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<th>Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines</th>
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**Preauthorization is required.**

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

The use of thiopurines, medications for treating inflammatory bowel disease (IBD) and other conditions, is limited by a high rate of drug toxicity. Susceptibility to drug toxicity has been linked to the level of activity of the enzyme thiopurine methyltransferase (TPMT), which converts thiopurines into metabolites. This variation in TPMT activity has been related to three distinct TPMT mutations. Pharmacogenomic analysis of TPMT status is proposed to identify patients at risk of thiopurine drug toxicity and adjust medication doses accordingly.

Measurement of metabolite markers has also been proposed.

**Summary of Evidence**

There are a large number of studies on the diagnostic performance of TMPT genotyping and phenotyping tests. A meta-analysis found a pooled sensitivity of about 80% and specificity near 100% for identifying patients with subnormal enzymatic activity. In addition, studies have found a greater likelihood of adverse drug reactions with low TPMT activity. One randomized controlled trial reporting evidence on health outcomes was identified; this study did not find a significant difference in outcomes in patients managed with and without TPMT genotyping testing, but the study may have been underpowered. One-time genotype or phenotype testing is considered medically necessary in select patients.

There is insufficient evidence from prospective studies on whether metabolite markers will lead to improved outcomes (primarily improved disease control and/or less adverse drug effects). Findings of studies evaluating the association between metabolite markers and clinical remission are mixed, and no prospective comparative trials have compared health outcomes in patients managed with metabolite markers compared with current approaches to care. Thus, analysis of metabolite markers is considered investigational.

**Policy**

One-time genotypic or phenotypic analysis of the enzyme TPMT may be considered medically necessary in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) OR in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction.

Genotypic and/or phenotypic analysis of the enzyme TPMT is considered investigational in all other situations.
Analysis of the metabolite markers of AZA and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is considered **investigational**.

**Policy Guidelines**

TPMT testing cannot substitute for complete blood count (CBC) monitoring in patients receiving thiopurines. Early drug discontinuation may be considered in patients with abnormal CBC results. Dosage reduction is recommended in patients with reduced TPMT activity. Alternate therapies may need to be considered for patients who have low or absent TPMT activity (homozygous for non-functional alleles). Accurate phenotyping results are not possible in patients who received recent blood transfusions. Genotyping and phenotyping of TPMT would only need to be performed once.

**Background**

Thiopurines or purine analogs are immunomodulators. They include azathioprine (AZA; Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, IBD and are used in solid organ transplantation. In particular, they are considered an effective immunosuppressive treatment of IBD, particularly in patients with corticosteroid-resistant disease. However, the use of thiopurines is limited by both its long onset of action (three to four months) and drug toxicities, which include hepatotoxicity, bone marrow suppression, pancreatitis, and allergic reactions.

**Pharmacogenomics**

Thiopurines are converted to 6-MP in vivo, where it is subsequently metabolized to two active metabolites; either 6-thioguanine nucleotides (6-TGN) by the enzyme IMPDH, or to 6-methyl-mercaptopurine ribonucleotides (6-MMRP) by the enzyme TPMT. TPMT also converts 6-MP to an inactive metabolite, 6-methyl-mercaptopurine (6-MMP). 6-TGNs are considered cytotoxic and thus are associated with bone marrow suppression, while 6-MMRP is associated with hepatotoxicity. In population studies, the activity of the enzyme TPMT has been shown to be trimodal, with 90% of subjects having high activity, 10% intermediate activity, and 0.3% with low or no activity. In patients with intermediate to low activity, the metabolism of 6-MP is shunted toward the IMPDH pathway with greater accumulation of 6-TGN; these patients are considered to be at risk for myelotoxicity (i.e., bone marrow suppression).

This variation in TPMT activity has been related to three distinct TPMT mutations and has permitted the development of TPMT genotyping based on a polymerase chain reaction. For example, patients with high TPMT activity are found to have two normal (wild-type) alleles for TPMT; those with intermediate activity are heterozygous (i.e., have a mutation on one chromosome), while those with low TPMT activity are homozygous for TPMT mutations (i.e., a mutation is found on both chromosomes). Genetic analysis has been explored as a technique to identify patients at risk for myelotoxicity; those with intermediate TPMT activity may be initially treated with lower doses of thiopurines, while those with low TPMT activity may not be good candidates for thiopurine therapy.

TPMT activity can also be measured by phenotypic testing. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in erythrocytes and can also be informative. Caution must be taken with phenotyping, because some coadministered drugs can influence measurement of TPMT activity in blood, and recent blood transfusions will misrepresent a patient’s actual TPMT activity.

Prospective TPMT genotyping or phenotyping may help identify patients who may be at increased risk of developing severe, life-threatening myelotoxicity.
**Metabolite Markers**

Monitoring of thiopurine therapy has been based on clinical assessment of response in addition to monitoring blood cell counts, liver function, and pancreatic function tests. However, there has been interest in monitoring intracellular levels of thiopurine metabolites (i.e., 6-TGN and 6-MMRP) to predict response and complications, with the ultimate aim of tailoring drug therapy to each individual patient.

While genotyping and phenotyping of TPMT would only be performed once, metabolite markers might be tested at multiple times during the course of the disease, i.e., to aid in determining initial dose and to evaluate ongoing dosing.

**Regulatory Status**

Prometheus® is a commercial laboratory that offers thiopurine genotype, phenotype and metabolite testing for those undergoing thiopurine therapy. The tests are referred to as Prometheus TPMT Genetics, Prometheus TMPT enzyme, and Prometheus thiopurine metabolites, respectively. Other laboratories that offer TPMT genotyping include Quest (TPMT Genotype) and Specialty Laboratories (TPMT GenoTypR™).

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


