Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237
Original Effective Date: 04/15/2009
Current Effective Date: 12/14/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a one-time genotypic or phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) 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 to be **eligible for coverage.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genotypic and/or phenotypic analysis of the thiopurine methyltransferase (TPMT) enzyme in all other situations to be **investigational.***

Based on review of available data, the Company considers analysis of the metabolite markers of azathioprine (AZA) and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN) to be **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 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. *TPMT* genotyping and phenotyping would only need to be performed once.

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.

Background/Overview

Thiopurines
Thiopurines or purine analogues are immunomodulators. They include azathioprine (Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, and inflammatory bowel disease, and are used in solid organ transplantation. They are considered an effective immunosuppressive treatment of inflammatory bowel disease, particularly in patients with the corticosteroid-resistant disease. However, the use of thiopurines is limited by both 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 two active metabolites: either 6-thioguanine nucleotides (6-TGN) by the inosine-5′-monophosphate dehydrogenase enzyme; or to 6-methyl-mercaptopurine ribonucleotides by the thiopurine methyltransferase (TPMT) enzyme. TPMT also converts 6-MP into an inactive metabolite, 6-methyl-mercaptopurine. The 6-TGN metabolites are considered cytotoxic and thus are associated

with bone marrow suppression, while the 6-methyl-mercaptopurine ribonucleotides are associated with hepatotoxicity. In population studies, the activity of the TPMT enzyme 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 inosine-5′-monophosphate dehydrogenase pathway with greater accumulation of 6-TGN; these patients are considered at risk for myelotoxicity (ie, bone marrow suppression).

This variation in TPMT activity has been related to three distinct *TPMT* variants and has permitted the development of *TPMT* genotyping using a polymerase chain reaction. For example, patients with high TPMT activity are found to have two normal (wild-type) *TPMT* alleles; those with intermediate activity are heterozygous (ie, have a variant on one chromosome), while those with low TPMT activity are homozygous for *TPMT* variants (ie, have a variant on both chromosomes). Genetic analysis has been explored as a technique to identify patients at risk for myelotoxicity. Patients with high TPMT activity may be treated with standard doses of thiopurines, patients 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. Phenotyping determines the level of thiopurine nucleotides or TPMT activity in erythrocytes. Caution must be taken with phenotyping, because some coadministered drugs can influence the 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 at increased risk of developing severe, life-threatening myelotoxicity.

The genotypic analysis of the *TPMT* gene is based on well-established polymerase chain reaction technology to detect three distinct variants. Currently, 3 alleles (*TPMT*2, TPMT*3A, TPMT*3C*) account for about 95% of subjects with reduced TPMT enzyme activity. Subjects homozygous for these alleles are TPMT-deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. A study by Hindorf and Appell (2012) addressed the concordance between *TPMT* genotyping and phenotyping. The investigators evaluated data from 7195 unselected and consecutive *TPMT* genotype and phenotype tests. The genotyping tests examined the three most common *TPMT* variants, previously noted. *TPMT* genotyping identified 6454 (89.7%) as *TPMT* wild-type, 704 (9.8%) as *TPMT* heterozygous, and 37 (0.005%) as *TPMT* homozygous. The overall

agreement between genotyping and phenotyping was 95%. Genotyping alone would have misclassified 3 (8%) of 37 homozygous patients as heterozygous; these 3 subjects were found to have uncommon variants. All three had low TPMT activity. The phenotype test would have misclassified 4 (11%) of 37 of homozygous patients because they had test results above the cutoff level for low TPMT activity (<2.5 U/mL red blood cells).

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 (ie, 6-TGN, 6-methyl-mercaptopurine ribonucleotides) to predict response and complications, with the ultimate aim of tailoring drug therapy to each patient.

Metabolite markers have been assessed using high-performance liquid chromatography technology. It would be optimal to assess metabolite markers in peripheral leukocytes because they reflect the status of bone marrow precursors. However, it is technically easier to measure metabolites in red blood cells than in leukocytes.

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 genotypes, 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®‡ TPMT enzyme, and Prometheus®‡ thiopurine metabolites, respectively. Other laboratories that offer *TPMT* genotyping include: Quest Diagnostics (TPMT Genotype); ARUP Laboratories (TPMT DNA); Specialty Laboratories (TPMT GenoTypR™‡); PreventionGenetics (TPMT Deficiency via the TPMT Gene); Genelex (TPMT); Fulgent Genetics (TPMT); and LabCorp (TPMT enzyme activity and genotyping).

Rationale/Source

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.

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 randomized controlled trials. The 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 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 randomized controlled trials (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 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 randomized controlled trial, which assessed phenotype *TPMT* testing, found no difference in treatment discontinuation rates due to adverse drug reactions between the two 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-mercaptoprine metabolite analysis, the evidence includes a systematic review as well as prospective and retrospective studies. The 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. 2.2019) 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 TPMT enzyme and thiopurine metabolite testing in pediatric IBD. Recommendations (high and moderate) included:

1. "TPMT testing is recommended before initiation of TPs [thiopurines] to identify individuals who are homozygous recessive or have extremely low TPMT activity....
2. Individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of TPs because of concerns for significant leucopenia.
3. ....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.
4. Metabolite testing can be used to determine adherence to TP therapy.
5. Metabolite testing can be used to guide dosing increases or modifications in patients with active disease….
6. Routine and repeat metabolite testing has little or no role in patients who are doing well and taking an acceptable dose of a TP."

American Gastroenterological Association Institute

Recommendations from the American Gastroenterological Association Institute (2017) guidelines on therapeutic drug monitoring in IBD are summarized in Table 1.

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

Recommendation	SOR	QOE
In adults with IBD being started on thiopurines, AGA suggests routine *TPMT* testing (enzymatic activity or genotype) to guide thiopurine dosing	Conditional	Low
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	Conditional	Very low
In adults with quiescent IBD treated with thiopurines, AGA suggests against routine thiopurine metabolite monitoring	Conditional	Very low

AGA: American Gastroenterological Association; IBD: inflammatory bowel disease; QOE: quality of evidence; SOR: strength of recommendation; *TPMT*: thiopurine methyltransferase.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02929706	Effectiveness of Thiopurine Dose Optimization by NUDT 15 R139C on Reducing Thiopurine-Induced Leucopenia in Inflammatory Bowel Disease	400	Aug 2018 (ongoing; last updated May 2018)
NCT03093818	PREemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE)	6892	Dec 2019
NCT02297126	A Prospective Trial to Assess Cost and Clinical Outcomes of a Clinical Pharmacogenomic Program at Eskenazi Hospital (INGenious)	4465	May 2018 (active, not recruiting; updated Aug 2019)

NCT: national clinical trial.

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Policy History

Original Effective Date: 04/15/2009
Current Effective Date: 12/14/2020

05/07/2009	Medical Director review
05/20/2009	Medical Policy Committee approval. New policy.
06/03/2010	Medical Policy Committee approval
06/16/2010	Medical Policy Implementation Committee approval. Policy title changed by taking out azathioprine (6-MP) and replacing it with “Thiopurines”. Policy statement changed to “a one-time genotypic or phenotypic analysis of the thiopurine methyltransferase (TPMT) gene 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 to be eligible for coverage."
06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/11/2013	Codes updated.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Statement added that genotypic and/or phenotypic analysis of the enzyme TPMT is considered investigational in all other situations.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2018	Coding update
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2019	Medical Policy Committee review

Coding

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Code Type	Code
CPT	0034U, 81335, 81401 Code added eff 4/1/2020: 0169U
HCPCS	No codes
ICD-10 Diagnosis	K50.00-K50.919, K50.90-K50.919, K51.00-K51.919, M05.00-M05.9, M06.00-M06.9, M08.00-M08.99, M12.00-M12.09 Added codes eff 10/1/2020: M05.7A, M05.8A, M06.0A, M06.8A, M08.0A, M08.2A, M08.4A, M08.9A

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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