Kansas City

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Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for pharmacogenomic and metabolite markers for patients treated with thiopurines when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

One-time genotypic **or** phenotypic analysis of the TPMT may be considered **medically necessary** 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.

When Policy Topic is not covered

Analysis of the metabolite markers of azathioprine and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is considered **investigational.**

Considerations

TPMT testing can not 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.

There are no specific CPT codes for genotypic analysis of the TPMT gene or metabolite markers of azathioprine and 6-mercaptopurine.

There is a CPT genetic testing modifier that is specific to TPMT:
-9A: TPMT, commonly called thiopurine methyltransferase (patients on antimetabolite therapy)

Effective in 2012, there is a CPT tier 2 molecular pathology code which includes TPMT testing for common variants:
81401: Molecular pathology procedure, Level 2 (eg, 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)

Description of Procedure or Service

Thiopurines or purine analogues are immunomodulators used to treat malignancies, rheumatic diseases, dermatologic conditions, inflammatory bowel disease and solid organ transplantation. These agents include azathioprine (AZA) (Imuran), mercaptopurine (6-MP) (Purinethol), and thioguanine (6-TG) (Tabloid). Thiopurines are converted by the enzyme thiopurine methyltransferase (TPMT) into

metabolites. Measurement of TPMT activity may help to identify patients at risk for excessive toxicity, most often myelosuppression, after receiving standard doses of thiopurine medications. Measurement of metabolites (metabolite markers) may help to tailor individualized drug therapy.

Thiopurines include azathioprine (Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are considered an effective immunosuppressive treatment of inflammatory bowel disease (IBD), particularly in patients with corticosteroid-resistant disease. However, the use of thiopurines is limited by both its long onset of action (3–4 months) and drug toxicities, which include hepatotoxicity, bone marrow suppression, pancreatitis, and allergic reactions.

Pharmacogenomics
Thiopurines are converted to mercaptopurine (6-MP) in vivo, where it is subsequently metabolized to 2 active metabolites; either 6-thioguanine nucleotides (6-TGN) by the enzyme IMPDH, or to 6-methyl-mercaptopurine ribonucleotides (6-MMRP) by the enzyme TPMT. TPMT also converts mercaptopurine (6-MP) to an inactive metabolite, 6-methyl-mercaptopurine (6-MMP). 6-thioguanine nucleotides (6-TGN) 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 mercaptopurine (6-MP) is shunted toward the IMPDH pathway with greater accumulation of 6-thioguanine nucleotides (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 3 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 myelotoxicity; 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.

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, since some co-administered 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 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.
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.

Prometheus® 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 TMPT enzyme, and Prometheus thiopurine metabolites, respectively. Other laboratories that offer TPMT genotyping include Quest (TPMT Genotype) and Specialty Laboratories (TPMT GenoTypR™).

Rationale

This policy was originally created in 2000 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period April 2012 through May 9, 2013. Following is a summary of the key literature to date:

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 thiopurine methyltransferase (TPMT) gene is based on well-established polymerase chain reaction technology (PCR) 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. (1) 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).

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 red blood cells (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). (2) A total of 19 studies on test performance were identified; most were cross-sectional or prospective observational studies and approximately 70% included patients with inflammatory bowel disease. 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 TPMT enzymatic activity than normal levels (pooled OR: 19.1, 95% CI: 4.6-80.2). It is worth noting that confidence intervals 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. (3) 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 inflammatory bowel disease (IBD) taking thiopurine drugs. (4) 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).

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; study designs have generally been cross-sectional or retrospective. For example, Cuffari and colleagues measured the metabolites 6-thioguanine nucleotides (6-TGN) and 6-methyl-mercaptopurine ribonucleotides (6-MMRP) in 25 pediatric patients with Crohn's disease. (5) Achievement of clinical remission was correlated with 6-thioguanine nucleotides (6-TGN), levels, but not 6-methyl-mercaptopurine ribonucleotides (6-MMRP).

Several studies have considered the optimal therapeutic cutoff level of metabolites. In 2000, Dubinsky and colleagues measured 6-thioguanine nucleotides (6-TGN), and 6-methyl-mercaptopurine ribonucleotides (6-MMRP) levels in 92 pediatric patients. (6) Higher median levels of 6-thioguanine nucleotides (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-thioguanine nucleotides (6-TGN) levels were greater than 235 (measured in pmol/8 x 10^8). The 6-methyl-mercaptopurine ribonucleotides (6-MMRP) levels did not correlate with disease activity, but elevated levels did correlate with hepatotoxicity, observed in 16 patients. Elevated 6-thioguanine nucleotides (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 pmol/8x10^8. (7) 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 pmol/8x10^8 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 azathioprine. (8) 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-thioguanine nucleotides (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 azathioprine. (9) 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 pmol/8x10^8, p=0.025). According to receiver operating curve (ROC) analysis, a cutoff of 220 pmol/8x10^8 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 pmol/8x10^8.

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. (10) The study included 346 patients taking thiopurines who underwent thiopurine metabolite analysis, a complete blood count (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-thioguanine nucleotides (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 thioprine 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 randomized controlled study (RCT), known as the TARGET study, randomized 333 patients to receive TPMT genotyping or usual care (no genotyping) prior to azathioprine therapy. (11) Study eligibility included age 16 years or older with a diagnosis of inflammatory bowel disease (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 azathioprine (i.e., 1.5 to 3 mg/kg/day) for individuals with wild-type TPMT, low-dose azathioprine (i.e., 25-50 mg/day) titrated to a maintenance dose for individuals with heterozygous TPMT variant alleles and an alternative therapy (no azathioprine) 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 azathioprine 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 azathioprine 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=.74. In the genotyping arm, the average starting dose of azathioprine 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=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 prospective studies examining variation in the efficacy of medication according to patient's TPTM status 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 azathioprine/mercaptopurine (6-MP) dose based on RBC TPMT activity prevented myelotoxicity; no patients in this study exhibited low activity. (12) 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. (13) This conclusion was based on a study of 52 patients with IBD who were started on azathioprine or mercaptopurine and who were followed up for 9 months, while 6-thioguanine nucleotides (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 inflammatory bowel disease, 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. (14) These authors concluded that determining TPMT activity prior to initiating treatment with azathioprine 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. (15) 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. For example, studies have reported that there is only weak correlation between metabolite levels and dose of drug. (16) In addition, studies have reported that levels obtained with testing are often outside of the therapeutic range. For example, the Gearry and colleagues study reported that 41% of values were within the therapeutic range. (17) and Armstrong and colleagues found that 32% of values were within therapeutic levels. (18) The review by Teml et al. concluded that at present therapeutic drug monitoring of 6-thioguanine nucleotides (6-TGN) can be recommended only to estimate patients' compliance. (19)

Summary
There are a large number of studies on the diagnostic performance of thiopurine methyltransferase (TMPT) 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 medically necessary 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). Moreover, there is a lack of consensus among studies on the optimal cutoff to use when measuring 6-thioguanine nucleotides (6-TGN) levels. Thus, analysis of metabolite markers is considered investigational.

Practice Guidelines and Position Statements
In 2013, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Committee on IBD published consensus recommendations on the role of TMPT and thiopurine metabolite testing in pediatric IBD. (20) Recommendations included:

- TPMT testing is recommended before initiation of thiopurines and individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of thiopurines because of risk of leucopenia.
- Individuals on thiopurines should have routine monitoring of blood counts to evaluate for leucopenia regardless of TPMT testing results.
- Metabolite testing can be used to determine adherence to thiopurine activity.
- Metabolite testing can be used to guide dosing changes in patients with active disease.
- Routine and repeat metabolite testing has little or no role in patients who are responding well to medication and taking an acceptable dose of thiopurines.

A 2011 guideline from the British Association of Dermatologists addressed the safe and effective prescribing of azathioprine. (21) The guideline included the following recommendations on analysis of *TMPT* activity:

- There is strong evidence that baseline testing before starting azathioprine predicts severe neutropenia in patients with absent TMPT activity
- There is good evidence that intermediate TMPT activity is associated with myelotoxicity in patients using conventional doses of azathioprine
- There is a continued need for regular monitoring of blood counts in addition to TMPT testing.

A 2010 guideline from the National Academy of Clinical Biochemistry (NACB) stated, "thiopurine methyltransferase (TPMT) genotyping is recommended as a useful adjunct to a regimen for prescribing azathioprine" (22) This is an "A-I" recommendation, indicating that the NACB strongly recommends adoption and the recommendation is based on evidence with consistent results from well-designed, well-conducted studies in representative populations.

A 2006 position statement from the American Gastroenterological Association included the following recommendations (23):

- "Current U.S. Food and Drug Administration (FDA) recommendations suggest that individuals should have thiopurine methyltransferase (TPMT) genotype or phenotype assessed before initiation of therapy with AZA or 6-MP in an effort to detect individuals who have low enzyme activity (or who are homozygous deficient in TPMT) in an effort to avert AZA or 6-MP therapy and thus avoid potential adverse events. Individuals who have intermediate or normal TPMT activity (wild type or heterozygotes) need measurement of frequent complete blood counts (as above) in addition to TPMT assessment because these individuals may still develop myelosuppression subsequent to use of AZA or 6-MP (Grade B)".
- "Thiopurine metabolite monitoring in the treatment of patients with 6-MP or AZA is useful when attempting to determine medical noncompliance and may be helpful for optimizing dose and monitoring for toxicity (Grade C)."

Evidence grades used in this guideline are:
"Grade A: Homogeneous evidence from multiple well-designed, randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power.
Grade B: Evidence from at least 1 large well-designed, clinical trial with or without randomization from cohort or case-control analytic studies or well-designed meta-analysis.
Grade C: Evidence based on clinical experience, descriptive studies, or reports of expert committees."

Medicare National Coverage
No national coverage determination.

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Billing Coding/Physician Documentation Information

There are no specific CPT codes for genotypic analysis of the TPMT gene or metabolite markers of azathioprine and 6-mercaptopurine. According to the laboratories offering this testing, they use a combination of the CPT codes listed below to code for this test (for example, Prometheus uses 83891, 83898 x3; 83896 x6; 83912):

81401 Molecular pathology procedure, Level 2 (eg, 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) ABL (c-abl oncogene 1, receptor tyrosine kinase) (eg, acquired imatinib resistance), T315I variant ACADM (acyl-CoA dehydrogenase, C-4 to C-12 straight chain, MCAD) (eg, medium chain acyl dehydrogenase deficiency), common variants (eg, K304E, Y42H) ADRB2 (adrenergic beta-2 receptor surface) (eg, drug metabolism), common variants (eg, G16R, Q27E) APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4) CBFB/MYH11 (inv(16)) (eg, acute myeloid leukemia), qualitative, and quantitative, if performed CCND1/IGH (BCL1/IgH, t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative, and quantitative, if performed CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2) (eg, macular degeneration), common variants (eg, Y402H [CFH], A69S [ARMS2]) CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4) (eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6) CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5) (eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6) DMPK (dystrophia myotonica-protein kinase) (eg, myotonic dystrophy, type 1), evaluation to detect abnormal (eg, expanded) alleles F11 (coagulation factor XI) (eg, coagulation disorder), common variants (eg, E117X

[Type II], F283L [Type III], IVS14del14, and IVS14+1G>A [Type I]) FGFR3 (fibroblast growth factor receptor 3) (eg, achondroplasia), common variants (eg, 1138G>A, 1138G>C) FIP1L1/PDGFRA (del[4q12]) (eg, imatinib-sensitive chronic eosinophilic leukemia), qualitative, and quantitative, if performed GALT (galactose-1-phosphate uridylyltransferase) (eg, galactosemia), common variants (eg, Q188R, S135L, K285N, T138M, L195P, Y209C, IVS2-2A>G, P171S, del5kb, N314D, L218L/N314D) HBB (hemoglobin, beta) (eg, sickle cell anemia, hemoglobin C, hemoglobin E), common variants (eg, HbS, HbC, HbE) HTT (huntingtin) (eg, Huntington disease), evaluation to detect abnormal (eg, expanded) alleles RUNX1/RUNX1T1 (t(8;21)) (eg, acute myeloid leukemia) translocation analysis, qualitative, and quantitative, if performed SEPT9 (Septin 9) (eg, colon cancer), methylation analysis TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), common variants (eg, *2, *3) VWF (von Willebrand factor) (eg, von Willebrand disease type 2N), common variants (eg, T791M, R816W, R854Q)

Additional Policy Key Words

N/A

Policy Implementation/Update Information

5/1/06	New policy; considered investigational.
5/1/07	No policy statement changes.
5/1/08	No policy statement changes. Removed “with Inflammatory Bowel Disease” from the title.
8/15/08	Policy statement on TPMT gene testing changed to medically necessary; other policy statements unchanged.
5/1/09	No policy statement changes.
5/1/10	Policy statement on TPMT testing changed to “One-time genotypic OR phenotypic testing”; “or in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction” was added as medically necessary; other policy statements unchanged. Policy title changed – azathioprine (6-MP) taken out, replaced with “Thiopurines”.
5/1/11	No policy statement changes.
5/1/12	No policy statement changes.
5/1/13	No policy statement changes.
12/1/13	Updated description. No policy statement changes.