Thiopurine S-Methyltransferase (*TPMT*) Genotyping

Disease Overview

Thiopurine drugs must be converted to thioguanine nucleotides, a process which may be interfered with by the presence of thiopurine S-methyltransferase (TPMT). In patients with reduced TPMT activity, thioguanine nucleotides can accumulate and result in myelosuppression.

Variants in the *TPMT* gene (6p22.3) can lead to reduced *TPMT* activity. Four variant alleles have been identified which are responsible for over 90% of reduced *TPMT* activity.

Uses for Test

- Identify patients who are at risk for abnormal drug metabolism and toxicity from thiopurine drugs metabolized by thiopurine S-methyltransferase (TPMT), including azathioprine, 6-mercaptopurine, and thioguanine.
- Identify genotypes shown to have a drug-gene variant relationship.
- Pharmacogenomic orders may be reviewed by a pharmacist for clinical appropriateness prior to test completion if clinical data is available.

Therapeutic Implications

TPMT genotyping may be used to help predict thiopurine drug toxicity thus helping identify patients at increased risk of hematologic toxicity.

Treatment Guidelines

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing guidelines for *TPMT* genotypes: https://cpicpgx.org/

Test Interpretation

- Clinical sensitivity: drug dependent
- Analytical sensitivity/specificity: 99%

Results

A detailed report is provided. This report is reviewed and signed out by the Laboratory Director.

No mutations detected is predictive for *1 functional alleles.

Test Limitations

- Only the targeted *TPMT* variants will be detected.
- Diagnostic errors can occur due to rare sequence variations.
- Because the *3A allele contains both of the variants found in the *3B and *3C alleles, this test cannot distinguish the *3A/negative genotype (intermediate enzyme activity) from the rare *3B/*3C genotype (no or low enzyme activity).
- *TPMT* enzyme activity, drug metabolism and risk for adverse reactions to thiopurines may be affected by additional genetic and non-genetic factors not evaluated by this test.
- This result does not replace the need for therapeutic drug or clinical evaluation and monitoring.

Related Tests

- Multiple genes can be involved in drug metabolism, drug activation and drug action on the target tissue. Additional genotyping tests are available for *CYP2D6, CYP2C19, CYP2C9, VKORC1, SLCO1B1, IFNL3, CYP4F2, CYP2C cluster, CYP3A5* and *DPYD* as individual tests or as a PGx Panel.
- The panel includes a comprehensive medication report based on the genotypes detected.
- Therapeutic drug monitoring and/or metabolic ratios may be useful for evaluating the pharmacokinetics of a particular drug, for a particular patient.

Sample Requirements

Collection

- Lavender-top tube (EDTA)
- All specimens should be sent in the original container and should not be aliquoted to another tube
- The specimen submitted should only be used for this testing and should not be shared with any other testing that would also utilize this specimen type

Specimen

- Whole blood, preferred Volume: 2 mL to 4 mL (1mL minimum)

Stability

- Room temp – 72 hours
- Refrigerated – 7 days
- Frozen – 7 days
- Not affected by hemolysis
- Not affected by lipemia

Tests Involved

- Thiopurine S-methyltransferase *(TPMT)* genotyping: 5 variants
- CPT code: 81335
- Lab Test ID: LBOR0150

Test Schedule

- Set up Monday to Friday
- Turn Around Time: 5-7 days

Additional information

- These tests are available through the Sanford Imagenetics program. Contact Sanford Laboratories at (605) 328-5464 or (800) 522-2561 for questions regarding this testing.

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References

• NIH, U.S. National Library of Medicine, Genetics Home Reference https://ghr.nlm.nih.gov/ • Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, Stein CM, Carrillo M, Evans WE, Klein TE; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther. 2011 Mar;89(3):387-91. doi: 10.1038/clpt.2010.320. Epub 2011 Jan 26. Erratum in: Clin Pharmacol Ther. 2011 Dec;90(6):894. • Cooper SC, Ford LT, Berg JD, Lewis MJ. Ethnic variation of thiopurine S-methyltransferase activity: a large, prospective population study. Pharmacogenomics. 2008 Mar;9(3):303-9. doi: 10.2217/14622416.9.3.303. • Black AJ, McLeod HL, Capell HA, Powrie RH, Matowe LK, Pritchard SC, Collie-Duguid ES, Reid DM. Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. Ann Intern Med. 1998 Nov 1;129(9):716-8. • Coulthard S, Hogarth L. The thiopurines: an update. Invest New Drugs. 2005 Dec;23(6):523-32. Review. • Evans WE, Hon YY, Bomgaars L, Coutre S, Holdsworth M, Janco R, Kalwinsky D, Keller F, Khatib Z, Margolin J, Murray J, Quinn J, Ravindranath Y, Ritchey K, Roberts W, Rogers ZR, Schiff D, Steuber C, Tucci F, Kornegay N, Krynetski EY, Relling MV. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. J Clin Oncol. 2001 Apr 15;19(8):2293-301. • Fotoohi AK, Coulthard SA, Albertioni F. Thiopurines: factors influencing toxicity and response. Biochem Pharmacol. 2010 May 1;79(9):1211-20. doi: 10.1016/j.bcp.2010.01.006. Epub 2010 Jan 21. • Lennard L. Implementation of TPMT testing. Br J Clin Pharmacol. 2014 Apr;77(4):704-14. doi: 10.1111/bcp.12226. • Schwab M, Schäffeler E, Marx C, Fischer C, Lang T, Behrens C, Gregor M, Eichelbaum M, Zanger UM, Kaskas BA. Azathioprine therapy and adverse drug reactions in patients with inflammatory bowel disease: impact of thiopurine S-methyltransferase polymorphism. Pharmacogenetics. 2002 Aug;12(6):429-36. • Stanulla M, Schaeffeler E, Flohr T, Cario G, Schrauder A, Zimmermann M, Welte K, Ludwig WD, Bartram CR, Zanger UM, Eichelbaum M, Schrappe M, Schwab M. Thiopurine methyltransferase (TPMT) genotype and early treatment response to mercaptopurine in childhood acute lymphoblastic leukemia. JAMA. 2005 Mar 23;293(12):1485-9.

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