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Medical Policy

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Title: Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Professional	Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are treated with thiopurines	Interventions of interest are: • Azathioprine and/or 6-mercaptoprine metabolites analysis	Comparators of interest are: • Standard management without metabolite analysis	Relevant outcomes include: • Change in disease status • Treatment-related mortality • Treatment-related morbidity

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 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.

BACKGROUND

Thiopurines

Thiopurines or purine analogues are immunomodulators. These agents include azathioprine (Imuran®), mercaptopurine (6-MP; Purinethol®), and thioguanine (6-TG; Tabloid®). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, and in solid organ transplantation. These agents are also considered an effective immunosuppressive

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treatment of inflammatory bowel disease (IBD), particularly in patients with corticosteroid-resistant disease. However, the use of thiopurines is limited by both a long onset of action (3 to 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-TGN) and 6-methylmercaptopurine (6-MMP). Thiopurine methyltransferase (TPMT) is 1 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-TGN 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% 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% to 21.2%). Studies in other populations are ongoing.[4,]

Phenotype Testing for Thiopurine Methyltransferase Activity
Testing involves incubation of red blood cell (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 TPMT. 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

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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

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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) a reactive strategy in response to either lack of clinical improvement or observed treatment-related toxicity or 2) routine proactive clinical care in patients with quiescent disease.

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.

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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.

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POLICY

A. One-time genotypic or phenotypic analysis of the thiopurine methyltransferase (TPMT) and nudix hydrolase (NUDT15) may be considered **medically necessary** in individuals:
   1. beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG)
      OR
   2. on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction

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

C. 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), is considered **experimental / 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.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 27, 2022.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes 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

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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 the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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 Therapy Purpose

The purpose of monitoring thiopurine metabolite (6-thioguanine [6-TGN] and 6-methylmercaptopurine [6-MMP]) levels in patients 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)

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The question addressed in this evidence review is: Does monitoring of thiopurine metabolite (6-TGN and 6-MMP) levels in patients treated with thiopurines improve the net health outcome in patients who are treated with thiopurines?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients 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 (RBC) 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 reactions). In contrast, empiric treatment changes, such as escalation of therapy in patients with suboptimal response, may result in excessively high 6-TGN levels, 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 RCTs;
- 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

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Systematic Reviews

The American Gastroenterological Association published a systematic review on the role of therapeutic drug monitoring in the management of inflammatory bowel disease (IBD) 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 versus empiric treatment changes. Two randomized studies that evaluated routine therapeutic drug monitoring to guide thiopurine dosing compared to empiric weight-based dosing were identified.

Randomized Controlled Trials

The first was a double-blind RCT conducted in the United States using thiopurine S-methyltransferase (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 the control arm.[10,] 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 10^8 RBCs versus standard azathioprine weight based dosing (2.5 mg/kg body weight).[11,] 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 an 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 therapeutic drug monitoring -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 (relative risk [RR], 1.44; 95% confidence interval [CI], 0.59 to 3.52). The rate of serious adverse events (requiring discontinuation of therapy) was comparable between the 2 arms (therapeutic drug monitoring-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 the overall quality of evidence was 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 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

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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.

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 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

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

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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 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 2. 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 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

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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 3.[15,1,]

Table 3. 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.

Ongoing and Unpublished Clinical Trials

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Some currently ongoing and unpublished trials that might influence this review are listed in Table 4.

Table 4. 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

NCT: national clinical trial.

No review or update is scheduled on this Medical Policy as it is unlikely that further published literature would change the policy position. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, your professional or institutional relations representative, or submit a predetermination request.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81335	TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)
84433	Thiopurine S-methyltransferase
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15)(e.g., thiopurine metabolism) gene analysis, common variants (i.e., TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5) [Mayo Clinic]
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism) gene analysis, common variants

ICD-10 DIAGNOSES	
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding

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ICD-10 DIAGNOSES	
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess
K51.218	Ulcerative (chronic) proctitis with other complication
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication

REVISIONS	
11-29-2010	Policy added to the bcbsks.com web site.
07-19-2011	Updated Description section
	In Policy section: ▪ Added the word "enzyme" to read, "One-time genotypic or phenotypic analysis of the enzyme TPMT (thiopurine methyltransferase) may be considered medically necessary in patients:"
	Updated Rationale section

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REVISIONS	
	Updated References
02-14-2012	In Coding section: ▪ Added CPT code: 81401 (effective 01-01-2012) ▪ Added the following notation: "81401 should be used for genotypic analysis of the TPMT gene effective 01-01-2012." ▪ Revised the following notation by removing the words "genotypic or" to read, "There are no specific CPT codes for phenotypic analysis of the TPMT gene or for metabolite markers of azathioprine, mercaptopurine (6-MP) or thioguanine."
08-13-2012	Description section updated
	In Policy section: ▪ Added in B. the abbreviation "(AZA)" to read, "B. Analysis of the metabolite markers of azathioprine (AZA) and…"
	Rationale section updated
	In Coding section: ▪ Updated nomenclature in CPT Code 81401.
	References updated
01-15-2013	In Coding section: ▪ Added CPT code: 81479 (effective 01-01-2013) ▪ Updated coding instructions to remove reference to 83891, 83896, 83898, and 83912 which are no longer effective as of 12-31-2012.
02-28-2014	Description section updated
	Rationale section updated
	In Coding section: ▪ Removed ICD-9 Diagnoses Codes: 555.9, 556.4, 556.5, 556.9 ▪ ICD-10 Diagnoses Codes added
	References updated
11-05-2015	Description section updated
	In policy section: ▪ Added "Genotypic and/or phenotypic analysis of the enzyme TPMT is considered experimental / investigational in all other situations." This addition did not change the policy from its original intent, but is more clear that any situation not meeting the criteria is considered E/I.
	Rationale section updated
	References updated
	Added Appendix Table 1. Categories of Genetic Testing Addressed in Policy
05-10-2017	Description section updated
	In Policy section: ▪ Policy Guidelines updated to add information on Genetic Counseling.
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References updated

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REVISIONS	
12-20-2017	Description section updated
	Rationale section updated
	In Coding section: ▪ Removed CPT Code: 81401 (Effective 12-31-2017) ▪ Added CPT Code: 81335 (Effective 01-01-2018)
	References updated
04-10-2019	Description section updated
	Rationale section updated
	In Coding section: ▪ Added PLA Code: 0034U (Effective 01-01-2018) ▪ Added ICD Codes: K50.10, K50.111, K50.112, K50.113, K50.114, K50.118, K50.80, K50.811, K50.812, K50.813, K50.814, K50.818, K51.80, K51.811, K51.812, K51.813, K51.814, K51.818
	References updated
04-16-2021	Description section updated
	In Policy section: • Added underlined section to Items A to read "One-time genotypic or phenotypic analysis of the thiopurine methyltransferase (TPMT)and nudix hydrolase (NUDT15) enzyme may be considered **medically necessary** in patients" and added underlined section to Item B to read "Genotypic and/or phenotypic analysis of the TPMT and NUDT15 enzyme is considered **experimental / investigational** in all other situations." • Added nudix hydrolase (NUDT15) to policy guidelines
	Rationale section updated
	In Coding section: • Added: 0169U • Deleted: 81479
	References section updated
01-03-2023	Updated Coding Section ▪ Added 84433 (eff 01-01-2023)
02-17-2023	Updated Description Section
	Updated Rationale Section
	Updated Policy Guideline Section ▪ Removed 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.

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REVISIONS	
	Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
	Updated References Section
02-17-2023	Archived

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