

# MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	<b>GENOTYPING OR PHENOTYPING FOR THIOPURINE METHYLTRANSFERASE (TPMT) FOR PATIENTS TREATED WITH AZATHIOPRINE (6-MP)</b>
Policy Number	<b>2.02.37</b>
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Product Disclaimer	<ul style="list-style-type: none"> <li>• <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i></li> <li>• <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i></li> <li>• <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i></li> </ul>

## POLICY STATEMENT

Based on criteria and review of peer-reviewed literature, genotyping or phenotyping for thiopurine methyltransferase (TPMT) mutations is considered **medically appropriate** prior to initiation of azathioprine (AZA) or 6-mercaptopurine (6-MP) therapy or if standard dosing of AZA/6-MP fails to produce a therapeutic response.

## POLICY GUIDELINES

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

## DESCRIPTION

Azathioprine, which is a prodrug of 6-mercaptopurine (6-MP), is considered an effective immunosuppressive treatment of inflammatory bowel disease, particularly in patients with steroid-resistant disease. For example, in the course of 1 year, 50% of patients with Crohn's disease will require steroids for its treatment; of these, 50% will either be steroid resistant or steroid dependent, and thus candidates for immunosuppressive therapy. Azathioprine therapy eliminates the need for corticosteroids in about 75% of patients; azathioprine is also considered an effective therapy for fistulizing disease. Results of a recent randomized clinical trial of children with Crohn's disease suggest that compared to prednisone alone, inclusion of azathioprine with prednisone at the time of initial diagnosis is associated with improved maintenance of remission while simultaneously decreasing the dose of prednisone.

However, the use of azathioprine is limited by both its long onset of action (3–4 months) and drug toxicities, which include hepatotoxicity, bone marrow suppression, pancreatitis, and allergic reactions. Long-term drug use has been associated with neoplasia. Due to these side effects, it is estimated that less than 5% of patients with Crohn's disease ever receive azathioprine.

Azathioprine is converted to 6-mercaptopurine in vivo, where it is subsequently metabolized to 2 active metabolites; either 6-thioguanine nucleotides (6-TG) by the enzyme IMPDH, or to 6-methyl-mercaptopurine ribonucleotides (6-

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MMRP) by the enzyme TPMT. TPMT also converts 6-MP to an inactive metabolite 6-methyl-mercaptopurine (6-MMP). 6-TG is considered cytotoxic and thus is 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-TG nucleotides; these patients are considered to be at risk for 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 (e.g., have a mutation on one chromosome), while those with low TPMT activity are homozygous for TPMT mutations (e.g., a mutation is found on both chromosomes.) Genetic analysis has been explored as a technique to identify patients at risk for bone marrow suppression; those with intermediate TPMT activity may be initially treated with lower doses of azathioprine, while those with low TPMT activity may not be good candidates for azathioprine therapy.

Prescribing information for azathioprine states that prospective TPMT genotyping or phenotyping may help identify patients who may be at increased risk of developing severe, life-threatening myelotoxicity.

Prometheus is a commercial laboratory that offers pharmacogenomic testing for those undergoing azathioprine therapy. The test is referred to as Pro-Predict Rx TPMT. Other laboratories that offer TPMT genotyping include Quest (TPMT Genotype) and Specialty Laboratories (TPMT GenoTypR™).

### **RATIONALE**

As with any diagnostic technology, there are 3 steps in the technology assessment process: evaluation of the technical feasibility, a determination of how the information will be used in the management of the patient, and whether the change in management results in an improved outcome.

*Technical Performance* - The genotypic analysis of the TPMT gene is based on well-established polymerase chain technology (PCR) to detect 3 distinct mutations.

*How Information May Be Used in the Management of Patients* - Ideally, one would like to have data reporting the sensitivity and specificity of genetic mutations in predicting toxicity. Several studies have correlated the presence of mutations to toxicity; however, the sensitivity and specificity cannot be calculated from the data published so far.

The following clinical applications of pharmacogenomics have been proposed:

- I. TPMT genotyping before the initiation of therapy may identify those patients who are at higher risk for hematologic toxicity and who may benefit from more intense surveillance.
- II. Patients with two TPMT mutations are at highest risk for bone marrow toxicity and therefore alternative therapy may be considered.
- III. In patients with one TPMT mutation, azathioprine therapy may be safely initiated, but a lower (50%) dose may be considered.
- IV. In patients with no TPMT mutations, azathioprine may be initiated at a higher dose.
- V. Azathioprine is typically given orally, but in some cases, it may be initially given intravenously to accelerate its onset of action. IV dosing may be considered contraindicated in patients with two TPMT mutations.

*Improvement in Health Outcomes* - The use of pharmacogenomics creates the possibility of tailoring a drug regimen for each individual patient, with the ultimate goal of attaining disease remission and elimination of steroid therapy.

A systematic review by Teml, et al. (2007) notes that patients with TPMT deficiency treated with standard doses of azathioprine/mercaptopurine have double the risk of developing severe myelosuppression within a few weeks of starting

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therapy. As noted here, this risk is explained by a marked increase of 6-TGN levels. The review also notes that the data are more limited in those who are heterozygous for TPMT activity. However, for patients who developed myelotoxicity, the reviewers noted that it tended to occur earlier (1 to 1.5 months into treatment) for those who were heterozygous, compared to about 3 months in wild-type patients. This review notes that TPMT testing is reliable and cost effective to prevent severe hepatotoxicity in TPMT variant patients.

In a study from New Zealand, Gardiner, et al. (2008) noted that initial target doses to attain therapeutic levels in patients with inflammatory bowel disease might be 1 and 3 mg/kg/d in intermediate (heterozygous) and normal (wild-type) metabolizers. This conclusion was based on a study of 52 patients with inflammatory bowel disease who were started on azathioprine or 6-mercaptopurine and who were followed up for 9 months while 6-TGN levels and clinical status were assessed. Thus, this study suggests that knowledge of TPMT activity can assist with initial dosing.

In a study from Europe on 394 patients with inflammatory bowel disease, Gisbert, et al (2006) noted that the probability of myelotoxicity was 14.3% in the TPMT intermediate group compared to 3.5% in those with high (wild-type) activity. These authors concluded that determining TPMT activity prior to initiating treatment with azathioprine could help to minimize the risk of myelotoxicity.

A meta-analysis by Dong et al. (2010) evaluated the relationship between TPMT polymorphisms and adverse-drug reactions in patients with inflammatory bowel disease (IBD) taking thiopurine drugs. Analysis of data from 6 studies, 39 of 273 (14%) patients with an adverse drug reaction were TPMT heterozygous or homozygous compared to 39 of 708 (55%) patients without an adverse drug reaction. This difference was statistically significant (odds ratio [OR]: 2.93, 95% confidence interval [CI]: 1.68-5.09). In analyses of specific adverse reactions, there was a statistically significant association between the presence of TPMT alleles and bone marrow toxicity, but not hepatotoxicity or pancreatitis. In the non-statistically significant analyses, the number of events was small and the analyses have been underpowered. There is still no prospective study that has evaluated the cost-effectiveness and utility of the TPMT phenotyping test before taking thiopurine medication.

In summary, the data from the published literature indicates that reduced TPMT activity results in increased likelihood of myelotoxicity, a serious side-effect of azathioprine treatment. In addition, the data suggest that knowledge of TPMT activity is helpful in selecting the initial dose of drug. Thus, this one-time testing is considered medically necessary.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Committee on IBD published consensus recommendations on the role of TPMT and thiopurine metabolite testing in pediatric IBD (2013) and recommend TPMT testing before initiation of thiopurines. For individuals who are homozygous recessive or have extremely low TPMT activity, the use of thiopurines should be avoided because of risk of leucopenia. In addition, individuals on thiopurines should have routine monitoring of blood counts to evaluate for leucopenia regardless of TPMT testing results. Metabolite testing may be performed to determine adherence to thiopurine activity or to guide dosing changes in patients with active disease. Routine and repeat metabolite testing has little or no role in patients who are responding well to medication and taking an acceptable dose of thiopurines.

## **CODES**

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- ***CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.***
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

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**CPT Codes**

Code	Description
81335	TPMT (Thiopurine s-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15)(eg, thiopurine metabolism), gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5) (Mayo Clinic)
Modifier 9A	TPMT, commonly called (thiopurine Methyltransferase) (patients on antimetabolite therapy)

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**HCPCS Codes**

Code	Description
None	

**ICD10 Codes**

Code	Description
K50.00-K50.919	Crohn's disease [regional enteritis] (code range)
K51.00-K51.919	Ulcerative colitis (code range)

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\*Key Article

**KEY WORDS**

Azathioprine, Inflammatory Bowel Disease, TPMT, 6-mercaptopurine.

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**CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS**

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ContrId=298&ver=119&ContrVer=1&CtrctrSelected=298\\*1&Ctrctr=298&s=41&DocType=2&bc=AAgAAAQAAAA&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ContrId=298&ver=119&ContrVer=1&CtrctrSelected=298*1&Ctrctr=298&s=41&DocType=2&bc=AAgAAAQAAAA&)