# Protocol

# Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

(20419)

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| **Medical Benefit** | | **Effective Date**: 07/01/12 | **Next Review Date**: 03/15 |
| **Preauthorization** | Yes | **Review Dates**: 04/07, 09/08, 05/09, 03/10, 03/11, 03/12, 03/13, 03/14 | |

*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed.* ***Preauthorization is required; the ordering/requesting physician should submit documentation to Utilization Management.*** *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**

Thiopurines or purine analogues are immunomodulators used to treat malignancies, rheumatic diseases, dermatologic conditions, inflammatory bowel disease (IBD), and in solid organ transplantation. Thiopurines are converted by the enzyme thiopurine methyltransferase (TPMT) into metabolites. Measurement of TPMT activity may help to identify patients at risk for excessive toxicity, most often myelosuppression, after receiving standard doses of thiopurine medications. Measurement of metabolites (metabolite markers) may help to tailor individualized drug therapy.

*Background*

Thiopurines include azathioprine (Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are considered an effective immunosuppressive treatment of inflammatory bowel disease (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 mercaptopurine (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 mercaptopurine (6-MP) to an inactive metabolite, 6-methyl-mercaptopurine (6-MMP). 6-thioguanine nucleotides (6-TGN) 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 mercaptopurine (6-MP) is shunted toward the IMPDH pathway with greater accumulation of 6-thioguanine nucleotides (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 (PCR). 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, since some co-administered 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 recently 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™).

**Policy (Formerly Corporate Medical Guideline)**

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.

Analysis of the metabolite markers of azathioprine and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is considered **investigational**.

**Policy Guideline**

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.

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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.

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