TPMT Testing for Thiopurine Drug Response

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is thiopurine drug toxicity

Definition

These drugs have a relatively narrow therapeutic window and adverse drug reactions are frequent, with estimates ranging from 5% to 40%.1-2 Drug toxicity can result in myelosuppression or hepatotoxicity, and can be life-threatening.3 People taking thiopurine should have regular complete blood cell count (CBC) monitoring.4

- The thiopurine drugs – azathioprine (AZA), 6-mercaptopurine (6-MP), and 6-thioguanine (6-TG) – are commonly used to treat hematological malignancies, autoimmune conditions, inflammatory bowel disease, and solid organ transplant rejections.1
- These drugs are metabolized by the enzyme TPMT (thiopurine methyltransferase). Genetic variants in the TPMT gene are associated with lower enzyme activity, leading to an increased risk for drug toxicity.3
- TPMT enzyme activity is largely influenced by polymorphisms (changes) in the TPMT gene. About 29 TPMT variants have been identified. TPMT*2, TPMT*3A, TPMT*3C and account for 85-90% of intermediate or low TPMT enzyme activity.5
- About 1 in 300 (0.3%) people have deficient or undetectable TPMT activity, 11% have low (intermediate) activity and 89% have normal activity. Evidence of a fourth
group of ultra-high TPMT activity has recently been found in about 2% of the population.\textsuperscript{4-6}

- The overall distribution of low, intermediate and normal TPMT activity does not appear to vary among Caucasians, Asians or African-Americans. However, the TPMT variants are not equally distributed among ethnic populations. The frequency of the variant alleles for which commercial genetic testing is currently available is highest in Caucasians and African-Americans. These variants are less common in Southeast (Indonesian, Thai, Filipino, Taiwanese) and Southwest (Indian, Pakistani) Asians.\textsuperscript{4,7}

- TPMT activity can account for up to 75% of the cases of neutropenia associated with thiopurines. People with absent TPMT activity treated with normal doses of thiopurines are at approximately 100% risk of developing severe or fatal myelosuppression.\textsuperscript{7} People with low TPMT activity have a 30-40% risk of developing adverse reactions to thiopurines when treated with standard doses.\textsuperscript{7}

**Test information**

- **Phenotyping** quantifies TPMT enzyme activity. Testing laboratories generally interpret results as normal, intermediate, or low. Some also report a high enzyme activity level. Phenotyping will detect any lowered enzyme activity, regardless of the specific underlying genetic variation. However, phenotyping results may not be accurate for:
  - People who have received recent blood transfusions (within the last four months).\textsuperscript{4}
  - People currently treated with thiopurine drugs.\textsuperscript{4}
  - People currently taking drugs that inhibit TPMT, including: naproxen, ibuprofen, ketoprofen, furosemide, sulfasalazine, mesalamine, olsalazine, mefenamic acid, thiazide diuretics, and benzoic acid inhibitors. Patients should abstain from these drugs for at least 48 hours prior to blood collection.\textsuperscript{2}

- **Genotyping** for TPMT sensitivity is done by targeted analysis for the most common variant alleles. TPMT\textsuperscript{*1} is the normal (wild-type) allele; the TPMT\textsuperscript{*2}, *3A, *3B, and *3C alleles are variants common in the general population. Genetic test results are not affected by medication use or blood transfusion.

  - Although FDA labeling for thiopurine drugs does not specify a testing method, phenotyping (for enzyme activity) is more common and preferred over genotyping (identifying specific variants), in the absence of a contraindication.\textsuperscript{6}

**Guidelines and evidence**

- The US Food and Drug Administration (2004) revised the labeling for azathioprine, 6-mecaptopurine and 6-thioguanine:
o Azathioprine: “It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are TPMT*2, TPMT*3A and TPMT*3C. Patients with two non-functional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. TPMT testing may also be considered in patients with abnormal CBC results that do not respond to dose reduction. Early drug discontinuation in these patients is advisable.”

o 6-mecaptopurine (6-MP): “Homozygous-deficient patients (two non-functional alleles), if given usual doses of Mercaptopurine, accumulate excessive cellular concentrations of active thioguanine nucleotides predisposing them to Mercaptopurine toxicity. Heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active thioguanine nucleotides than people with normal TPMT activity and are more likely to experience Mercaptopurine toxicity. TPMT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TPMT activity.”

o 6 thioguanine (6-TG): “There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of Thioguanine and prone to developing rapid bone marrow suppression following the initiation of treatment. Substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in these patients. Prescribers should be aware that some laboratories offer testing for TPMT deficiency.”

• Guidelines from the American College of Gastroenterology (2010) and the American Gastroenterological Association (2017) mirror the FDA recommendations and support testing of TPMT activity for people treated with thiopurines.

• Ideally, TPMT activity testing should occur prior to initiating treatment with thiopurines, so that alternative treatment strategies can be considered in those at higher risk for toxicity.

• Thiopurine use in patients with deficient TPMT activity is contraindicated.

• Patients with intermediate TPMT activity should be treated with a reduced dose. Some guidelines have suggested a reduction of 50-67%.

• TPMT testing may also be considered in patients with abnormal blood cell counts or when clinical evidence of severe toxicity does not respond to dose reduction.

• The TARGET trial (TPMT: Azathioprine Response to Genotyping and Enzyme Testing) was a randomized controlled trial evaluating TPMT genotyping prior to treatment with azathioprine. Results from this trial indicated that individuals with homozygous TPMT variants were at risk for severe neutropenia whereas
heterozygotes were not at increased risk when taking standard doses of azathioprine.  

Criteria
TPMT testing by phenotyping or genotyping is indicated in individuals considering treatment with any thiopurine drug:

- azathioprine (AZA, Imuran®, Azasan®)
- 6-mercaptopurine (6-MP, Mercaptopurinum®, Purinethol®)
- thioguanine (6-TG, Tabloid®, Thioguanine®)

References

