BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 2.04.19 Pharmacogenomic and Metabolite Markers for Individuals Treated With Thiopurines

### Annual Effective Policy Date: April 1, 2026

### Original Policy Date: December 2011

### Related Policies:

None

# Pharmacogenomic and Metabolite Markers for Individuals Treated With Thiopurines

## Description

## 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. The *TPMT* and *NUDT15* genes encode for the enzymes thiopurine S-methyltransferase (TPMT) and Nudix Hydrolase (NUDT15), respectively. These enzymes are involved in the metabolism of thiopurines. Genetic variants in *TPMT* and *NUDT15* genes affect drug hydrolysis and hence, increase susceptibility to drug-induced toxicity. Mercaptopurine and thioguanine are directly metabolized by the TPMT enzyme. Susceptibility to drug toxicity is linked to the level of TPMT activity. The variation in TPMT activity has been related to 3 distinct TPMT variants. TPMT can be assessed through genetic analysis for polymorphisms in leukocyte DNA (genotype) or by measurement of the enzyme activity in circulating red blood cells (RBCs; phenotype). NUDT15 is measured by genetic analysis only (genotype). Pharmacogenomic analysis of TPMT/NUDT15 status is proposed to identify individuals at risk of thiopurine drug toxicity and adjustment of medication doses accordingly. Measurement of metabolite markers has also been proposed.

## OBJECTIVE

The objective of this evidence review is to determine whether metabolite marker analysis improves the net health outcome in individuals treated with thiopurines.

# POLICY STATEMENT

One time genotypic or phenotypic analysis of thiopurine methyltransferase (*TPMT*) and nudix hydrolase (*NUDT15*) may be considered **medically necessary** in individuals beginning therapy with azathioprine, mercaptopurine, or thioguanine OR in individuals on thiopurine therapy with abnormal complete blood count results that do not respond to dose reduction.

Genotypic and/or phenotypic analysis of the *TPMT* and *NUDT15* genes is considered **investigational** in all other situations.

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

# POLICY GUIDELINES

Thiopurine methyltransferase (*TPMT*) and/or nudix hydrolase (*NUDT15*) testing cannot substitute for complete blood count monitoring in individuals receiving thiopurines. Early drug discontinuation may be considered in individuals with abnormal complete blood count results. Dosage reduction is recommended in individuals with reduced TPMT/NUDT15 activity. Alternative therapies may need to be considered for individuals who have low or absent TPMT/NUDT15 activity (homozygous for nonfunctional alleles). Accurate phenotyping results are not possible in individuals who have received recent blood transfusions. *TPMT/NUDT15* genotyping and phenotyping would only need to be performed once.

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

# BENEFIT APPLICATION

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

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.

# FDA REGULATORY STATUS

Some Plans may have contract or benefit exclusions for genetic testing or have state mandates for biomarker testing coverage.

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 (CLIA). Several thiopurine genotype, phenotype, and metabolite tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

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).

## Food and Drug Administration Labeling on Pharmacogenomic Test for Thiopurines

The FDA has included pharmacogenomics information in the physician prescribing information 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[7,]

- 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 the 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[8,]

- 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 complete blood count (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[9,]

- 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 (RBC 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.

## RATIONALE

### Summary of Evidence

For individuals who are treated with thiopurines and receive thiopurines metabolite monitoring to guide treatment, the evidence includes 1 systematic review and 2 randomized controlled trials (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 in patients being treated with thiopurines includes only retrospective studies that were not included in this review. The pooled analysis of both RCTs reported in the systematic review did not show a statistically significant difference in clinical remission in patients who underwent routine therapeutic drug monitoring-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. Both trials were terminated early due to slow recruitment and the inability to meet the predetermined enrollment targets. Additionally, both trials experienced significant participant dropout rates, ranging from 33% to 46%. Based on 2 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 insufficient to determine that the technology results in an improvement in the net health outcome.

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 U.S. Food and Drug Administration -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.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American Gastroenterological Association Institute

Recommendations from the American Gastroenterological Association Institute (2017) guidelines on therapeutic drug monitoring in inflammatory bowel disease (IBD) are summarized in Table 2.[12,1,]

**Table 1. Summary of Findings of the American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Disease**

| 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 |

IBD: inflammatory bowel disease; QOE**:** quality of evidence; *TPMT*: thiopurine methyltransferase.

### National Comprehensive Cancer Network

National Comprehensive Cancer Network (v.2.2025) guidelines on adult and adolescent/young adult acute lymphoblastic leukemia state:[13,]

- "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. Testing for both TPMT and NUDT15 [Nudix Hydrolase] variant status should be considered, especially for patients of East Asian origin."

National Comprehensive Cancer Network (v.1.2026) guidelines for pediatric acute lymphoblastic leukemia state:[14,]

- Genetic testing for no function alleles of TPMT and NUDT-15 should be considered prior to the initiation of thiopurine therapy, or 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 3. Dosing recommendations for patients who are heterozygous or homozygous for *NUDT15* no function allele are summarized in Table 4.
- 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 2. Dosing Guidelines for Thiopurines based on *TPMT* Phenotype

| Genotype/Phenotype | Dosing Recommendations for 6-MP | Dosing Recommendations for 6-TG |
|---|---|---|
| Homozygous for normal function alleles (eg *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 (eg *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 (eg *2/*3A, *3/*4); poor metabolizer | Starting dose at approximately 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 approximately 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 a reduced starting dose of thiopurines (<75 mg/m$^2$/day of 6-MP or <40 mg/m$^2$/day of 6-TG), a further dose reduction may not be needed.
6-MP: mercaptopurine; 6-TG: 6-thioguanine; *TPMT*: thiopurine methyltransferase.

### Table 3. Dosing Guidelines for Thiopurines based on *NUDT15* Phenotype

| Genotype/Phenotype | Dosing recommendations for 6-MP | Dosing recommendations for 6-TG |
|---|---|---|
| Homozygous for normal function alleles (eg, *1/*1); normal metabolizer | Starting dose should be based on treatment protocol. Allow 2 weeks to achieve steady state prior to making dose adjustments. | Starting dose should be based on treatment protocol. Allow 2 weeks to achieve steady state prior to making dose adjustments. |
| Heterozygous for no function allele (eg, *1/*2, *1/*3, *1/*9); intermediate metabolizer[d] | Start at 30% to 80% of full dose. Adjust based on degree of myelosuppression as dictated by protocol. Allow 2 to 4 weeks to achieve steady state prior to making dose adjustments. | Start at 50% 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 dose adjustments. |
| Homozygous for no function alleles (eg, *2/*3); poor metabolizers | Start at 10 mg/m$^2$/day. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 4 to 6 weeks to achieve steady state prior to making dose adjustments. | Start at 25% 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 dose adjustments. |

[a]For patients who are intermediate metabolizers of *NUDT15* who are already receiving reduced starting doses of thiopurines (<75 mg/m$^2$/day of 6-MP or <40 mg/m$^2$/day of 6-TG), a further dose reduction may not be needed.
6-MP: mercaptopurine; 6-TG: 6-thioguanine; *NUDT15*: Nudix hydroxylase.

## 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.

# REFERENCES


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# POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| December 2011 | New policy | |
| December 2012 | Replace policy | Policy updated with literature search, References updated, Policy statements unchanged. |
| September 2013 | Replace policy | Policy updated with literature search. References 7,9,15 and 20 added; other references renumbered or removed. Policy statements unchanged. |
| September 2014 | Replace policy | Policy updated with literature review. References 5, 6, and 18 added. Policy statements unchanged. |
| September 2015 | Replace policy | Policy updated with literature review; references 4, 11 and 21 added. Policy statements unchanged. |
| March 2017 | Replace policy | Policy updated with literature review through November 3, 2016; references 6-7 and 14 added. Policy statements unchanged. |
| March 2018 | Replace policy | Policy updated with literature review through September 11, 2017; references 14, 17, and 29 added. Policy statements unchanged. |
| March 2019 | Replace policy | Policy updated with literature review through September 9, 2018; references 19-21, 23, and 25 added. Policy statements unchanged. |

| Date | Action | Description |
|---|---|---|
| March 2020 | Replace policy | Policy updated with literature review through September 9, 2019, no references added. Policy statements unchanged. |
| March 2021 | Replace policy | Policy updated with literature review through September 25, 2020; references added. Extensive editorial revisions were made to convert format from a "testing" to a "therapeutic" framework. FDA approved language in the prescribing labels for phenotype/genotype testing was added to the Regulatory Status section and forms the basis of medically necessary policy statements. Review of evidence for phenotype/genotype testing was deleted. Updated evidence review for thiopurine metabolite monitoring provided. Policy statement on NUDT15 gene was added to medically necessary statements; other policy statements unchanged. |
| March 2022 | Replace policy | Policy updated with literature review through September 8, 2021, no references added. Policy statements unchanged. |
| March 2023 | Replace policy | Policy updated with literature review through September 27, 2022, reference added. Minor editorial refinements to policy statements; intent unchanged. |
| December 2023 | New policy - FEP | FEP New Benefit and Policy |
| March 2024 | Replace policy | Policy updated with literature review through September 21, 2023, no references added. A second indication was added to clarify that evidence related to phenotype or genotype analysis for thiopurine methyltransferase and nudix hydrolase was not reviewed. The policy statements are based on the recommendations made in the FDA approved prescribing labels of thiopurines. Policy statements unchanged. |
| March 2025 | Replace policy | Policy updated with literature review through September 30, 2024; no references added. Policy statements unchanged. |
| March 2026 | Replace policy | Policy updated with literature review through September 30, 2025; no references added, guidelines updated. Minor editorial refinements to policy statements, including title change; intent unchanged. |