

Policy: MPA G2115

Section: Medical Policy

Subject: Metabolite Markers of Thiopurines Testing

Applicable Lines of Business

Commercial	x	CHIP	x
Medicare	x	ACA	x
Medicaid	x		

I. Policy: Metabolite Markers of Thiopurines Testing

II. Purpose/Objective: To provide a policy of coverage regarding

III. Responsibility:

- A. Medical Directors
- B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

Commercial

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicare

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

CHIP

Geisinger Health Plan Kids (GHP Kids) is a Children’s Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicaid

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age.

Metabolite Markers of Thiopurines Testing

Policy Number: AHS – G2115 – Metabolite Markers of Thiopurines Testing

Original Effective Date: 06/01/2022
Current Effective Date: 02/01/2026

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Policy Description

Thiopurines are a class of purine antimetabolite immunomodulators with diverse clinical applications in treatment of autoimmune disorders, transplant rejection, and acute lymphoblastic leukemia.¹ Their therapeutic efficacy, bone marrow toxicity, and liver toxicity have been reported to be related to levels of their downstream metabolites. Due to their complex metabolism, patient response varies considerably between individuals, both in achieving therapeutic drug levels as well as in developing adverse reactions.²

Please note that this policy discusses the monitoring of thiopurine metabolite levels in individuals.

Related Policies

Policy Number	Policy Title
N/A	Not Applicable

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- 1) One-time phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) **MEETS COVERAGE CRITERIA** for any of the following situations:

- a) Prior to initiating treatment with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG).
 - b) For individuals on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction.
- 2) For individuals with inflammatory bowel disease, monitoring of thiopurine metabolite levels **MEETS COVERAGE CRITERIA** for **any** of 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).
 - 3) For individuals with acute lymphoblastic leukemia, monitoring of thiopurine metabolite levels **MEETS COVERAGE CRITERIA** for **any** of the following situations:
 - a) For individuals showing signs of a lack of myelosuppression while on therapy.
 - b) For individuals who do not tolerate thiopurines.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 4) For all other situations not addressed above, phenotypic analysis of the enzyme TPMT **DOES NOT MEET COVERAGE CRITERIA**.
- 5) For all other situations not addressed above, analysis of the metabolite markers of azathioprine and 6-mercaptopurine, including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), **DOES NOT MEET COVERAGE CRITERIA**.

Table of Terminology

Term	Definition
6-MMRP	6-methyl-mercaptopurine ribonucleotides
6-MMP	6-methyl-mercaptopurine
6-MP	6-mercaptopurine
6-TG	6-thioguanine
6-TGN	6-thioguanine nucleotides
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
ASC	Acute severe colitis
ALL	Acute lymphoblastic leukaemia
AZA	Azathioprine
BNF	British National Formulary
BNFC	British National Formulary for Children
BSG	British Society of Gastroenterology
CBC	Complete blood count
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers for Medicare and Medicaid Services
CPIC	Clinical Pharmacogenetics Implementation Consortium
ECCO	European Crohn's and Colitis Organization
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology and Nutrition

FDA	Food and Drug Administration
HPLC	High-performance liquid chromatography
IBD	Inflammatory bowel disease
IVCS	Intravenous corticosteroids
LCA	Local coverage article
LCD	Local coverage determination
LDT	Laboratory-developed test
LFT	Liver function test
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NRH	Nodular regenerative hyperplasia
NUDT15	Nudix hydrolase 15
RBC	Red blood count
RCT	Randomized controlled trial
SFR	Steroid-free clinical remission
TDM	Therapeutic drug monitoring
TIL	Thiopurine-induced leukopenia
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis

Scientific Background

The thiopurine drugs 6-mercaptopurine (6-MP), azathioprine (AZA), and thioguanine remain a mainstay of immunomodulator therapy.^{1,3,4} However, several metabolites of these drugs (particularly 6-thioguanine [6-TG] and 6-methylmercaptopurine [6-MMP]) have been associated with harmful side effects, such as lowered therapeutic efficacy, hepatotoxicity, bone marrow toxicity, and more. The management of these toxic metabolites is further complicated by the many polymorphisms (and therefore efficacy in metabolism) of the genes responsible for metabolizing these drugs. Due to these toxic side effects, there has been significant investigation on monitoring of these metabolites to identify the optimal dose of a thiopurine for an individual patient. This process is called therapeutic drug monitoring (TDM).⁴

Two enzymes are responsible for catalyzing these reactions: thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase. TPMT enzyme activity is a major factor determining AZA and 6-MP metabolism, and therefore 6-TG and 6-MMP levels. The majority of the population has wild type *TPMT* and normal enzyme activity, while 11% are heterozygous and have corresponding low TPMT enzyme activity, and 0.3% (1 in 300) have negligible activity.⁴⁻⁶ Intermediate and normal metabolizers can have up to a threefold difference in initial target doses of AZA and 6-MP to achieve therapeutic 6-TG concentrations.⁷ Measurement of TPMT enzyme activity before instituting AZA or 6-MP may help prevent toxicity by identifying individuals with low or absent TPMT enzyme activity as well as identify those with higher than average TPMT activity who may remain refractory to conventional dosages.⁴ Dosing strategies involving such testing may be cost-effective.⁸⁻¹⁰ However, prediction of toxicity is not consistently reliable, as other enzymes are also likely to play a role in determining toxicity, such as glutathione-S-transferase,¹¹ and drug interactions must be taken into account.¹²⁻¹⁴ Thus, even though TPMT testing is recommended, a complete blood count (CBC), and also liver function tests, must still be obtained.^{1,15}

Another enzyme that may contribute to thiopurine metabolism is nucleoside diphosphate-linked moiety X motif 15, NUDIX 15 (NUDT15). Variants in this enzyme's genotype and subsequent phenotype may lead to drastically reduced tolerance of 6-MP.³ Moriyama et al. proposed that NUDT15 variants cause thiopurines'

mechanism of action to fail by preventing the thiopurine metabolites' incorporation into DNA. This causes these metabolites to remain active and therefore toxic.¹⁶ The frequency of these NUDT15 variants varies across populations, with the "poor metabolizer" phenotype reaching as high as one in 50 in East Asian populations. Despite the data indicating NUDT15's role in thiopurine toxicity, guidelines for its assessment have not reached a consensus, and expert opinions and practices are mixed.³

Therapeutic drug monitoring (TDM) is the measurement of serum, plasma, or urinary concentrations of a given drug. This can be measured in a variety of ways, including high performance liquid chromatography (HPLC) or mass spectrometry approaches such as GC-MS.¹⁷ TDM is proposed to allow a clinician to identify the "optimal" dose of a drug (such as a thiopurine) for a patient, thereby maximizing therapeutic efficacy and minimizing harmful side effects. Non-TDM approaches typically involve starting at low doses, then adjusting if the patient is tolerating the drug well or poorly, whereas TDM takes a more proactive approach in managing dose.⁴ Several studies have attempted to identify standardized ranges of "optimal" metabolite concentrations. For example, the optimal concentration of the 6-TGN metabolite was found to be between 230 and 400 picomoles per 8×10^8 erythrocytes by Dubinsky et al. In that same study, bone marrow toxicity was found to correlate with levels above 400 picomoles per 8×10^8 erythrocytes.¹⁸ Although there are potential limitations to TDM for thiopurines (such as intra-individual variability, lack of correlation with toxicity for 6-MMP, and so on), TDM used in conjunction with TPMT and NUDT15 assessment may allow clinicians to increase the therapeutic efficacy of thiopurines.^{3,4}

Clinical Utility and Validity

Haines, et al. (2011) performed a retrospective study of the utility of measuring thiopurine metabolites in "inadequately controlled" inflammatory bowel disease (IBD). A total of 63 patients with IBD were included, and these patients were treated with AZA or 6-mercaptopurine. On weight-based criteria, 50% patients were underdosed. However, metabolite study suggested that "7 (11%) patients were noncompliant, 18 (29%) were being underdosed, 33 (52%) were refractory to treatment with either appropriate (41%) or elevated (11%) metabolite concentrations, and 6 (10%) had a raised 6-methyl mercaptopurine: 6-thioguanine nucleotide ratio consistent with aberrant thiopurine metabolism." The clinical outcome of 87% of patients improved when the treatment was shifted to a metabolite-based algorithm, whereas three of 17 patients improved when the discordant action was taken. The authors concluded that "Thiopurine metabolite testing is a potentially powerful tool for optimizing thiopurine usage in IBD."¹⁹

Lee, et al. (2017) evaluated 165 patients undergoing thiopurine treatment for Crohn's Disease. Thiopurine metabolite levels were measured, and both *TPMT* and *NUDT15* were genotyped. The authors found 95 patients responded to treatment whereas 45 did not. The median 6-TGN (the primary metabolite of 6-thioguanine) was significantly higher in responders than nonresponders. At a 6-TGN level of 230 pmol/ 8×10^8 blood cells, the odds ratio was 4.63 for responders to nonresponders. *NUDT15* variants were also found to be associated with "severe, early, leukopenia" with an average reduction of 88.2% from baseline white blood cell count at four weeks. The authors concluded that their findings "support the role of therapeutic drug monitoring in thiopurine maintenance treatment to optimize thiopurine therapy, especially, for non-responding CD patients."²⁰

Spencer, et al. (2019) compared "standard" and "optimized" thiopurine dosing regimens in 216 pediatric IBD patients. The "optimal" level was decided at "6-TGN >235 pmol/ 8×10^8 RBC," and the metabolite levels were correlated between the primary outcome of "steroid-free clinical remission (SFR)." Both groups were found to have similar initial and six month metabolite levels. SFR was achieved in 74% of the 180 patients on thiopurines at six months. The authors concluded that "steroid-free clinical remission and 6-TGN levels at 6 months were no different between a standardized, fixed dosing strategy and a metabolite-driven, optimized dosing strategy."²¹

Meijer, et al. (2017) evaluated the effects of thiopurine metabolites on clinical signs and if patient characteristics affected metabolite generation. A total of 940 "laboratory findings" from 424 patients were examined. 6-TGN (a metabolite of azathioprine [AZA] and mercaptopurine) was found to negatively correlate with RBC count, WBC count, and neutrophil count. However, in patients using 6-thioguanine, those 6-TGN

concentrations correlated positively with WBC count. An inverse correlation was observed between age and 6-TGN concentrations in AZA or 6-thioguanine patients, as well as between body mass index and 6-TGN in AZA or mercaptopurine patients. The authors concluded that “thiopurine derivative therapy influenced bone marrow production and the size of red blood cells. Age and body mass index were important pharmacokinetic factors in the generation of 6-TGN.”²²

Estevinho, et al. (2017) performed a meta-analysis to “assess the clinical value of 6-thioguanine nucleotide thresholds; and ii] to compare mean 6-thioguanine nucleotide concentrations between patients in clinical remission vs. those with active disease.” A total of 22 records were used in cut-off comparisons and 12 were used in the 6-thioguanine nucleotide mean differences analysis. The authors calculated the global odds ratio for remission in patients with 6-thioguanine nucleotides above predefined thresholds to be 3.95. The authors also found an odds ratio for remission of 2.25 for the 235 pmol/8 x 10⁸ RBC threshold, and an odds ratio of 4.71 for the 250 pmol /8 x 10⁸ RBC threshold. Finally, the authors found a “pooled difference” of 63.37 pmol/8 x 10⁸ RBC between patients in clinical remission and those not in remission. Overall, the authors concluded that the study reinforced the link between 6-thioguanine nucleotide levels and clinical remission in inflammatory bowel diseases.²³

Toksvang, et al. (2019) performed a meta-analysis focusing on “incidence of hepatotoxicity in patients [with childhood acute lymphoblastic leukaemia, ALL or inflammatory bowel disease, IBD] treated with 6TG [6-thioguanine].” A total of 42 reports were included, further broken down into “four randomised controlled trials (RCTs) including 3,993 patients, 20 observational studies including 796 patients, and 18 case reports including 60 patients.” The authors measured hepatotoxicity by “sinusoidal obstruction syndrome,” which occurred in 9-25% of ALL patients in two of the four RCTs at a dosage of 40–60 mg/m²/day. The authors also noted that at a dosage of 23 mg/m²/day, nodular regenerative hyperplasia (NRH) occurred in 14% of IBD patients. At a dosage of 12 mg/m²/day, NRH occurred in 6% of IBD patients, which was noted to be similar to background incidence. The authors therefore concluded that doses at or under 12 mg/m²/day can “probably be considered safe.”²⁴

Zhu, et al. (2019) evaluated the “predictive sensitivity based on 6TGN [6-thioguanine nucleotide] by subgrouping patients according to their *NUDT15* R139C genotypes.” The authors included 411 patients with Crohn’s Disease. Two subgroups of *NUDT15* genotypes were created, “CC” (n = 342) and “CT” (n = 65), with the final four patients harboring a TT genotype. Thiopurine-induced leukopenia (TIL) was the primary clinical endpoint measured. The authors found that of the 342 patients with a CC genotype, only 35 developed TIL (10.2%), but of the 65 CT patients, 33 developed TIL (50.2%). All four of the TT patients developed TIL. The authors also found that in both CC and CT genotypes, the median 6TGN level was higher in patients with TIL than patients without TIL (for CC, 474.8 pmol/8 × 10⁸ RBC vs 306.0 pmol/8 × 10⁸ RBC, for CT 291.7 / 8 × 10⁸ RBC vs 217.6/8 × 10⁸ RBC). From this data, the authors calculated the “cut-off” (a threshold to identify an optimal number of cases) of the CT genotype to be 319.2 pmol/8 × 10⁸ RBC and the cut-off for CC to be 411.5 pmol/8 × 10⁸ RBC). Overall, the authors concluded that “The predictive sensitivity of TIL based on 6TGN is dramatically increased after subgrouping according to *NUDT15* R139C genotypes. Applying 6TGN cut-off levels to adjust thiopurine therapies based on *NUDT15* is strongly recommended.”²⁵

Ioannou, et al. (2025) studied the genetic polymorphisms on thiopurine-associated leukopenia in Hispanic people. The study included 2225 participants, all of whom were Hispanic. The researchers looked for variants to *NUDT15* and *TPMT*. The authors found that *NUDT15* and *TPMT* variants were rare, but all *NUDT15* variants were inherited on an Amerindian haplotype. The authors concluded that “*NUDT15* testing should become standard clinical practice before prescribing thiopurines in individuals with Amerindian/Alaska Native ancestry, including Hispanic individuals.”²⁶

Yassin, et al. (2024) studied the use of thiopurine metabolite testing in autoimmune hepatitis patients who were unsuccessfully treated with thiopurines. The study included 21 patients, with a total of 25 thiopurine metabolite tests. Three tests had high thiopurine metabolites levels and resulted in a decrease in drug dose. Eleven tests had low levels of 6-thioguanine nucleotide and resulted in an increase to drug dose in 8 patients. The authors concluded that “in cases of suboptimal response to thiopurine treatment, measuring thiopurine metabolites had

an important role in optimizing therapy.”²⁷

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

In version three of the 2025 guidelines for Pediatric Acute Lymphoblastic Leukemia, the NCCN recommends that “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.” The NCCN also writes that “genetic testing for no function alleles of TPMT and NUDT15 should be considered prior to the initiation of thiopurine therapy or if excessive toxicity is encountered following treatment with thiopurines.”²⁸

In version one of the 2025 guidelines for Acute Lymphoblastic Leukemia, the NCCN notes that “quantification of 6-MP metabolites can be very useful in determining whether lack of myelosuppression is due to non-adherence or hypermetabolism.” The guidelines also state, “for patients receiving 6-MP, consider testing for TPMT 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 descent.”²⁹

Toronto Ulcerative Colitis Consensus Group/American College of Gastroenterology (ACG)

Bressler, et al. (2015) published clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis on behalf of the Toronto Ulcerative Colitis Consensus Group, which reaffirmed recommendations from the American College of Gastroenterology, Practice Parameters Committee³¹ for thiopurine therapy.³⁰ The authors stated that “...a TPMT assay is necessary before initiation of treatment to identify patients at risk for severe dose-dependent myelosuppression...therefore, thiopurine metabolite levels may be helpful to guide therapy. Note that TPMT testing does not replace the need for mandatory monitoring of complete blood cell count.”³⁰

American College of Gastroenterology (ACG)

The ACG published a guideline for the “Management of Crohn's Disease in Adults.” Their relevant recommendations include:

“Genetic variants, including HLADQA1*05, HLA-DRB1*03, nudix hydrolase 15 (NUDT15), and thiopurine methyltransferase (TPMT), can affect individual treatment response and identify potential risks for adverse effects of drug therapy in CD. These are clinically useful in disease management and should be measured in select patients.”

“We recommend TPMT testing before initial use of azathioprine or 6-mercaptopurine to treat patients with CD (strong recommendation, low level of evidence).”³²

The ACG also published a guideline for ulcerative colitis in adults. Their relevant recommendations include:

“The patient with nonresponse or loss of response to anti-TNF therapy should be assessed with trough serum concentrations of drug to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.”

“There is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission.”³³

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Committee

In 2013, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Committee on Inflammatory Bowel Disease published consensus recommendations on the role of TPMT and thiopurine metabolite testing in pediatric IBD. The recommendations included the following:³⁴

- “TPMT testing is recommended before initiation of TPs to identify individuals who are homozygote recessive or have extremely low TPMT activity, with the latter having more reliability than the former. (HIGH)”
- “Individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of TPs because of concerns for significant leukopenia. (HIGH)”
- “TPMT testing does not predict all cases of leukopenia and has no value to predict hypersensitivity adverse effects such as pancreatitis. Any potential value to reduce the risk of malignancy has not been studied. All individuals on TPs should have routine monitoring with CBC and WBC count differential to evaluate for leukopenia regardless of TPMT testing results. (HIGH)”
- “Metabolite testing can be used to determine adherence to TP therapy. (HIGH)”
- “Metabolite testing can be used to guide dose increases or modifications in patients with active disease. Consideration would include either increasing the dose, changing therapy or for those with elevated transaminases or an elevated 6-MMP, using adjunctive allopurinol to help raise 6-TG metabolites and suppress formation of 6-MMP. (MODERATE)”
- “Routine and repetitive metabolite testing has little or no role in patients who are doing well and taking an acceptable dose of a TP. (MODERATE)”

American Gastroenterological Association (AGA)

In 2017, the AGA published guidelines on Therapeutic Drug Monitoring in Inflammatory Bowel Disease which recommend:³⁵

- “In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes.”
- “In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring.”

The AGA published an Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases in the same year. In it, they note that IBD patients treated with thiopurines may benefit from reactive TDM to guide treatment changes.³⁶

In the 2020 AGA guidelines for “Management of Moderate to Severe Ulcerative Colitis,” the AGA remarks that “therapeutic drug monitoring to guide the use of biologic therapy has been addressed in separate AGA guidelines.” The “separate AGA guidelines” refer to the 2017 edition above.³⁷

In the 2024 update to the AGA guidelines for “Pharmacological Management of Moderate-to-Severe Ulcerative Colitis,” the AGA recommends: “Patients should have both general and therapy-specific pretreatment workup before initiation of such treatments. These include screening for hepatitis B and tuberculosis exposure before any biologic or advanced small molecule treatments, thiopurine methyl transferase testing before initiation of thiopurines, and a baseline electrocardiogram before use of S1P receptor modulators. There are other treatment- and patient-specific tests that should be performed in accordance with the labels from regulatory agencies.”³⁸

In 2025 the AGA published an expert review on “Noncolorectal Cancer Screening and Vaccinations in Patients With Inflammatory Bowel Disease” that mentions the appropriate use of thiopurines. They state “Adult women with IBD should follow age-appropriate screening for cervical dysplasia. Data are insufficient to determine whether patients receiving combined immunosuppression or thiopurines require more frequent screening. Shared decision making and individual risk stratification are encouraged.” They also state “All adult patients with IBD should follow skin cancer primary prevention practices by avoiding excessive exposure to the sun’s

ultraviolet radiation. Patients on immunomodulators, anti-tumor necrosis factor biologic agents, or small molecules should undergo yearly total body skin exam. Patients with any history of thiopurine use should continue with yearly total body skin exam even after thiopurine cessation.”³⁹

Clinical Pharmacogenetics Implementation Consortium (CPIC)

In their guideline for “Thiopurine Dosing Based on TPMT and NUDT15 Genotypes,” CPIC notes that “mercaptopurine and azathioprine are generally used for nonmalignant immunologic disorders, mercaptopurine for lymphoid malignancies, and thioguanine for myeloid leukemias.” However, CPIC also writes that “variants in NUDT15 have been identified that strongly influence thiopurine tolerance in patients with acute lymphoblastic leukemia (ALL) and those with inflammatory bowel diseases.”¹⁵

In 2020, the authors of this guideline added recommendations for TPMT and NUDT15 indeterminate phenotypes. That update is as follows:

- “For TPMT and NUDT15 indeterminate phenotypes, (i.e. combination of uncertain and/or unknown function alleles):
 - TPMT indeterminate: Consider evaluating TPMT erythrocyte activity to assess TPMT phenotype.
 - NUDT15 indeterminate: If thiopurines are required and NUDT15 status is unknown, monitor closely for toxicity.”⁴⁰

British Society of Gastroenterology (BSG)

The BSG published “consensus guidelines” on management of inflammatory bowel disease in adults. They recommend checking TPMT status in “all patients considered for thiopurine therapy.” They also recommend testing the NUDT15 genotype if “available.”

The BSG also writes that thiopurine metabolites should be checked if a patient experiences myelotoxicity as a side effect. Similarly, if a patient demonstrates “newly abnormal LFTs [liver function tests],” thiopurine metabolites should be checked. Also, BSG states that “all IBD patients considered for thiopurine therapy should have assessment of thiopurine methyltransferase (TPMT) status.”⁴¹

Overall, the BSG writes that thiopurine metabolites can be used to “optimize drug dosing” and “suggest that metabolite monitoring may be used for those with inadequate response to therapy or toxicity, but should not be a substitute for routine monitoring blood tests.”⁴¹

Canadian Association of Gastroenterology (CAG)

The Canadian Association of Gastroenterology published a guideline on “the Medical Management of Pediatric Luminal Crohn’s Disease.” The guidelines “suggested that testing for TPMT by genotype or enzymatic activity be done prior to initiating thiopurine therapy to guide dosing.”⁴²

An additional guideline for [Adult] Luminal Crohn’s Disease specifies “because some patients may have low or absent levels of the enzyme (thiopurine methyltransferase (TPMT) needed to metabolize thiopurines, a TPMT assay should be performed before initiation of treatment to identify patients at risk for severe toxicity.”⁴³

National Institute for Health and Care Excellence (NICE)

The NICE, released guidelines on Crohn’s Disease Management in 2019. In it, they recommend to “Monitor the effects of azathioprine, mercaptopurine, and methotrexate as advised in the British national formulary (BNF) or British national formulary for children (BNFC).”⁴⁴

European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ECCO and ESPGHAN)

These joint guidelines note that “measuring...6-TG and 6-MMP levels after two to three months, may aid in optimizing thiopurine dosing.” Measuring thiopurine metabolites is recommended in the following scenarios:

- In patients with incomplete response on stable thiopurine dosage
- In patients who present with leucopenia or elevated transaminases
- After acute severe colitis (ASC) responsive to intravenous corticosteroids (IVCS)
- When poor compliance is suspected.⁴⁵

Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
80299	Quantitation of therapeutic drug, not elsewhere specified
82657	Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen
84433	Thiopurine S-methyltransferase (TPMT)

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

Evidence-based Scientific References

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Revision History

Effective Date	Summary
02/01/2026	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
01/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Addition of CPT code 84433
12/01/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: All CC edited for clarity and consistency, including replacing “patient” with “individual”
06/01/2022	Initial Policy Implementation

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

LINE OF BUSINESS:

Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health

Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.