Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/24**
(See policy history boxes for previous effective dates)

Title: Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Description/Background

Thiopurines

Thiopurines or purine analogues 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, inflammatory bowel disease (IBD), and 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.

Thiopurines are metabolized by a complex pathway to several metabolites including 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). Thiopurine methyltransferase (TPMT) is one of the key enzymes in thiopurine metabolism. Patients with low or absent TPMT enzyme activity can develop bone marrow toxicity with thiopurine therapy due to excess production of 6-TG metabolites, while elevated 6- MMP levels have been associated with hepatotoxicity.[1] 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. Variants in another metabolizing enzyme, NUDT15 (nudix hydrolase, NUDIX 15), have been identified that strongly influence thiopurine tolerance in patients with IBD.[2] Homozygous carriers of NUDT15 variants are intolerant of thiopurine compounds because of risk of bone marrow suppression. Individuals with this variant are sensitive to 6-MP and have tolerated only 8 percent of the standard dose. Several variant alleles have been identified with varying prevalence among different populations and varying degrees of functional effects.[3] NUDT deficiency is most common among East Asians (22.6%), followed by South Asians (13.6%), and Native American populations (12.5%-21.2%). Studies in other populations are ongoing.[4]

Phenotype Testing for Thiopurine Methyltransferase Activity

The testing involves incubation of RBC lysate in a multisubstrate cocktail. The enzymatically generated thiomethylated products are measured by liquid chromatography tandem mass spectrometry to produce an activity profile for thiopurine methyltransferase. Multiple assays are available and use different reference standards. Results are based on the quantitative activity level of TPMT (in categories) along with clinical interpretation. Two commercial tests are illustrated below as examples:

ARUP Labs:[5]

- Normal TPMT activity levels: Individuals are predicted to be at low risk of bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine therapy; no dose adjustment is recommended.
- Intermediate TPMT activity levels: Individuals are predicted to be at intermediate risk of bone marrow toxicity (myelosuppression), as a consequence of standard thiopurine therapy; a dose reduction and therapeutic drug management is recommended.
- Low TPMT activity: Individuals are predicted to be at high risk of bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine dosing. It is recommended to avoid the use of thiopurine drugs.
- High TPMT activity: Individuals are not predicted to be at risk for bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine dosing, but may be at risk for therapeutic failure due to excessive inactivation of thiopurine drugs. Individuals may require higher than the normal standard dose. Therapeutic drug management is recommended.

Lab Corp:[6]

- Normal: 15.1 to 26.4 units/ml RBC
- Heterozygous for low TPMT variant: 6.3 to 15.0 units/ml RBC
- Homozygous for low TPMT variant: <6.3 to units/ml RBC

Genotype Testing for Thiopurine Methyltransferase Activity/Nudix Hydrolase (*NUDT15*) Gene Polymorphism

The genotypic analysis of the *TPMT/NUDT15* gene is based on polymerase chain reaction technology to detect distinct variants. These are listed in Table 1.

Table 1. Identified Genetic Variants for TPMT/NUDT15 Testing[4]

***TPMT* Allele**	**cDNA Nucleotide Change**	**Amino Acid Change**	**Effect on Enzyme Metabolism**
***1**	None (wild type)	None (wild type)	Normal function
***2**	c.238G>C	p.Ala80Pro (p.A80P)	No activity
***3A**	c.460G>A and c.719A>G	p.Ala154Thr (p.A154T) and p.Tyr240Cys (p.Y240C)	No activity
***3B**	c.460G>A	p.Ala154Thr (p.A154T)	No activity
***3C**	c.719A>G	p.Tyr240Cys (p.Y240C)	No activity
***4**	c.626-1G>A	Not applicable, splice site	No activity
***5**	c.146T>C	p.Leu49Ser (p.L49S)	No activity
***8**	c.644G>A	p.Arg215His (p.R215H)	Reduced activity
***12**	c.374C>T	p.Ser125Leu (p.S125L)	Reduced activity
NUDT15 Allele	**cDNA Nucleotide Change**	**Amino Acid Change**	**Effect on Enzyme Metabolism**
***1**	None (wild type)	None (wild type)	Normal activity

***2 or *3**	c.415C>T	p.Arg139Cys (p.R139C)	No activity
***4**	c.416G>A	p.Arg139His (p.R139H)	No activity
***5**	c.52G>A	p.Val18Ile (p.V18I)	No activity

Metabolite Markers
The therapeutic effect of thiopurines has been associated with the level of active 6-TGN metabolites, and hepatotoxicity has been associated with higher levels of the inactive metabolites 6-MMP and 6-methylmercaptopurine ribonucleotides. Therefore, it has been proposed that therapeutic monitoring of these metabolites may improve patient outcomes by identifying the reason for a non-response or sub-optimal response. Conversely by measuring 6-MMP levels, a subgroup of patients can be identified who preferentially convert 6-MP to 6-MMP (toxic metabolite) and often do not achieve sufficient 6-TGN levels. This group of patients, often described as “shunters,” may be susceptible to hepatotoxicity because thiopurine dose escalation leads to 6-MMP accumulation.

Therapeutic monitoring of thiopurine metabolite levels is typically performed in patients with IBD as 1) reactive strategy in response to either lack of clinical improvement or observed treatment-related toxicity 2) routine proactive clinical care in patients with quiescent disease.

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™).

FDA Labeling on Pharmacogenomic Test for Thiopurines
The FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, the FDA has given clear and specific directives on use of pharmacogenomic testing for azathioprine (a prodrug for mercaptopurine), mercaptopurine, and thioguanine. Therefore, evidence for these indications is not reviewed in the Rationale section.

Mercaptopurine[8]

- Consider testing for TPMT and NUDT15 deficiency in patients who experience severe myelosuppression or repeated episodes of myelosuppression Homozygous Deficiency in either TPMT or NUDT15: Patients with homozygous deficiency of either enzyme typically require 10% or less of the recommended dosage. Reduce the recommended starting dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency.
- Heterozygous Deficiency in TPMT and/or NUDT15: Reduce the dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended dosage, but some require dose reduction based on adverse reactions. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dose reductions.

Azathioprine[9]

- Patients with TPMT and/or NUDT15 Deficiency: Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction
- Homozygous deficiency in either TPMT or NUDT15: Because of the risk of increased toxicity, consider alternative therapies for patients who are known to have TPMT or NUDT15 deficiency
- Heterozygous deficiency in TPMT and/or NUDT15: Because of the risk of increased toxicity, dosage reduction is recommended in patients known to have heterozygous deficiency of TPMT or NUDT15. Patients who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions.

Thioguanine[10]

- Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression.
- Evaluate patients with repeated severe myelosuppression for TPMT or NUDT15 deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions.

Medical Policy Statement

The safety and effectiveness of one-time genotypic or phenotypic analysis of the enzyme TMPT and Nudix hydrolase (NUDT15) has been established. It may be considered a useful tool to guide therapy in specified situations.

Monitoring of thiopurine metabolite levels in individuals with inflammatory bowel disease and acute lymphoblastic leukemia has been established. It may be considered a useful tool in specific situations.

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) in all other conditions not listed below, is considered experimental/investigational.

Inclusionary and Exclusionary Guidelines

Inclusions:
One-time genotypic or phenotypic analysis of the enzyme TMPT/NUDT15 may be considered established in the following situations:

- 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.

Monitoring of thiopurine metabolite levels in individuals with inflammatory bowel disease may be considered established for the following indications:

a. To measure blood levels in individuals suspected of having toxic responses to AZA and/or 6-MP (e.g., hepatotoxicity or myelotoxicity);
b. To measure drug levels in individuals who have not responded to therapy (e.g., persistent fever, further weight loss, and bloody diarrhea).

Monitoring of thiopurine metabolite levels in individuals with acute lymphoblastic leukemia may be considered established in the following situations:

a. For patients showing signs of a lack of myelosuppression while on therapy
b. For patients with normal function for TPMT and NUDT15 who do not appear to tolerate thiopurines

Exclusions:

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) in all other conditions.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81401	81306	81335	82657	0034U	80299

Other codes (investigational, not medically necessary, etc.):

0169U

Rationale

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function¾including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

THIOPURINE METABOLITE MONITORING

Clinical Context and Test Purpose

The purpose of monitoring thiopurine metabolite (6-TGN and 6-MMP) levels in individuals treated with thiopurines is to provide an advantage over no therapeutic drug monitoring with empiric treatment changes or standard weight-based dosing.

Potential benefits of monitoring thiopurine metabolite levels may include the following:

- to guide treatment changes in the event of observed drug toxicity or lack of efficacy (reactive strategy)
- routine use to guide thiopurine dosing (proactive strategy)

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals treated with thiopurines.

Interventions

The therapy being considered is monitoring of thiopurine metabolite levels. Commercial tests are available from multiple labs and companies. Metabolite markers are measured from red blood cell samples using high-performance liquid chromatography.

Comparators

The relevant comparator is no monitoring for thiopurine metabolite levels with empiric treatment changes or standard weight-based dosing.

Outcomes

The general outcomes of interest are change in disease status, treatment-related mortality and treatment-related morbidity.

Potential beneficial outcomes of interest are improvement in disease status and reduction or elimination of toxicity associated with thiopurines (e.g., bone marrow toxicity, hepatotoxicity, pancreatitis, gastric intolerance, skin reaction). In contrast, empiric treatment changes, such as escalation of therapy in patients with suboptimal response, may result in excessively high 6-TGN level, which increases risk of leukopenia, or excessively high 6-MMP levels due to shunting, which increases risk of hepatotoxicity. Inappropriate treatment changes can also potentially delay use of more effective therapy.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
The American Gastroenterological Association published a systematic review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases in 2017.[1] The authors did not identify any randomized trials or prospective comparative studies in thiopurine treated IBD patients comparing reactive therapeutic drug monitoring to guide treatment changes vs. empiric treatment changes. Two small, randomized studies that evaluated routine therapeutic drug monitoring to guide thiopurine dosing compared to empiric weight-based dosing were identified.

Randomized Controlled Trials
Dassopoulos et al (2014) reported the results of a double-blind RCT conducted in the United States using TPMT phenotype testing to guide initial dosing, followed by prospective 6-TGN guided dose adaptation compared with empiric weight-based dosing with gradual dose escalation if well tolerated (regardless of TPMT activity) in control arm.[11] The second RCT was an open-label randomized trial conducted in Germany which investigated scheduled thiopurine metabolite testing with successive adaptation of azathiopurine therapy to a target 6-TGN concentration of 250 to 400 pmol/8 X 108 RBCs vs standard AZA weight based dosing (2.5 mg/kg body weight).[12] Both studies were terminated early due to slow recruitment and failure to meet prespecified enrollment targets. Additionally, there was a high attrition rate in both trials (33% to 46%), although the analyses were conducted in intention-to-treat manner with worst-case scenario imputation. In the pooled analysis of both trials reported in the systematic review, there was a numerically higher proportion of patients achieving clinical remission in patients who underwent routine TDM-guided dose adaptation compared with standard weight-based dosing (21 of 50 [42%] vs. 18 of 57 [31.6%]) at 16 weeks, but the difference was not statistically significant (RR, 1.44; 95% CI, 0.59 to 3.52). The rate of serious adverse events (requiring discontinuation of therapy) was comparable between the 2 arms (TDM-guided dose adaptation vs. empiric dosing: 16 of 50 [32.0%] vs. 15 of 57 [26.3%]; RR, 1.20; 95% CI, 0.50 to 2.91). The systematic review concluded overall quality of evidence as very low quality.[1]

Section Summary: Thiopurine Metabolite Monitoring
The evidence for the use of reactive thiopurine metabolite monitoring to guide treatment changes in patients being treated with thiopurines includes only retrospective studies that were not included in this review. The evidence for the use of routine thiopurine drug monitoring to guide treatment changes in patients being treated with thiopurines includes 2 small, randomized studies. Both studies were terminated early due to slow recruitment and failure to meet prespecified enrollment targets. Additionally, there was high attrition rate in both trials (33% to 46%). The pooled analysis of both trials reported in the systematic review did not show a statistically significant difference in clinical remission in patients who underwent routine TDM-guided dose adaptation compared with standard weight-based dosing. The rate of serious adverse events (requiring discontinuation of therapy) was also comparable between

the 2 arms. Based on 2 small RCTs at high risk of bias, there is uncertainty whether reactive or routine thiopurine metabolite monitoring to guide treatment changes are superior to empirical clinical-based or standard weight-based dosing changes.

Thiopurine Methyltransferase and Nudix Hydrolase Phenotype or Genotype Analysis

For individuals who receive thiopurine methyltransferase and nudix hydrolase phenotype or genotype analysis to guide treatment, the evidence included FDA-approved labels for azathioprine (a prodrug for mercaptopurine), mercaptopurine, and thioguanine that include clear and specific directives on use of pharmacogenomic testing. Evidence for these indications was not evaluated.

SUMMARY OF EVIDENCE

For individuals who receive thiopurines metabolite monitoring to guide treatment changes, the evidence includes 2 RCTs. Relevant outcomes are change in disease status, treatment-related mortality and treatment-related morbidity. The evidence for the use of reactive thiopurine metabolite monitoring to guide treatment changes in patients being treated with thiopurines includes only retrospective studies that were not included in this review. The evidence for the use of routine thiopurine drug monitoring to guide treatment changes in patients being treated with thiopurines includes 2 small, randomized studies. Both studies were terminated early due to slow recruitment and failure to meet prespecified enrollment targets. Additionally, there was high attrition rate in both trials (33% to 46%). The pooled analysis of both trials reported in the systematic review did not show statistical significant difference in clinical remission in patients who underwent routine TDM-guided dose adaptation compared with standard weight-based dosing. The rate of serious adverse events (requiring discontinuation of therapy) was also comparable between the 2 arms. Based on 2 small RCTs at high risk of bias, there is uncertainty whether reactive or routine thiopurine metabolite monitoring to guide treatment changes are superior to empirical clinical based or standard weight-based dosing changes. The evidence is sufficient to determine the effects of technology on net health outcomes.

For individuals who are treated with thiopurines and who receive thiopurine methyltransferase and nudix hydrolase phenotype or genotype analysis to guide treatment, the evidence includes FDA-approved labels for azathioprine (a prodrug for mercaptopurine), mercaptopurine, and thioguanine that include clear and specific directives on use of pharmacogenomic testing. Evidence for these indications was not evaluated.

Ongoing and Unpublished Clinical Trials

Some currently 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
Unpublished			
NCT02929706	Effectiveness of Thiopurine Dose Optimization by NUDT15 R139C on Reducing Thiopurine-Induced Leucopenia in Inflammatory Bowel Disease	400	Aug 2018 (unknown; last updated May 2018)
NCT03093818	PREemptive Pharmacogenomic Testing for Preventing Adverse Drug REactions (PREPARE)	6950	Apr 2021

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

National Comprehensive Cancer Network (v.3.2023) 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."

National Comprehensive Cancer Network (v.3.2024) guidelines for pediatric acute lymphoblastic leukemia state:

- Genetic testing for no function alleles of TPMT and NUDT-15 should be considered prior to the initiation of thiopurine therapy, of if excessive toxicity is encountered following treatment with thiopurines.
- Dosing recommendation for patients who are heterozygous or homozygous for TPMT no function allele are summarized in Table 2.
- For patients homozygous for normal function TPMT and NUDT15, who do not appear to tolerate thiopurines, consider measuring erythrocyte thiopurine metabolites and/or erythrocyte TPMT activity. Genetic testing may fail to identify rare or previously undiscovered no function alleles.

Table 3. Dosing Guidelines for Thiopurines on TPMT Phenotype

Genotype/Phenotype	Dosing Recommendations for 6-MP	Dosing Recommendations for 6-TG
Homozygous for normal function alleles (e.g., *1/*1); normal metabolizer	Starting dose should be based on treatment protocol (typically 75 mg/m^2/day). Allow 2 weeks to achieve steady state prior to making dosing adjustments	Starting dose should be based on treatment protocol (typically 60 mg/m^2/day). Allow 2 weeks to achieve steady state prior to making dosing adjustments
Heterozygous for no function alleles (e.g., *1/*2, 3A, 3B , 3C or 4); intermediate metabolizer	Starting dose at 30 to 80% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2 to 4 weeks to achieve steady state prior to making dosing adjustments.	Reduce starting dose by 30 to 80%.[a] Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2 to 4 weeks to achieve steady state prior to making dosing adjustments.
Homozygous for no function alleles (e.g., *2/*3A, *3/*4); poor metabolizer	Starting dose at approx 10% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 4 to 6 weeks to achieve steady state prior to making dosing adjustments.	Starting dose at approx 10% of full dose as dictated by protocol. Allow 4 to 6 weeks to achieve steady state prior to making dosing adjustments.

[a] For patients already receiving reduced starting dose of thiopurines (<75 mg/m2/day of 6-MP or <40 mg/m2/day of 6-TG) further dose reduction may not be needed.

American Gastroenterological Association Institute

Recommendations from a 2017 American Gastroenterological Association Institutes guidelines on therapeutic drug monitoring in IBD are summarized in Table 4.

Table 4. Summary of Findings of American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of IBD

Key Question	Conclusion	QOE
In patients with IBD being started on thiopurines, is routine TPMT measurement (to guide dosing) superior to no TPMT measurement (with empiric weight-based dosing of thiopurines)?	Benefit is uncertain but may avoid serious harm in a small fraction of patients	Low
In patients with active IBD treated with thiopurines or with side effects thought to be due to thiopurine toxicity, is reactive therapeutic drug monitoring to guide treatment changes superior to no therapeutic drug monitoring with empiric treatment changes?	May be a benefit	Very low
In patients with IBD treated with thiopurines, is routine therapeutic drug monitoring to guide thiopurine dosing superior to empiric weight-based dosing?	Benefit is uncertain	Very low

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Government Regulations

National:

There are no national or local coverage determinations on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

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16. Blue Cross Blue Shield Association. Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines. MPRM. 2.04.19. Published December 2000. Last updated December 2023.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/20/04	5/20/04	6/10/04	Joint policy established
3/01/07	1/17/07	2/05/07	Policy updated: changed from investigational to established
1/01/09	10/13/08	12/30/08	Routine maintenance
12/1/12	9/27/12	9/27/12	Policy reformatted to mirror BCBSA policy. Previously titled "Pharmacogenomic and Metabolite Markers for Patients with Inflammatory Bowel Disease (IBD) Who Have Been Treated with Azathioprine (6-MP)"
3/1/14	12/10/13	1/6/14	Title changed from "Pharmacogenomic and Metabolite Markers for Patients with Inflammatory Bowel Disease (IBD) Who Have Been Treated with Azathioprine (6-MP)" to "Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines." No change in policy status.
7/1/15	4/24/15	5/8/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Updated rationale and references (added 6, 7, 14, 25-28). No change in medical policy status.
5/1/18	2/20/18	2/20/18	Code update, added 81335 as established. Updated rationale and references (added 14, 17 and 29). No change in policy status.
11/1/18	8/21/18	8/21/18	Added code 82657 for phenotype testing and 0034U effective 1/1/18.
5/19/19	2/19/19		Added code 81306, Rationale reformatted, references # 19-21, 23 and 25 added. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Added nudix hydrolase (NUDT15) to MPS. Extensive editorial revisions made to convert it from a "test" to a

			“therapeutic” rubric. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance, no change in policy status.
5/1/23	3/29/23		Expanded coverage under inclusion section to align with our vendor-Avalon. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor Managed: Avalon (ds)

Next Review Date: 1st Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: PHARMACOGENOMIC AND METABOLITE MARKERS FOR PATIENTS TREATED WITH THIOPURINES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply,
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.