Medical Policy
Pharmacogenomic and Metabolite Markers for Patients Treated with
Thiopurines

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Policy Number: 096
BCBSA Reference Number: 2.04.19
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

One-time genotypic or phenotypic analysis of the enzyme TPMT may be 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 INVESTIGATIONAL in all other situations.

Analysis of the metabolite markers of azathioprine (AZA) and mercaptopurine (6-MP), including 6-methylmercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.
**Prior Authorization Information**

**Inpatient**
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed inpatient.

**Outpatient**
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<tr>
<td>Prior authorization is <strong>not required</strong>.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<td>Prior authorization is <strong>not required</strong>.</td>
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<tr>
<td>Medicare HMO Blue&lt;sup&gt;SM&lt;/sup&gt;</td>
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**CPT Codes / HCPCS Codes / ICD Codes**

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

*The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:*

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tr>
<td>81335</td>
<td>TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)</td>
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</table>

*The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:*

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**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. There are 3 distinct TPMT mutations, and these are associated with the level of TPMT activity.

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.
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 (3-4 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 2 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 (ie, bone marrow suppression).

This variation in TPMT activity has been related to 3 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 2 normal (wild-type) alleles for TPMT; those with intermediate activity are heterozygous (ie, have a mutation on 1 chromosome), while those with low TPMT activity are homozygous for TPMT mutations (ie, 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 recently in monitoring intracellular levels of thiopurine metabolites (ie, 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 ie, to aid in determining initial dose and to evaluate ongoing dosing.

Summary
There are a large number of studies on the diagnostic performance of thiopurine methyltransferase (TMPT) genotyping and phenotyping tests. A recent 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). Moreover, there is a lack of consensus among studies on the optimal cutoff to use when measuring 6-thioguanine nucleotides (6-TGN) levels. Thus, analysis of metabolite markers is considered investigational.

**Policy History**

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<th>Date</th>
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<td>9/2018</td>
<td>Local Coverage Determination (LCD) Molecular Pathology Procedures (L35000) added. 9/2018</td>
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<td>1/2018</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>1/2018</td>
<td>Clarified coding information.</td>
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<td>12/2016</td>
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<td>9/2015</td>
<td>Added coding language.</td>
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<td>7/2015</td>
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<td>7/2014</td>
<td>Coding information clarified.</td>
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<td>8/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<tr>
<td>1/1/2010</td>
<td>BCBS Association National Policy Review Title change. No changes to policy statements.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


