BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.19 Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines

Effective Policy Date: April 1, 2023

Original Policy Date: December 2011

Related Policies:

None

Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines

Description

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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 patients 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 patients 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 patients 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.

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

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).

FDA 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 receive thiopurines metabolite monitoring to guide treatment changes, the evidence includes 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 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 randomized studies. 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%). 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 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. 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.

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.

National Comprehensive Cancer Network

National Comprehensive Cancer Network (v.1.2022) guidelines on adult and adolescent/young adult acute lymphoblastic leukemia state:[12,]

- "For patients receiving 6-MP, 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 variant status should be considered, especially for patients of East Asian origin."

National Comprehensive Cancer Network (v.1.2022) guidelines for pediatric acute lymphoblastic leukemia state:[13,]

- 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 1.
- 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 1. Dosing Guidelines for Thiopurines 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 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 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.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (2013) committee on inflammatory bowel disease (IBD) published consensus recommendations on the role of the TPMT enzyme and thiopurine metabolite testing in pediatric IBD.[14,] 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 2.[15,1,]

Table 2. Summary of Findings of the 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

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

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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.
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.