Pharmacogenic and Metabolite Markers for Patients Treated with Thiopurines

**Description**

The thiopurine class of drugs—which include azathioprine (a pro-drug for mercaptopurine), mercaptopurine, and thioguanine—are used to treat a variety of diseases; however, it is recommended the use of thiopurines be limited due to a high rate of drug toxicity. Mercaptopurine and thioguanine are directly metabolized by the thiopurine S-methyltransferase (TPMT) enzyme. Susceptibility to drug toxicity is linked to the level of TPMT activity. The variation in TPMT activity has been related to three distinct TPMT variants. 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.

**OBJECTIVE**

The objective of this evidence review is to determine whether genotypic or phenotypic analysis of thiopurine methyltransferase function or metabolite marker analysis improves the net health outcome in patients treated with thiopurines.

**POLICY STATEMENT**

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

Genotypic and/or phenotypic analysis of the TPMT enzyme is considered **investigational** in all other situations.

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

**POLICY GUIDELINES**

Thiopurine methyltransferase (TPMT) testing cannot substitute for complete blood count monitoring in patients receiving thiopurines. Early drug discontinuation may be considered in patients with abnormal
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complete blood count results. Dosage reduction is recommended in patients with reduced TPMT activity. Alternative therapies may need to be considered for patients who have low or absent TPMT activity (homozygous for nonfunctional alleles). Accurate phenotyping results are not possible in patients who received recent blood transfusions. While genotyping and phenotyping of TPMT would only be performed once, metabolite markers might be tested multiple times during the course of the disease to aid in determining the initial dose and in evaluating any ongoing dosing.

GENETIC COUNSELING
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION
Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Several thiopurine genotype, phenotype, and metabolite tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus, a commercial laboratory, offers thiopurine genotype, phenotype, and metabolite testing for those on 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 Diagnostics (TPMT Genotype); ARUP Laboratories (TPMT DNA); Specially Laboratories (TPMT GenoTypR™); PreventionGenetics (TPMT Deficiency via the TPMT Gene); Genelex (TPMT); Fulgent Genetics (TPMT); and LabCorp (TPMT enzyme activity and genotyping).

RATIONALE
Summary of Evidence
For individuals who are treated with thiopurines who receive TPMT genotype analysis or TPMT phenotype analysis, the evidence includes studies of diagnostic performance, systematic reviews, and RCTs. Relevant outcomes are symptoms, morbid events, and change in disease status. A large number of studies have assessed the diagnostic performance of TPMT genotyping and phenotyping tests. The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
most recent meta-analysis reported genotyping sensitivity and specificity of 90% and 100%, respectively, and a phenotyping sensitivity and specificity of 76% and 99%, respectively, for identifying patients with subnormal enzymatic activity. Three RCTs (total N=1145 patients) have compared TPMT genotype/phenotype testing with no testing and empirical weight-based thiopurine dosing. There were no significant differences in the incidence of hematologic adverse events, treatment discontinuation rates, or clinical remission rates. However, secondary analysis of a small number of individuals who had intermediate enzymatic activity (a heterozygous genotype) or a low enzymatic activity (a homozygous genotype) showed that TPMT testing to guide dosing was associated with statistically significant risk reduction in hematologic adverse events with a wide margin of error. In summary, 200 patients would have to be genotyped to avoid 1 episode of a hematologic adverse drug reaction (7.4% vs 7.9%; ie, 0.5% risk difference). The number needed to treat to avoid 1 episode of a hematologic adverse drug reaction would be 5 for at-risk individuals (risk difference in patients with a genetic variant, 20.3%; 2.6% vs 22.9%). In addition, a small, inadequately powered RCT, which assessed phenotype TPMT testing, found no difference in treatment discontinuation rates due to adverse drug reactions between the 2 arms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are treated with thiopurines who receive azathioprine and/or 6-mercaptopurine metabolite analysis, the evidence includes a systematic review as well as prospective and retrospective studies. Relevant outcomes are symptoms, morbid events, and change in disease status. The systematic review, which assessed the diagnostic accuracy of metabolite testing, reported that the ability of the metabolite tests to predict clinical outcomes and toxicity was inconsistent across studies. There is insufficient evidence from prospective studies to determine whether knowledge of metabolite marker status will lead to improved outcomes (primarily improved disease control and/or less adverse drug events). Findings from studies evaluating the association between metabolite markers and clinical remission are mixed, and no prospective comparative trials have compared health outcomes in patients managed using metabolite markers with current approaches to care. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
National Comprehensive Cancer Network (v.1.2018) guidelines on acute lymphoblastic leukemia state:

- “For patients receiving 6-MP [mercaptopurine], consider testing for TPMT [thiopurine methyltransferase] gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP.”
- “Determination of patient TPMT genotype using genomic DNA is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses.”
- “Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to non-compliance or hypermetabolism.”

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (2013) on inflammatory bowel disease (IBD) published consensus recommendations on the role of the TMPT enzyme and thiopurine metabolite testing in pediatric IBD.
Recommendations (high and moderate) included:

- “TPMT testing is recommended before initiation of TPs [thiopurines] to identify individuals who are homozygous recessive or have extremely low TPMT activity…
- Individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of TPs because of concerns for significant leucopenia.
- … All individuals on TPs should have routine monitoring of CBC [complete blood cell] and WBC [white blood cell] counts to evaluate for leucopenia regardless of TPMT testing results.
- Metabolite testing can be used to determine adherence to TP therapy.
- Metabolite testing can be used to guide dosing increases or modifications in patients with active disease…. 
- Routine and repeat metabolite testing has little or no role in patients who are doing well and taking an acceptable dose of a TP.”

**British Association of Dermatologists**

The guidelines from the British Association of Dermatologists (2011) addressed the safe and effective prescribing of azathioprine for the management of autoimmune and inflammatory skin diseases.

The guidelines included the following recommendations on the analysis of TMPT activity and azathioprine toxicity:

- “There is strong evidence that baseline testing predicts severe neutropenia in patients with absent TMPT activity.
- There is good evidence that intermediate TMPT activity is associated with myelotoxicity in patients using conventional azathioprine doses.
- TMPT testing only identifies … haematological toxicity, hence the continued need for regular monitoring of blood counts irrespective of TMPT status.”

The guidelines also provided recommendations on azathioprine dosing:

- “Patients with normal TPMT activity are at low risk of profound neutropenia and may be prescribed standard doses of azathioprine … (Strength of recommendation: A; level of evidence: 1+).
- Patients with intermediate (heterozygous) range TPMT activity … have an increased risk of neutropenia and should receive lower doses of azathioprine maintenance dose … (Strength of recommendation: C; level of evidence: 2+).
- Patients with … [low] TPMT activity … are at very high risk of profound neutropenia and should in general not be prescribed azathioprine (Strength of recommendation: A; level of evidence: 1+).”

**American Gastroenterological Association Institute**

Recommendations from the American Gastroenterological Association Institute (2017) guidelines on therapeutic drug monitoring in IBD are summarized in Table1.30 31

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Table 1. Evidence-Based Clinical Guidelines on Therapeutic Drug Monitoring in IBD

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<thead>
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<th>Recommendation</th>
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<th>QOE</th>
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<td>In adults with IBD being started on thiopurines, AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing</td>
<td>Conditional</td>
<td>Low</td>
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<tr>
<td>In adults treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes</td>
<td>Conditional</td>
<td>Very low</td>
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<tr>
<td>In adults with quiescent IBD treated with thiopurines, AGA suggests against routine thiopurine metabolite monitoring</td>
<td>Conditional</td>
<td>Very low</td>
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U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


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POLICY HISTORY

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<td>December 2012</td>
<td>Update Policy</td>
<td>Policy updated with literature search, References updated, Policy statements unchanged.</td>
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<td>Policy updated with literature search. References 7,9,15 and 20 added; other references renumbered or removed. Policy statements unchanged.</td>
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