** in the enzyme(s) responsible for metabolizing that class of drug. Identifying genetic polymorphisms that affect drug metabolism can significantly increase therapeutic efficacy through individualized drug and dosage selection, and decrease the potential for negative side effects.¹ An important example of this is the thiopurine S-methyltransferase (TPMT) genetic polymorphism, which can negatively influence tolerance to thiopurine-based drugs, causing dosage-related hematopoietic toxicity, myelosuppression and possibly death.^{2,3}

TPMT Enzymatic Activity & Drug Toxicity

TPMT is the primary enzyme responsible for **thiopurine drug-based metabolism** (see Table 1). Enzyme activity, deficient or otherwise, is inherited but is subject to individual and ethnic variability. TPMT enzyme activity determines the amount of thiopurine-based drugs that are able to be metabolized.⁴ Patients with low TPMT enzyme activity (poor metabolizers) are considered TPMT-deficient and at high risk for dosage-related side-effects.⁵ TPMT-deficient patients accumulate higher concentrations of thiopurines when they receive standard dosages, greatly

increasing the potential for drug-induced toxicity.^{1,5} Approximately 90% of the population have high TPMT enzyme activity, 10% have intermediate and 1 in 300 have low.^{5,6} Essentially all TPMT-deficient patients will develop hematopoietic toxicity upon administration of conventional thiopurine dosages.²

Mutation Analysis

Mutation analysis provides a simple and reliable method for **identifying at-risk patients** who may benefit from thiopurine dosage reduction to avoid life-threatening hematopoietic toxicity or treatment failure.⁷ Mutant haplotypes G238C (TPMT*2), G460A and A719G (TPMT*3A), G460A (TPMT*3B) and A719G (TPMT*3C) account for 95% of TPMT mutations in Caucasian, African-American and Asian populations, and are responsible for 80-95% of low and intermediate TPMT enzyme activity.^{4,5} Patients who are heterozygous for one mutant haplotype have intermediate levels of metabolism relative to normal individuals. Patients with homozygous mutations and patients heterozygous for two different mutant haplotypes have low or deficient TPMT metabolism. The ability to optimize thiopurine dosages in TPMT-deficient patients increases therapeutic efficacy equal to that of patients with normal TPMT activity.¹

Clinical Utility

- ?? Helps identify patients who will benefit from a substantial decrease in dosage⁷
- ?? Pre-therapy identification of at-risk patients allows for drug adjustment, maximizing therapeutic efficacy^{4,5}
- ?? TPMT status is an early indicator of bone marrow toxicity and dose-related myelosuppression in at-risk patients⁸
- ?? Approximately 40% of Inflammatory Bowel Disease patients receiving 6-MP/Azathioprine (AZA) therapy either fail to respond or are intolerant³
- ?? In AZA-treated Rheumatoid Arthritis patients, intermediate TPMT activity is indicative of severe side effects, necessitating cessation of therapy⁹

Ordering Information & Specimen Requirements

Test Code	Test Name	Specimen Requirements
5353	TPMT Mutation Analysis G238C, G460A, A719G	5 mL Whole Blood ACD or EDTA; Ambient. Ship immediately by overnight courier. DO NOT FREEZE.
<i>Specify "Send TPMT Mutation Analysis to Specialty Laboratories"</i>		

For immediate attention and sample pick-up, call 800-421-4449.

Methodology

INVADER²-based detection of the normal and mutant TPMT alleles in genomic DNA

Table 1. Thiopurine-based Drugs & Their Uses^{4,5}

Drug	Disease Area
6-MP (Purinethol [®])	Leukemias – AML, ALL
6-MP Azathioprine (Imuran [®])	Inflammatory Bowel Disease – Crohn's Disease
Azathioprine (Imuran [®])	Rheumatoid Arthritis
Azathioprine (Imuran [®])	Organ Transplant Recipients
Azathioprine (Imuran [®])	Autoimmune Hepatitis

References

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4. Evans WE, Hon YY, Bomgaars L, et al. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine and azathioprine. *J Clin Oncol* 2001;19:2293-301.
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6. McLeod HL, Siva C. The thiopurine S-methyltransferase gene locus – implications for clinical pharmacogenomics. *Pharmacogenomics* 2002;3:89-98.
7. Colombel J-F, Ferrari N, Debuysere H, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology* 2000;118:1025-30.
8. Lennard L. TPMT in the treatment of Crohn's disease with azathioprine. *Gut* 2002;51:143-6.
9. Stolk JN, Boerbooms AMT, de Abreu RA, et al. Reduced thiopurine methyltransferase activity and development of side effects of azathioprine treatment in patients with rheumatoid arthritis. *Arthritis Rheum* 1998;41:1858-66.

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www.specialtylabs.com and sign-up for our e-mail notification program.**