APPENDIX to Pharmacogenomic and Metabolite Markers in Inflammatory Bowel Disease Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

Pharmacogenomics

Azathioprine is converted to mercaptopurine (6-MP) in vivo, where it is subsequently metabolized to two active metabolites; either 6-thioguanine nucleotides (6-TGN) by the enzyme inosine monophosphate dehydrogenase (IMPDH), or to 6-methyl-mercaptopurine ribonucleotides (6-MMRP) by the enzyme thiopurine methyltransferase (TPMT). Thiopurine methyltransferase also converts mercaptopurine (6-MP) to an inactive metabolite, 6-methyl-mercaptopurine (6-MMP). 6-thioguanine nucleotides are considered cytotoxic and 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 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. 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 mutation on one chromosome). Patients 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 azathioprine, while those with low TPMT activity may not be good candidates for azathioprine therapy. Currently three alleles, TPMT*2, TPMT*3A and TPMT*3C, account for about 95% of individuals with reduced TPMT activity.

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.

The following clinical applications of pharmacogenomics have been proposed:

- TPMT genotyping before the initiation of therapy may identify those patients who are at higher risk for hematologic toxicity and who may benefit from more intense surveillance
- Patients with two TPMT mutations are at highest risk for bone marrow toxicity and therefore alternative therapy may be considered
- In patients with one TPMT mutation, azathioprine therapy may be safely initiated, but a lower (50%) dose may be considered
- In patients with no TPMT mutations, azathioprine may be initiated at a higher dose

Azathioprine is typically given orally, but in some cases, it may be initially given intravenously to accelerate its onset of action. Intravenous dosing may be considered contraindicated in patients with two TPMT mutations.

Some small studies have evaluated prospective use of pharmacogenomics. In a study that involved 131 patients with inflammatory bowel disease (IBD), investigators from Europe did not find the choice of azathioprine/ mercaptopurine (6-MP) dose based on red blood cell (RBC) TPMT activity prevented myelotoxicity; no patients in this study exhibited low activity (Gisbert et al., 2006). Guidelines from the American Gastroenterological Association supported the use of these tests with Grade B evidence for TPMT testing and Grade C evidence for the metabolite markers (Lichtenstein et al., 2006).

A review article by Teml et al., (2007) noted that patients with TPMT deficiency treated with standard doses of azathioprine/ mercaptopurine (6-MP) have double the risk of developing severe myelosuppression within a few weeks of starting therapy. As noted here, this risk is explained by a marked increase of 6-thioguanine nucleotides (6-TGN) levels. The review also stated that the data are more limited in those who are heterozygous for TPMT activity. However, for patients who developed myelotoxicity, the reviewers affirmed that it tended to occur earlier (one to 1.5 months into treatment) for those who were heterozygous, compared to about three months in wild-type patients. This review reported TPMT testing as reliable and cost effective to prevent severe hepatotoxicity in TPMT variant patients. In a study from New Zealand, Gardiner

et al., (2008) noted initial target doses to attain therapeutic levels in patients with IBD might be 1 and 3 milligrams per kilogram per day in intermediate (heterozygous) and normal (wild-type) metabolizers. This conclusion was based on a study of 52 patients with IBD who were started on azathioprine or mercaptopurine (6-MP) and who were followed up for nine months while 6-thioguanine nucleotides (6-TGN) levels and clinical status were assessed. Thus, this study suggested knowledge of TPMT activity can assist with initial dosing. In a study from Europe on 394 patients with IDB, Gisbert et al., (2006) noted 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 azathioprine could help to minimize the risk of myelotoxicity.

Winter et al., (2007) conducted a prospective study in the United Kingdom to look for a correlation between TPMT genotype and enzyme activity level (phenotyping) and to determine the relationship between TPMT status (genotyping and phenotyping) and the development of adverse events. Inflammatory bowel disease patients (n = 130) taking azathioprine were identified and azathioprine tolerance recorded. Blood was collected for measurement of TPMT enzyme activity (phenotyping) and TPMT*3C, TPMT*3A and TPMT*2 genotypes. All patients with normal enzyme activity did have the wild-type genotype. However, only 65% of patients with intermediate TPMT enzyme activity were heterozygous for the TPMT gene. About one-third of patients with intermediate enzyme activity had side effects, similar with normal enzyme activity. The authors concluded there was no increased risk of adverse events with intermediate enzyme activity or heterozygous genotype, but very low TPMT activity caused severe myelosuppression.

In a review article, Wong and Bass, (2008) discussed laboratory evaluations for patients with IBD. The authors made the following comments regarding thiopurine monitoring:

- TPMT activity can be assessed either by directly measuring enzyme activity (phenotype) or by determining TPMT genotype
- Current recommendations support pretreatment determination of TPMT enzyme phenotype/genotype as a safety measure to avoid early catastrophic bone marrow failure
- The literature however, remains somewhat controversial regarding use of metabolite levels

The product information for Imuran® (azathioprine) contained the following statements:

- TPMT genotyping or phenotyping (RBC TPMT activity) can help identify patients who are at an increased risk for developing IMURAN toxicity
- TPMT Testing: It is recommended that consideration be given to either genotype or phenotype patients for TPMT

The product information for Purinethol® (mercaptopurine (6-MP)) enclosed the following statement:

> Individuals who are homozygous for an inherited defect in the TPMT (thiopurine-S-methyltransferase) gene are unusually sensitive to the myelosuppressive effects of mercaptopurine (6-MP) and prone to developing rapid bone marrow

suppression following initiation of treatment. Laboratory tests are available, both genotypic and phenotypic to determine the TPMT status.

The product information for Tabloid® (thioguanine) contained the following statements:

- There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and prone to developing rapid bone marrow suppression following initiation of treatment
- Prescribers should be aware that some laboratories offer testing for TPMT deficiency

In summary, the data from the published literature indicated reduced TPMT activity resulted in increased likelihood of myelotoxicity, a serious side-effect of azathioprine treatment. In addition, the data suggested knowledge of TPMT activity is helpful in selecting the initial dose of drug. Thus, this one-time testing is considered medically necessary.

Metabolite Markers

Monitoring of azathioprine 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 azathioprine 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.

Metabolite markers have been assessed using high performance liquid chromatography 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 RBC instead of leukocytes. Cuffari and colleagues (1996) reported RBC and leukocyte 6-thioguanine nucleotides (6-TGN) levels were directly correlated.

Several case series have explored the correlation between levels of 6-thioguanine nucleotides (6-TGN), toxicity of azathioprine, and treatment effectiveness. Cuffari and colleagues (1996) measured the metabolites 6-thioguanine nucleotides (6-TGN) and 6-methyl-mercaptopurine ribonucleotides (6-MMRP) in 25 pediatric patients with Crohn's disease. Achievement of clinical remission was correlated with 6-thioguanine nucleotides (6-TGN), levels, but not 6-methyl-mercaptopurine ribonucleotides (6-MMRP). Dubinsky and colleagues (2000) measured 6-thioguanine nucleotides (6-TGN), and 6-methyl-mercaptopurine ribonucleotides (6-MMRP) levels in 92 pediatric patients. 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 picomole/ 8 x 10 to the eighth). 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. In contrast, Gupta and colleagues (2001) reported discordant results in a case series of 54 patients with IBD being treated with azathioprine. A total of 36% of patients in relapse had 6-thioguanine nucleotides (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-thioguanine nucleotides (6-TGN) levels greater than 230. These results questioned the 235 cut-off point suggested by Dubinsky. Similarly, Lowry and colleagues (2001) reported that the 6-thioguanine nucleotides (6-TGN) concentration did not correlate with disease activity or leukopenia in a case series of 170 patients with IBD.

The following clinical applications of metabolite testing have been proposed:

- Based on the Dubinsky and colleagues study (2000), patients may undergo metabolite monitoring to tailor azathioprine therapy. When 6-thioguanine nucleotides (6-TGN) levels reach a target of 235, tapering of steroids may be considered. In the past, the onset of leukopenia was considered a target point for steroid tapering. The use of 235 as a cut-off is challenged by the results of Gupta et al., (2001) and Lowry et al., (2001) as reviewed here
- Non-compliance may be suspected in patients with very low 6-thioguanine nucleotides (6-TGN) levels
- 6-TG levels higher than 400 are associated with an increased risk of myelosuppression; dose reduction may be suggested
- Excessive TPMT activity may be suspected when 6-thioguanine nucleotides (6-TGN) levels are low, while 6-methyl-mercaptopurine ribonucleotides (6-MMRP) levels are elevated. This profile may provide an explanation for drug resistance

No prospective comparative trials have been identified in which use of metabolite markers was compared to current approaches to care. Morales et al., (2007) reported there is only weak correlation between metabolite levels and dose of drug. In addition, studies have reported that levels obtained with testing are often outside of the therapeutic range; one study reported that 41% of values were within the therapeutic range (Gearry et al., 2005). The review by Temlet al., (2007) concluded that at present, therapeutic drug monitoring of 6-thioguanine nucleotides (6-TGN) can be recommended only to estimate patient compliance. The question of whether or not prospective use of these markers will lead to improved outcomes (primarily improved disease control and/or less adverse drug effects) has not been answered.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	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), commons variants (eg, K304E, Y42H) ADRB2 (adrenergic beta-2 receptor surface) (eg
HCPC	None	
ICD9 Procedure	None	
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Pharmacogenomics

Key / Related Searchable Words

N/A

References

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
12/7/2006	Policy Adopted - BCBSA MPP	Medical Policy Committee
1/7/2011	Policy title change from Pharmacogenomic and Metabolite Markers for Patients Treated with Azathioprine (6-MP) Policy revision with position change	Medical Policy Committee
2/22/2013	Coding Update	Administrative Review

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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