BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy #: 162
Category: Laboratory

Latest Review Date: December 2019
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **one-time genotypic or phenotypic analysis of the enzyme TPMT (thiopurine methyltransferase)** as a **covered benefit** for**:**

- Patients beginning azathioprine (AZA), 6-mercaptopurine (6-MP) or thioguanine (6-TG) therapy, **OR**
- Patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction

Blue Advantage will treat **genotypic and/or phenotypic analysis of the enzyme TPMT** as a **non-covered benefit** and as **investigational** in all other situations**.**

Blue Advantage will treat the **analysis of the metabolite markers of azathioprine (AZA) and 6-mercaptopurine (6-MP)**, **including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN),** as a **non-covered** benefit and as **investigational.**

*NOTE: TPMT testing cannot substitute for complete blood count (CBC) monitoring in patients receiving thiopurines. Early drug discontinuation may be considered in patients with abnormal CBC results. Dosage reduction is recommended in patients with reduced TPMT activity. Alternate therapies may need to be considered for patients who have low or absent TPMT activity (homozygous for non-functional alleles). Accurate phenotyping results are not possible in patients who received recent blood transfusions. Genotyping and phenotyping of TPMT would only need to be performed once.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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 that the use of thiopurines be limited due to a high rate of drug toxicity. Mercaptopurine and thioguanine are directly metabolized by the thiopurine S-methyltransferase (TPMT) enzyme. Susceptibility to drug toxicity is linked to the level of TPMT activity. The variation in TPMT activity has been related to three distinct TPMT variants. Pharmacogenomic analysis of TPMT status is proposed to identify patients at risk of thiopurine drug toxicity and adjust medication doses accordingly; measurement of metabolite markers has also been proposed.

Thiopurines
Thiopurines or purine analogues are immunomodulators. They include azathioprine (Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, IBD and are used in solid organ transplantation. They are considered an effective immunosuppressive treatment of IBD, particularly in patients with the corticosteroid-resistant disease. However, use of thiopurines is limited by both its long onset of action (three to four months) and drug toxicities, which include hepatotoxicity, bone marrow suppression, pancreatitis, and allergic reactions.

Pharmacogenomics
Thiopurines are converted to 6-MP in vivo, where it is subsequently metabolized to two active metabolites; either 6-thioguanine nucleotides (6-TGN) by the inosine-5′-monophosphate dehydrogenase (IMPDH) enzyme, or to 6-methyl-mercaptopurine ribonucleotides (6-MMPR) by the thiopurine methyltransferase (TPMT) enzyme. TPMT also converts 6-MP into an inactive metabolite, 6-methyl-mercaptopurine. 6-TGNs are considered cytotoxic and thus are associated with bone marrow suppression, while 6-MMPR is associated with hepatotoxicity. 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. In patients with intermediate-to-low activity, the metabolism of 6-MP is shunted toward the IMPDH pathway with greater accumulation of 6-TGN; these patients are considered at risk for myelotoxicity (i.e., bone marrow suppression).

This variation in TPMT activity has been related to three distinct TPMT variants and has permitted the development of TPMT genotyping based on a polymerase chain reaction (PCR). For example, patients with high TPMT activity are found to have two normal (wild-type) alleles for TPMT; those with intermediate activity are heterozygous (i.e., have a variant on one chromosome), while those with low TPMT activity are homozygous for TPMT variants (i.e., a variant is found on both chromosomes). Genetic analysis has been explored as a technique to identify patients at risk for myelotoxicity. Patients with high TPMT activity may be treated with standard doses of thiopurines, patients with intermediate TPMT activity may be initially treated with lower doses of thiopurines, while those with low TPMT activity may not be good candidates for thiopurine therapy.

TPMT activity can also be measured by phenotypic testing. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in erythrocytes and can also be informative. Caution must be taken with phenotyping, because some coadministered drugs can influence measurement of TPMT activity in blood, and recent blood transfusions will misrepresent a patient's actual TPMT activity.

Prospective TPMT genotyping or phenotyping may help identify patients who may be at increased risk of developing severe, life-threatening myelotoxicity.

The genotypic analysis of the TPMT gene is based on well-established polymerase chain reaction technology to detect three distinct variants. Currently, three alleles (TPMT*2, TPMT*3A, TPMT*3C) account for about 95% of subjects with reduced TPMT enzyme activity. Subjects homozygous for these alleles are TPMT-deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. A study by Hindorf and Appell (2012) addressed the concordance between TPMT genotyping and phenotyping. The investigators evaluated data from 7195 unselected and consecutive TPMT genotype and phenotype tests. The genotyping tests examined the three most common TPMT variants, previously noted. TPMT genotyping identified 6454 (89.7%) as TPMT wild-type, 704 (9.8%) as TPMT heterozygous, and 37 (0.005%) as TPMT homozygous. The overall agreement between genotyping and phenotyping was 95%. Genotyping alone would have misclassified three (8%) of 37 homozygous patients as heterozygous; these three subjects were found to have uncommon variants. All three had low TPMT activity. The phenotype test would have misclassified four (11%) of 37 of homozygous patients because they had test results above the cutoff level for low TPMT activity (<2.5 U/mL red blood cells).

Metabolite Markers
Monitoring of thiopurine therapy has been based on clinical assessment of response in addition to monitoring blood cell counts, liver function, and pancreatic function tests. However, there has been interest in monitoring intracellular levels of thiopurine metabolites (i.e., 6-TGN and 6-MMRP) to predict response and complications, with the ultimate aim of tailoring drug therapy to each individual patient.

Metabolite markers have been assessed using high-performance liquid chromatography technology. It would be optimal to assess metabolite markers in peripheral leukocytes because they reflect the status of bone marrow precursors. However, it is technically easier to measure metabolites in red blood cells than in leukocytes.

While genotyping and phenotyping of TPMT would only be performed once, metabolite markers might be tested at multiple times during the course of the disease to aid in determining initial dose and to evaluate ongoing dosing.

KEY POINTS:
The most recent literature review was updated through September 9, 2019

Summary of Evidence
For individuals who are treated with thiopurines who receive TPMT genotype analysis or TPMT phenotype analysis, the evidence includes studies of diagnostic performance, systematic reviews, and randomized controlled trials (RCTs). The relevant outcomes are symptoms, morbid events, and change in disease status. A large number of studies have assessed the diagnostic performance of TMPT genotyping and phenotyping tests. The most recent meta-analysis reported genotyping sensitivity and specificity of 90% and 100%, respectively, and a phenotyping sensitivity and specificity of 76% and 99%, respectively, for identifying patients with subnormal enzymatic activity. Three RCTs (total n=1145 patients) compared TPMT

genotype/phenotype testing with no testing and empirical weight-based thiopurine dosing. There was no significant difference in the incidence of hematologic adverse events, treatment discontinuation rates, or clinical remission. However, secondary analysis of a small number of individual who had intermediate enzymatic activity (a heterozygous genotype) or low enzymatic activity (a homozygous genotype) showed that TPMT testing to guide dosing was associated with statistically significant risk reduction in hematologic adverse events with a wide margin of error. In summary, 200 patients would have to be genotyped to avoid one episode of a hematologic adverse drug reaction (7.4% vs 7.9%; i.e., 0.5% risk difference). The number needed to treat to avoid one episode of a hematologic adverse drug reaction would be five for at-risk individuals (risk difference in patients with a genetic variant, 20.3%; 2.6% vs 22.9%). In addition, a small inadequately powered RCT that assessed phenotype TPMT testing found no difference in treatment discontinuation rates due to adverse drug reactions between the two arms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are treated with thiopurines who receive azathioprine (AZA) and/or 6-mercaptoprine metabolites analysis, the evidence includes a systematic review as well as prospective and retrospective studies. The relevant outcomes are symptoms, morbid events, and change in disease status. The systematic review, which assessed the diagnostic accuracy of metabolite testing, reported that the ability of the metabolite tests to predict clinical outcomes and toxicity was inconsistent across studies. There is insufficient evidence from prospective studies on whether knowledge of metabolite marker status will lead to improved outcomes (primarily improved disease control and/or less adverse drug effects). Findings of studies evaluating the association between metabolite markers and clinical remission are mixed, and no prospective comparative trials have compared health outcomes in patients managed with metabolite markers compared with current approaches to care. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
National Comprehensive Cancer Network (v.2.2019) guidelines on acute lymphoblastic leukemia state:

- "For patients receiving 6-MP [mercaptopurine], consider testing for TPMT [thiopurine methyltransferase] gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP."
- "Determination of patient TPMT genotype using genomic DNA is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses."
- "Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to non-compliance or hypermetabolism."

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
In 2013, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition on IBD published consensus recommendations on the role of TPMT enzyme and thiopurine metabolite testing in pediatric IBD. Recommendations (high and moderate) included:

- "TPMT testing is recommended before initiation of TPs [thiopurines] to identify individuals who are homozygous recessive or have extremely low TPMT activity…
- Individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of TPs because of concerns for significant leucopenia.
- … 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.
- Metabolite testing can be used to determine adherence to TP therapy.
- Metabolite testing can be used to guide dosing increases or modifications in patients with active disease….
- 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 a 2017 American Gastroenterological Association Institute guidelines on therapeutic drug monitoring in IBD are summarized in the table below.

Table. Evidence-Based Clinical Guidelines on Therapeutic Drug Monitoring in IBD

Recommendation	SOR	QOE
In adults with IBD being started on thiopurines, AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing	Conditional	Low
In adults treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes	Conditional	Very low
In adults with quiescent IBD treated with thiopurines, AGA suggests against routine thiopurine metabolite monitoring	Conditional	Very low

AGA: American Gastroenterological Association; IBD: irritable bowel disease; QOE: quality of evidence; SOR: strength of recommendation; TPMT: thiopurine methyltransferase.

U.S. Preventive Services Task Force Recommendations
Not applicable

KEY WORDS:

Pharmacogenomic Testing, Metabolite Testing, Prometheus Labs, Prometheus Reference Lab, Prometheus Reference Laboratory, Prometheus Laboratories, Inflammatory Bowel Disease, IBD, Genotypic Analysis, Metabolite Markers, Specialized Laboratory Tests, Serum Antibodies for Diagnosing Inflammatory Bowel Disease, TPMT, Thiopurines, Thiopurine Methyltransferase, Thiopurine therapy, azathioprine, mercaptopurine, thioguanine, 6-methyl-mercaptopurine ribonucleotides, 6-thioguanine nucleotides

APPROVED BY GOVERNING BODIES:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Several thiopurine genotypes, phenotype, and metabolite tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus® is a commercial laboratory that offers thiopurine genotype, phenotype and metabolite testing for those on thiopurine therapy. The tests are referred to as Prometheus TPMT Genetics, Prometheus TMPT enzyme, and Prometheus thiopurine metabolites, respectively. Other laboratories that offer TPMT genotyping include Quest Diagnostics (TPMT Genotype), ARUP Laboratories (TPMT DNA), Specialty Laboratories (TPMT GenoTypR™), PreventionGenetics (TPMT Deficiency via the TPMT Gene), Genelex (TPMT), and Fulgent Genetics (TPMT); and LabCorp (TPMT enzyme activity and genotyping).

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT codes:

81335	TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)
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)

PREVIOUS CODING:

CPT codes:

81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) – includes TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), common variants (e.g., *2, *3)

REFERENCES:

1. Aberra FN and Lichtenstein GR. Review article: Monitoring of immunomodulators in inflammatory bowel disease, Alimentary Pharmacology Therapy 2005; 21(4): 307-319.
2. AlHadithy AF, et al. Thiopurines in inflammatory bowel disease: Pharmacogenetics, therapeutic drug monitoring, and clinical recommendations, Digestive Liver Disease, April 2005; 37(4): 282-297.
3. Ansari A, Hassan C, Duley J et al. Thiopurine methyltransferase activity and the use of azathioprine in inflammatory bowel disease. Aliment Pharmacol Ther 2002; 16(10): 1743-50.
4. Armstrong L, Sharif JA, Galloway P et al. Evaluating the use of metabolite measurement in children receiving treatment with a thiopurine. Aliment Pharmacol Ther 2011; 34(9):1106-14.
5. Armstrong VW, et al. Analytic aspects of monitoring therapy with thiopurine medications, Therapeutic Drug Monitoring, April 2004; 26(2): 220-226.

6. Belaiche J, Desager JP, Horsmans Y et al. Therapeutic drug monitoring of azathioprine and 6-mercaptopurine metabolites in Crohn disease. Scand J Gastroenterol 2001; 36(1): 71-6.
7. Benkov K, Lu Y, Patel A et al. Role of thiopurine metabolite testing and thiopurine methyltransferase determination in pediatric IBD. J Pediatr Gastroenterol Nutr 2013; 56(3):333-40.
8. Black AJ, McLeod HL, Capell HA et al. Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. Ann Intern Med 1998; 129(9): 716-8.
9. Bloomfeld RS, Onken JE. Mercaptopurine metabolite results in clinical gastroenterology practice. Aliment Pharmacol Ther 2003; 17(1): 69-73.
10. Booth RA, Ansari MT, Loit E et al. Assessment of thiopurine S-methyltransferase activity in patients prescribed thiopurines: a systematic review. Ann Intern Med 2011; 154(12):814-23, W-295-8.
11. Campbell S, Kingstone K, Ghosh S. Relevance of thiopurine methyltransferase activity in inflammatory bowel disease patients maintained on low-dose azathioprine. Aliment Pharmacol Ther 2002; 16(3):389-98.
12. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of patients with variants in TPMT and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. Gastroenterology. Oct 2015; 149(4):907-917 e907.
13. Colombel JF, Ferrari N, Debuysere H et al. Genotypic analysis of the thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology 2000; 118(6): 1025-30.
14. Corominas H, Domenech M, Laiz A et al. Is thiopurine methyltransferase genetic polymorphism a major factor for withdrawal of azathioprine in rheumatoid arthritis patients? Rheumatology (Oxford) 2003; 42(1): 40-5.
15. Cuffari C, Hunt S, Bayless T. Utilization of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patents with inflammatory bowel disease. Gut 2001; 48(5): 642-6.
16. Cuffari C, Seidman EG, Latour S et al. Quantitation of 6-thioguanine in peripheral blood leukocyte DNA in Crohn's disease patients on maintenance 6-mercaptopurine therapy. Can J Physiol Pharmacol 1996; 74(5): 580-5.
17. Cuffari C, Theoret Y, Latour S et al. 6-mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity. Gut 1996; 39(3): 401-6.
18. Dhaliwal HK, Anderson R, Thornhill EL et al. Clinical significance of azathioprine metabolites for the maintenance of remission in autoimmune hepatitis. Hepatology 2012; 56(4):1401-8.
19. Dong XW, Zheng Q, Zhu MM et al. Thiopurine S-methyltransferase polymorphisms and thiopurine toxicity in treatment of inflammatory bowel disease. World J Gastroenterol 2010; 16(25):3187-95.
20. Donnan JR, Ungar WJ, Mathews M et al. Systematic review of thiopurine methyltransferase genotype and enzymatic testing strategies. Ther Drug Monit 2011; 33(2):192-9.

21. Dubinsky MC, Lamothe S, Yang HY et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology 2000; 118(4): 705-13.
22. Dubinsky MC, Reyes E, Ofman J, et al. A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. Am J Gastroenterol 2005; 100(10):2239-2247.
23. Dubinsky MC, Yang H, Hassard PV et al. 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. Gastroenterology 2002; 122(4): 904-15.
24. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. Sep 2017; 153(3):827-834.
25. Friedman AB, Brown SJ, Bampton P, et al. Randomised clinical trial: efficacy, safety and dosage of adjunctive allopurinol in azathioprine/mercaptopurine nonresponders (AAA Study). Aliment Pharmacol Ther. Apr 2018; 47(8):1092-1102.
26. Garritsen FM, van der Schaft J, Bruijnzeel-Koomen CAF, et al. Thiopurine metabolite levels in patients with atopic dermatitis and/or chronic hand/foot eczema treated with azathioprine. J Dermatolog Treat. Jun 2018; 29(4):375-382.
27. Gardiner SJ, Gearry RB, Begg EJ, et al. Thiopurine dose in intermediate and normal metabolizers of thiopurine methyltransferase may differ three-fold. Clin Gastroenterol Hepatol, June 2008; 6(6): 654-660.
28. Gearry RB and Barclay ML. Azathioprine and 6-mercaptopurine pharmacogenetics and metabolite monitoring in inflammatory bowel disease, Journal of Gastroenterology and Hepatology, August 2005; 20(8): 1149-1157.
29. Gearry RB, Barclay ML, Burt MJ et al. Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2003; 18(4): 395-400.
30. Gearry RB, et al. Thiopurine methyltransferase and 6-thioguanine nucleotide measurement: Early experience of use in clinical practice, Internal Medicine Journal, October 2005; 35(10): 580-585.
31. Gilissen LP, Wong DR, Engels LG et al. Therapeutic drug monitoring of thiopurine metabolites in adult thiopurine tolerant IBD patients on maintenance therapy. J Crohns Colitis 2012; 6(6):698-707.
32. Gisbert JP, Luna M, Mate J et al. Choice of azathioprine or 6-mercaptopurine dose based on thiopurine methyltransferase (TPMT) activity to avoid myelosuppression. A prospective study. Hepatogastroenterology 2006; 53(69):399-404.
33. Gisbert JP, Rodrigo L, et al. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: Long-term follow-up study of 394 patients. Am J Gastroenterol, December 2006; 101(12): 2769-2776.
34. Goldenberg BA, et al. The utility of 6-thioguanine metabolite levels in managing patients with inflammatory bowel disease, September 2004; 99(9): 1744-1748.
35. Goldberg R, Moore G, Cunningham G, et al. Thiopurine metabolite testing in inflammatory bowel disease. J Gastroenterol Hepatol. Mar 2016; 31(3):553-560.

36. Gupta P, Gokhale R, Kirschner BS. 6-mercaptopurine metabolite levels in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2001; 33(4): 450-4.
37. Higgs JE, Payne K, Roberts C et al. Are patients with intermediate TPMT activity at increased risk of myelosuppression when taking thiopurine medications? Pharmacogenomics 2010; 11(2):177-88.
38. Hindorf U, Appell ML. Genotyping should be considered the primary choice for pre-treatment evaluation of thiopurine methyltransferase function. J Crohns Colitis 2011.
39. Hindorf U, et al. Pharmacogenetics during standardised initiation of thiopurine therapy in inflammatory bowel disease, Gut, March 2006.
40. Kennedy NA, Asser TL, Mountifield RE et al. Thiopurine metabolite measurement leads to changes in management of inflammatory bowel disease. Intern Med J 2013; 43(3):278-86.
41. Konidari A, Anagnostopoulos A, Bonnett LJ et al. Thiopurine monitoring in children with inflammatory bowel disease: a systematic review. Br J Clin Pharmacol 2014.
42. Kopylov U, Amre D, Theoret Y, et al. Thiopurine metabolite ratios for monitoring therapy in pediatric Crohn disease. J Pediatr Gastroenterol Nutr. Oct 2014; 59(4):511-515.
43. Lennard L. TPMT in the treatment of Crohn's disease with azathioprine, Gut, August 2002; 51(2): 143-146.
44. Liang JJ, Geske JR, Boilson BA et al. TPMT genetic variants are associated with increased rejection with azathioprine use in heart transplantation. Pharmacogenet Genomics 2013; 23(12):658-65.
45. Lichtenstein GR, Abreu MT, Cohen R et al. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006; 130(3):935-9.
46. Liu YP, Wu HY, Yang X, et al. Association between thiopurine S-methyltransferase polymorphisms and thiopurine-induced adverse drug reactions in patients with inflammatory bowel disease: a meta-analysis. PLoS One. 2015; 10(3):e0121745.
47. Lowry PW, Franklin CL, Weaver AL et al. Measurement of thiopurine methyltransferase activity and azathioprine metabolites in patients with inflammatory bowel disease. Gut 2001; 49(5): 665-70.
48. Meggitt SJ, Anstey AV, Mohd Mustapa MF et al. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. Br J Dermatol 2011; 165(4):711-34.
49. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomized controlled trial. Lancet 2006; 367(9513):839-46.
50. Meijer B, Kreijne JE, van Moorsel SAW, et al. 6-methylmercaptopurine-induced leukocytopenia during thiopurine therapy in inflammatory bowel disease patients. J Gastroenterol Hepatol. Jun 2017; 32(6):1183-1190.
51. Morales A, Salguti S, Miao CL and Lewis JD. Relationship between 6-mercaptopurine dose and 6-thioguanine nucleotide levels in patients with inflammatory bowel disease. Inflamm Bowel Dis, April 2007; 13(4): 380-385.

52. National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines: guidelines and recommendations for laboratory analysis and application of pharmacogenetics to clinical practice 2010. Available online at: www.guideline.gov.
53. National Comprehensive Cancer Network (NCCN). Acute Lymphoblasic Leukemia Version 3. 2017; www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed September 18, 2017.
54. Newman WG, Payne K, Tricker K et al. A pragmatic randomized controlled trial of thiopurine methyltransferase genotyping prior to azathioprine treatment: the TARGET study. Pharmacogenomics 2011; 12(6):815-26.
55. Nguyen TV, Vu DH, Nguyen TM et al. Relationship between azathioprine dosage and thiopurine metabolites in pediatric IBD patients: identification of covariables using multilevel analysis. Ther Drug Monit 2013; 35(2):251-7.
56. Requeiro M, Mardini H. Determination of thiopurine methyltransferase genotype or phenotype optimizes initial dosing of azathioprine for the treatment of Crohn's disease. J Clin Gastroenterol 2002; 35(3): 240-4.
57. Reuther LO, et al. Pharmacological monitoring of azathioprine therapy, Scandinavian Journal of Gastroenterology, September 2003; 38(9): 972-977.
58. Robbin X, et al. 6-thioguanine monitoring in steroid-dependent patients with inflammatory bowel diseases receiving azathioprine, Alimentary Pharmacology and Therapeutics, April 2005; 21(7): 829-839.
59. Roy LM, Zur RM, Uleryk E, et al. Thiopurine S-methyltransferase testing for averting drug toxicity in patients receiving thiopurines: a systematic review. Pharmacogenomics. Apr 2016; 17(6):633-656.
60. Sayani FA, Prosser C, Bailey RJ, et al. Thiopurine methyltransferase enzyme activity determination before treatment of inflammatory bowel disease with azathioprine: effect on cost and adverse events. Can J Gastroenterol. Mar 2005; 19(3):147-151.
61. Seidman EG. Clinical use and practical application of TPMT enzyme and 6-mercaptopurine metabolite monitoring in IBD. Rev Gastroenterol Disord 2003; 3(suppl): S30-S38.
62. Siegel CA. Review article: Practical management of inflammatory bowel disease patients taking immunomodulators, Alimentary Pharmacology and Therapeutics, July 2005; 22(1): 1-16.
63. Smith M, Blaker P, Patel C, et al. The impact of introducing thioguanine nucleotide monitoring into an inflammatory bowel disease clinic. Int J Clin Pract. Feb 2013; 67(2):161-169.
64. Stanulla M, Schaeffeler E, Fhohr T et al. Thiopurine methyltransferase (TMPT) genotype and early treatment response to mercaptopurine in childhood acute lymphoblastic leukemia. JAMA 2005; 293(12):1485-9.
65. Su C and Lichtenstein G. Treatment of inflammatory bowel disease with azathioprine and 6-mercaptopurine, Gastroenterology Clinics, June 2004, Vol., 33, No. 2.
66. Teml A, Schaeffeler E, Herrlinger KR, et al. Thiopurine treatment in inflammatory bowel disease: Clinical pharmacology and implication of pharmacogenetically guided dosing. Clin Pharmacokinet 2007; 46(3): 187-208.

67. Thervet E, Anglicheau D, Toledano N et al. Long-term results of TPMT activity monitoring in azathioprine-treated renal allograft recipients. J Am Soc Nephrol 2001; 12(1): 170-6.
68. Waljee AK, Joyce JC, Wang S et al. Algorithms outperform metabolite tests in predicting response of patients with inflammatory bowel disease to thiopurines. Clin Gastroenterol Hepatol 2010; 8(2):143-50.
69. Wong DR, Coenen MJ, Derijks LJ, et al. Early prediction of thiopurine-induced hepatotoxicity in inflammatory bowel disease. Aliment Pharmacol Ther. Feb 2017; 45(3):391-402.
70. Wright S, et al. Clinical significance of azathioprine active metabolite concentrations in inflammatory bowel disease, Gut 2004; 53(8): 1123-1128.
71. Zur RM, Roy LM, Ito S, et al. Thiopurine S-methyltransferase testing for averting drug toxicity: a meta-analysis of diagnostic test accuracy. Pharmacogenomics J. Aug 2016; 16(4):305-311.

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Medical Policy Group, August 2011
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Medical Policy Group, June 2012
Medical Policy Group, December 2012
Medical Policy Group, September 2013
Medical Policy Group, June 2014
Medical Policy Group, July 2015
Medical Policy Group, December 2015
Medical Policy Group, November 2016
Medical Policy Group, November 2017
Medical Policy Group, December 2017
Medical Policy Group, November 2018
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research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.