



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

**Policy #** 00237

**Original Effective Date:** 04/15/2009

**Current Effective Date:** 06/18/2014

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **When Services Are Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a one-time genotypic or phenotypic analysis of the thiopurine methyltransferase (TPMT) gene in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) or in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction to be **eligible for coverage**.

### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers 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) to be **investigational**.\*

### **Background/Overview**

The use of thiopurines, medications for treating inflammatory bowel disease (IBD) and other conditions, is limited by a high rate of drug toxicity. Susceptibility to drug toxicity has been linked to the level of activity of the enzyme TPMT which converts thiopurines into metabolites. There are 3 distinct TPMT mutations, and these are associated with the level of TPMT activity.

Pharmacogenomic analysis of TPMT status is proposed to identify individuals at risk of thiopurine drug toxicity and adjust medication doses accordingly. Measurement of metabolite markers has also been proposed.

Thiopurines are converted to 6-MP in vivo, where it is subsequently metabolized to 2 active metabolites; either 6-TGN by the enzyme IMPDH, or to 6-MMRP by the enzyme TPMT. Thiopurine methyltransferase also converts 6-MP to an inactive metabolite, 6-methyl-mercaptopurine (6-MMP). 6-thioguanine nucleotides are considered cytotoxic and thus are associated with bone marrow suppression, while 6-MMRP is associated with hepatotoxicity. In population studies, the activity of the enzyme TPMT 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

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Page 1 of 10



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237

Original Effective Date: 04/15/2009

Current Effective Date: 06/18/2014

pathway with greater accumulation of 6-TGN; these patients are considered to be at risk for myelotoxicity (i.e., bone marrow suppression).

This variation in TPMT activity has been related to three distinct TPMT mutations 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 2 normal (wild-type) alleles for TPMT; those with intermediate activity are heterozygous (i.e., have a mutation on 1 chromosome), while those with low TPMT activity are homozygous for TPMT mutations (i.e., a mutation is found on both chromosomes.) Genetic analysis has been explored as a technique to identify patients at risk for bone marrow suppression; those 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.

Thiopurine methyltransferase 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, since 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.

## **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 recently in monitoring intracellular levels of AZA metabolites to predict response and complications, with the ultimate aim of tailoring drug therapy to each individual patient.

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 i.e. to aid in determining initial dose and to evaluate ongoing dosing.

## **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

Prometheus<sup>®‡</sup> is a commercial laboratory that offers thiopurine genotype, phenotype and metabolite testing for those undergoing 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 (TPMT Genotype) and Specialty Laboratories (TPMT GenoTypR<sup>™</sup>)<sup>‡</sup>.

Centers for Medicare and Medicaid Services (CMS)

No national coverage determination.

## **Rationale/Source**

This policy was originally created in 2009 and was updated regularly with literature searches. Following is a summary of the key literature to date:

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237  
Original Effective Date: 04/15/2009  
Current Effective Date: 06/18/2014

As with any diagnostic technology, there are 3 steps in the technology assessment process: evaluation of technical feasibility, evaluation of ability to accurately diagnose a clinical condition in comparison with the gold standard, and determination of whether use of the test results in an improved patient outcome. These factors are discussed below, both for pharmacogenomics and metabolite markers.

### Technical Performance

#### *Pharmacogenomics*

The genotypic analysis of the TPMT gene is based on well-established PCR technology to detect 3 distinct mutations. Currently, 3 alleles, TPMT\*2, TPMT\*3A and TPMT\*3C, account for about 95% of individuals with reduced TPMT activity. Individuals homozygous for these alleles are TPMT-deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. A 2011 study from Sweden addressed the concordance between TPMT genotyping and phenotyping. The investigators evaluated data from 7,195 unselected and consecutive TPMT genotype and phenotype tests. The genotype tests examined the 3 most common TPMT variants, noted above. TPMT genotyping identified 89% as TPMT wild type, 704 (10%) as TPMT heterozygous, and 37 (0.5%) as TPMT homozygous. The overall agreement between genotyping and phenotyping was 95%. Genotyping alone would have misclassified 3 of 37 (8%) homozygous patients as heterozygous; these 3 individuals were found to have uncommon mutations. All 3 had low TPMT activity. The phenotype test would have misclassified 4 of 37 (11%) of homozygous patients as they had test results above the cut-off level for low TPMT activity (< 2.5 U/mL red blood cells [RBCs]).

#### *Metabolite Markers*

Metabolite markers have been assessed using high performance liquid chromatography (HPLC) technology. It would be optimal to assess metabolite markers in peripheral leukocytes, since they reflect the status of bone marrow precursors. However, it is technically easier to measure metabolites in RBCs instead of leukocytes.

### Diagnostic Performance

#### *Pharmacogenomics*

Several systematic reviews of studies on the diagnostic performance of TPMT genotyping have been published. Among the most recent studies was a 2011 review by Booth and colleagues that was sponsored by the Agency for Healthcare Research and Quality (AHRQ). A total of 19 studies on test performance were identified; most were cross-sectional or prospective observational studies and approximately 70% included patients with IBD. Among the 1,735 total patients, 184 were heterozygous and 16 were homozygous for variant alleles, a small total sample of individuals with variant alleles. A pooled analysis of data from 19 studies found a sensitivity of 79.9% (95% confidence interval [CI]: 74.8% to 84.6%) for correctly identifying individuals with subnormal (intermediate or low) enzymatic activity. The specificity of the wild-type genotype for correctly identifying individuals with normal or high enzymatic activity approached 100%. Seventeen studies addressed the association between TPMT status and thiopurine toxicity. The studies included a total of 2,211 patients, of which 357 had intermediate and 74 had low enzymatic activity. In a pooled analysis of 3 studies (92 patients, 10 events), there were greater odds of myelotoxicity with low TPMT enzymatic activity than intermediate activity (pooled odds ratio [OR]: 14.5, 95% CI: 2.78-76.0). Similarly, in a pooled analysis of 3 studies (403 patients, 29 events), there were greater odds of myelotoxicity with low

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237

Original Effective Date: 04/15/2009

Current Effective Date: 06/18/2014

TPMT enzymatic activity than normal levels (pooled OR: 19.1, 95% CI: 4.6-80.2). It is worth noting that CIs were wide due to few events and small sample sizes.

Another systematic review published in 2011, by Donnan and colleagues, identified 17 studies that reported the performance characteristics of TPMT genotyping tests (12 studies) and phenotyping (6 studies) compared to a reference standard. No true gold standard was available. The enzymatic test was used as the reference standard in 9 studies, and the remainder used a genotyping test; 3 studies compared 2 methods of genotyping. All of the studies used a method of genotyping as either the investigational test or the reference standard; the tests varied somewhat in the number and type of polymorphisms they were designed to detect. Sixteen of 17 studies either reported sensitivity and specificity, or reported sufficient data for these measures to be calculated. Only 3 studies considered confounding factors such as concurrent medications and blood transfusions in their exclusion criteria. The authors of the systematic review did not pool study findings. In the included studies, sensitivity of enzymatic tests ranged from 92% to 100% and specificity ranged from 86% to 98%. The sensitivity of the genotype tests ranged from 55% to 100% and the specificity ranged from 94% to 100%. In general, the enzymatic tests had a high sensitivity and low-positive predictive value when genotype tests were used as the reference standard. Genotype tests showed a lower sensitivity and high positive-predictive value when enzymatic tests were used as the gold standard. The inconsistent use of a reference standard complicated the interpretation of the findings.

A 2010 meta-analysis by Dong and colleagues evaluated the relationship between TPMT polymorphisms and adverse-drug reactions in patients with IBD taking thiopurine drugs. The review included cross-sectional studies, prospective cohort studies, and case-control studies conducted in patients 18 years and older with IBD. In addition, studies needed to compare TPMT polymorphism frequencies in thiopurine-tolerant and thiopurine-intolerant patients and report at least one of several outcome measures related to adverse drug reactions. The investigators identified a total of 181 publications, 17 of which were considered potentially appropriate after applying initial eligibility criteria e.g. publication type and study population. Another 8 studies were excluded because relevant outcome variables were not reported or could not be calculated. The final sample consisted of 9 studies with 1,309 participants. In a pooled analysis of data from 6 studies, 39 of 273 (14%) patients with an adverse drug reaction were TPMT heterozygous or homozygous compared to 39 of 708 (55%) patients without an adverse drug reaction. This difference was statistically significant (OR: 2.93, 95% CI: 1.68-5.09). In analyses of specific adverse reactions, there was a statistically significant association between the presence of TPMT alleles and bone marrow toxicity, but not hepatotoxicity or pancreatitis. In the non-statistically significant analyses, the number of events was small and the analyses have been underpowered. For example, 3 of 37 (8%) IBD patients with hepatotoxicity were TPMT heterozygous/ homozygous compared to 82 of 1,017 (81%) patients without hepatotoxicity (OR: 1.51, 95% CI: 0.54 to 4.19).

No systematic reviews of studies on TPMT genotyping or phenotyping tests in patients undergoing solid organ transplantation were identified. One study was identified that addressed this population and provided support for genotype analysis. In 2013, Liang and colleagues published data on 93 heart transplant patients treated with AZA. A total of 83 patients had the wild-type genotype and 10 were heterozygous for mutations. The TPMT activity level was significantly lower in the heterozygous individuals (13.1, standard deviation [SD]: 2.8 U/ml) than individuals with the wild-type genotype (21, SD: 4.5 U/ml RBCs),  $p < 0.001$ . Moreover,

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237

Original Effective Date: 04/15/2009

Current Effective Date: 06/18/2014

there was a significantly higher rate of severe rejection in heterozygous individuals (7 of 10, 70%) than individuals with a wild-type genotype (12 of 83, 15%),  $p < 0.001$ . In addition, heterozygous individuals developed severe rejection earlier than wild-type individuals, a median of 29 versus 36 days,  $p = 0.046$ . There were not statistically significant associations between TMPT genotype and the development of hepatotoxicity or leukopenia.

### *Metabolite Testing*

Studies on the diagnostic accuracy of metabolite testing have focused on assessing the association between metabolite levels and disease remission or adverse drug effects. One systematic review was identified and this focused on studies conducted in the pediatric population. In a literature search through January 4, 2013, Konidari and colleagues identified 15 studies including a total of 1026 children with IBD. There were 9 retrospective and 6 prospective case series and no randomized controlled trials (RCTs). The authors did not pool study findings. Among studies that evaluated the association between metabolite markers and clinical remission, 5 found significantly higher rates of remission with higher levels of 6-TGN and 6 studies did not find significant differences in 6-TGN levels between responders and non-responders. Moreover, 5 studies found significant associations between 6-MMRP levels and hepatotoxicity and 3 studies did not find significant associations.

Several studies have considered the optimal therapeutic cutoff level of metabolites. In 2000, Dubinsky and colleagues measured 6-TGN, and 6-MMRP levels in 92 pediatric patients. Higher median levels of 6-TGN were observed at points of clinical response versus non-response. Quartile analysis on all samples revealed that the best probability of treatment occurred when 6-TGN levels were greater than 235 (measured in  $\text{pmol}/8 \times 10^8$ ). The 6-MMRP levels did not correlate with disease activity, but elevated levels did correlate with hepatotoxicity, observed in 16 patients. Elevated 6-TGN levels were also associated with hematologic toxicity. Results of a study published in 2012 by Glissen and colleagues in the Netherlands also found an optimal therapeutic 6-TGN cutoff level of  $235 \text{ pmol}/8 \times 10^8$ . This was a cross-sectional study with 100 IBD patients. Forty-one patients had an IBD exacerbation, and IBD was in clinical remission in 59 patients. Twenty-six of the 41 (63%) patients with an exacerbation had 6-TGN below the therapeutic threshold of  $235 \text{ pmol}/8 \times 10^8$  and 24 of 59 (41%) patients in remission had 6-TGN levels below this threshold. The association between 6-TGN level and remission was statistically significant,  $p = 0.04$ .

Other studies have identified somewhat different optimal 6-TGN cutoffs. Gupta and colleagues reported discordant results in 54 patients with IBD being treated with AZA. A total of 36% of patients in relapse had 6-TGN levels greater than 230, compared with 30% of those in remission. Conversely, 57% of patients with 6-TGN levels less than 230 were in remission, versus 50% of patients with 6-TGN levels greater than 230. In 2012, Dhaliwal and colleagues in the U.K. published findings of a study that included 70 patients with autoimmune hepatitis who were at the maintenance of remission stage of treatment and were being treated with AZA. Blood samples were taken at baseline and at each clinic visit over the following 2 years. During the study period, 53 of 70 patients (76%) maintained remission. Levels of 6-TGN were significantly higher in patients who maintained remission compared to those who did not (mean of 237 versus 177  $\text{pmol}/8 \times 10^8$ ,  $p = 0.025$ ). According to receiver operating curve (ROC) analysis, a cutoff of  $220 \text{ pmol}/8 \times 10^8$  best discriminated between patients who did and did not stay in remission. Sixty-two percent of patients in remission and 18% of those not in remission had a 6-TGN concentration higher than  $220 \text{ pmol}/8 \times 10^8$ .

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237

Original Effective Date: 04/15/2009

Current Effective Date: 06/18/2014

A 2010 cross-sectional study by Waljee et al. compared the ability of metabolite tests and a clinical algorithm using routine laboratory values (CBC and chemistry panel) and patient age to predict the clinical response of patients with IBD to thiopurines. The study included 346 patients taking thiopurines who underwent thiopurine metabolite analysis, a CBC, and a comprehensive chemistry analysis in one 24-hour period. Clinical response was determined through medical record review. Data on clinical response were available for 240 patients; 119 (49.6%) were classified as responders. Using area under the curve (AUC) analysis, an algorithm using patient age and laboratory values differentiated clinical responders from nonresponders with an AUC of 0.86. In comparison, the metabolite marker 6-TGN had an AUC of 0.59 for differentiating between clinical response and nonresponse. The difference between these two areas was statistically significant,  $p < 0.001$ . The variables with the strongest independent associations with clinical response were neutrophil count, alkaline phosphatase, red cell distribution width, age, and white blood cell count. When 6-TGN levels were added as an independent variable to a model containing the above variables, it did not significantly improve the AUC (which increased from 0.856 to 0.862). The authors noted that a limitation of the study was that data were obtained from a tertiary care center, and it is possible that patients in whom metabolites performed poorly were likely to be referred to that center. The authors concluded that the algorithm they developed and tested using routine laboratory tests for differentiating thiopurine clinical responders and nonresponders performed significantly better than metabolite monitoring in predicting clinical response.

### Improvement in Health Outcomes

The use of pharmacogenomics and thiopurine metabolite testing creates the possibility of tailoring a drug regimen for each individual patient, with the ultimate goal of attaining disease remission and elimination of steroid therapy. The preferred study design would compare patient management (e.g., drug choice) and health outcomes in patients managed with and without testing.

### Pharmacogenomics

A RCT, known as the TARGET study, randomized 333 patients to receive TPMT genotyping or usual care (no genotyping) prior to AZA therapy. Study eligibility included age 16 years or older with a diagnosis of IBD. In the testing arm, test results were generated within 1 week, and the study clinician was informed of the results. Clinicians were advised to recommend the following: maintenance dose of AZA (i.e., 1.5 to 3 mg/kg/day) for individuals with wild-type TPMT, low-dose AZA (i.e., 25-50 mg/day) titrated to a maintenance dose for individuals with heterozygous TPMT variant alleles and an alternative therapy (no AZA) for patients homozygous for TPMT variant alleles. All final treatment decisions were at the discretion of the individual provider (i.e., this was a pragmatic RCT). Genotyping was also done on samples from patients in the control group, but results were not made available until the end of the study.

Data were available for 322/333 (97%) patients at 4 months. The primary study endpoint was stopping AZA due to any adverse drug reaction in the first 4 months of treatment. At 4 months, a total of 91 of 322 (28%) patients had stopped taking AZA due to an adverse drug reaction, 47 of 163 (29%) in the genotyping group and 44 of 159 (28%) in the non-genotyping group. The difference between groups was not statistically significant,  $p = 0.74$ . In the genotyping arm, the average starting dose of AZA was significantly lower in TPMT heterozygotes than wild-type individuals ( $p = 0.008$ ), suggesting that clinicians were following dosing recommendations. However, at 4 months, the mean dose was similar across both arms (1.68 mg/kg/day,  $p$

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237  
Original Effective Date: 04/15/2009  
Current Effective Date: 06/18/2014

= 0.25), and there was no difference in dose between individuals heterozygous or wild type for TPMT variant alleles ( $p = 0.99$ ). Moreover, at 4 months, there was not a significant difference between groups in the level of clinical symptoms between groups. The mean Harvey-Bradshaw symptom index score was 4.5 in each group,  $p = 0.80$  (54 patients in the genotyping group and 56 patients in the non-genotyping group were included in this analysis). It is important to note that, in this study, few individuals had non-wild type gene variants. In the genotyping group, there were 7 heterozygous patients and in the non-genotyping group, there were 2 heterozygous patients and 1 homozygous patient. Thus, the study was underpowered to evaluate the impact of TPMT genotyping on patients with variant alleles.

Several uncontrolled prospective studies have also been published. For example, in a study that involved 131 patients with IBD, investigators from Europe did not find that the choice of AZA/6-MP dose based on RBC TPMT activity prevented myelotoxicity; no patients in this study exhibited low activity. In a 2008 study from New Zealand, Gardiner et al. noted that initial target doses to attain therapeutic levels in patients with IBD might be 1 mg/kg/d and 3 mg/kg/d in intermediate (heterozygous) and normal (wild-type) metabolizers. This conclusion was based on a study of 52 patients with IBD who were started on AZA or 6-MP and who were followed up for 9 months while 6-TGN levels and clinical status were assessed. This study suggested that knowledge of TPMT activity can assist with initial dosing. In a study from Europe including 394 patients with IBD, Gisbert et al. noted that the probability of myelotoxicity was 14.3% in the TPMT intermediate group compared to 3.5% in those with high (wild-type) activity. These authors concluded that determining TPMT activity prior to initiating treatment with AZA could help to minimize the risk of myelotoxicity.

### *Metabolite Testing*

No prospective comparative trials were identified in which use of metabolite markers was compared to current approaches to care. In 2012, Kennedy and colleagues published a study retrospectively reviewing medical records of patients who had undergone metabolite testing after it was introduced in South Australia. The analysis reported on 151 patients with IBD who had been taking a thiopurine for at least 4 weeks, underwent at least 1 metabolite test, and were managed at 1 of the study sites. The 151 patients had a total of 157 tests. Eighty of 157 tests (51%) were done because of flare or lack of medication efficacy, 18 (12%) were for adverse effects and 54 tests (34%) were routine tests. Forty-four of the 80 patients (55%) who had a metabolite test due to flare or lack of efficacy had improved outcomes after the test was performed. Outcomes were also improved after testing for 5 of 18 patients (28%) with a suspected adverse reaction to a thiopurine. For patients who had routine metabolite tests, 7 of 54 (13%) had improved outcomes following testing. The rate of benefit was significantly higher in patients tested due to flare or lack of efficacy compared to those who underwent routine metabolite testing ( $p < .001$ ). Changes in patient management included medication dose adjustments, change in medication and surgical treatment. The study lacked a control group and thus, outcomes cannot be compared to patients managed without metabolite testing. It is possible that, even in the absence of metabolite testing, patients who were not experiencing efficacy or who were experiencing adverse events would have had their treatments adjusted, which could lead to improved outcomes.

Other relevant studies have examined the association between drug dose and the level of metabolite markers. In general, studies have reported that there is only weak correlation between metabolite levels and dose of drug. One 2013 retrospective study, however, found a positive correlation between levels of 6-TGN



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237  
Original Effective Date: 04/15/2009  
Current Effective Date: 06/18/2014

and 6-MMP and weight-based AZA dose in children with IBD. In addition, studies have reported that levels obtained with testing are often outside of the therapeutic range. For example, the Geary and colleagues study reported that 41% of values were within the therapeutic range. and Armstrong and colleagues found that 32% of values were within therapeutic levels.

### Summary

There are a large number of studies on the diagnostic performance of TPMT genotyping and phenotyping tests. A recent meta-analysis found a pooled sensitivity of about 80% and specificity near 100% for identifying individuals with subnormal enzymatic activity. In addition, studies have found a greater likelihood of adverse drug reactions with low TPMT activity. One RCT reporting evidence on health outcomes was identified; this study did not find a significant difference in outcomes in patients managed with and without TPMT genotyping testing, but the study may have been underpowered. One-time genotype or phenotype testing is considered eligible for coverage in select patients.

There is insufficient evidence from prospective studies on whether metabolite markers will lead to improved outcomes (primarily improved disease control and/or less adverse drug effects). Thus, analysis of metabolite markers is considered investigational.

### References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines, 2.04.19, 5:2014.
2. Hindorf U, Appell ML. Genotyping should be considered the primary choice for pre-treatment evaluation of thiopurine methyltransferase function. *J Crohns Colitis* 2011.
3. 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.
4. 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.
5. 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.
6. 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.
7. Konidari A, Anagnostopoulos A, Bonnett LJ et al. Thiopurine monitoring in children with inflammatory bowel disease: a systematic review. *Br J Clin Pharmacol* 2014.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. Gardiner SJ, Geary RB, Begg EJ et al. Thiopurine dose in intermediate and normal metabolizers of thiopurine methyltransferase may differ three-fold. *Clin Gastroenterol Hepatol* 2008; 6(6):654-60; quiz 04.

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237

Original Effective Date: 04/15/2009

Current Effective Date: 06/18/2014

16. Gisbert JP, Nino P, 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* 2006; 101(12):2769-76.
17. Kennedy NA, Asser TL, Mountfield RE et al. Thiopurine metabolite measurement leads to changes in management of inflammatory bowel disease. *Intern Med J* 2013; 43(3):278-86.
18. Morales A, Salguti S, Miao CL et al. Relationship between 6-mercaptopurine dose and 6-thioguanine nucleotide levels in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2007; 13(4):380-5.
19. 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.
20. Gearry RB, Barclay ML, Roberts RL et al. Thiopurine methyltransferase and 6-thioguanine nucleotide measurement: early experience of use in clinical practice. *Intern Med J* 2005; 35(10):580-5.
21. 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.

### Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT)<sup>®</sup>†, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81401
HCPCS	No codes
ICD-9 Diagnosis	555.0, 555.9, 556.0 thru 556.9, 714.0 thru 714.9
ICD-9 Procedure	No codes

### Policy History

Original Effective Date: 04/15/2009

Current Effective Date: 06/18/2014

05/07/2009 Medical Director review

05/20/2009 Medical Policy Committee approval. New policy.

06/03/2010 Medical Policy Committee approval

06/16/2010 Medical Policy Implementation Committee approval. Policy title changed by taking out azathioprine (6-MP) and replacing it with "Thiopurines". Policy statement changed to "a one-time genotypic or

©2014 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237  
Original Effective Date: 04/15/2009  
Current Effective Date: 06/18/2014

phenotypic analysis of the thiopurine methyltransferase (TPMT) gene in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) or in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction to be eligible for coverage.”

06/02/2011 Medical Policy Committee review  
06/15/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
06/14/2012 Medical Policy Committee review  
06/20/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
01/11/2013 Codes updated.  
06/06/2013 Medical Policy Committee review  
06/25/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
06/05/2014 Medical Policy Committee review  
06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
Next Scheduled Review Date: 06/2015

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. reference to federal regulations.

\*\*Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. in accordance with nationally accepted standards of medical practice;
- B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.