Corporate Medical Policy

Metabolite Markers of Thiopurines AHS – G2115

Thiopurines are a class of purine antimetabolite immunomodulators with diverse clinical applications in treatment of autoimmune disorders, transplant rejection, and acute lymphoblastic leukemia (Belmont, 2017; MacDermott, 2017). Their therapeutic efficacy, bone marrow toxicity, and liver toxicity have been reported to be related to levels of their downstream metabolites. Due to their complex metabolism, there is wide individual variation in patient response, both in achieving therapeutic drug levels as well as in developing adverse reactions (Bradford & Shih, 2011).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for metabolite markers of thiopurines when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Metabolite Markers of Thiopurines is covered

1. One-time phenotypic analysis of the enzyme TPMT is considered medically necessary in patients prior to initiating treatment 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.

2. Monitoring of thiopurine metabolite levels in individuals with inflammatory bowel disease is considered medically necessary for the following indications:
   a. To measure blood levels in individuals suspected of having toxic responses to AZA and/or 6-MP (e.g., hepatotoxicity or myelotoxicity);
   b. To measure drug levels in individuals who have not responded to therapy (e.g., persistent fever, further weight loss, and bloody diarrhea).
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3. Monitoring of thiopurine metabolite levels in individuals with acute lymphoblastic leukemia is considered medically necessary in the following situations:
   a. For patients showing signs of a lack of myelosuppression while on therapy
   b. For patients with normal function for TPMT and NUDT15 who do not appear to tolerate thiopurines.

When Metabolite Markers of Thiopurines is not covered

Phenotypic analysis of the enzyme TPMT is considered investigational in all other situations.

Analysis of the metabolite markers of azathioprine and 6-mercaptopurine, including 6-methylmercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is considered all other situations.

Policy Guidelines

Background

The thiopurine drugs, 6-mercaptopurine (6-MP), azathioprine (AZA) remain a mainstay of immunomodulator therapy (Askanase et al., 2009; Belmont, 2017; Cade, Stein, Pickering, Schlein, & Spooner, 1976; Chehl et al., 2010; Hunter, Urowitz, Gordon, Smythe, & Ogryzlo, 1975; Kirk & Lennard-Jones, 1982; Leib, Restivo, & Paulus, 1979; Mason et al., 1969; Pagnoux et al., 2008; Urowitz, Gordon, Smythe, Puzanski, & Ogryzlo, 1973). Their use is often limited, as an estimated 30% to 50% of patients discontinue these drugs due to either side-effects or lack of clinical efficacy (Ansari et al., 2002; Jharap et al., 2010; Seinen, van Asseldonk, Mulder, & de Boer, 2010). The lack of response to these immunomodulators has been attributed to differences in individual variations in drug metabolism (Bradford & Shih, 2011; Dubinsky et al., 2000; Present et al., 1980).

The 6-thioguanine nucleotide (6-TGN) metabolite of 6-MP and AZA appears to be the predominant active metabolite responsible for therapeutic efficacy, whereas 6-methylmercaptopurine (6-MMP) levels correlate with the risk of hepatotoxicity and possibly myelotoxicity (Dubinsky et al., 2000; Hindorf et al., 2006; Osterman, Kundu, Lichtenstein, & Lewis, 2006). Several studies have demonstrated that therapeutic efficacy correlates with 6-TG concentrations between 230 and 400, bone marrow suppression correlates with 6-TG concentrations greater than 400, and liver toxicity correlates with 6-MMP concentrations greater than 5000 (Askanase et al., 2009; Belaiche, Desager, Horsmans, & Louis, 2001; Cuffari, Theoret, Latour, & Seidman, 1996; Dubinsky et al., 2000; Goldenberg, Rawsthorne, & Bernstein, 2004; Gupta, Gokhale, & Kirschner, 2001; MacDermott, 2017; Mardini & Arnold, 2003; Roblin et al., 2005; Wright, Sanders, Lobo, & Lennard, 2004). Although 6-TG and 6-MP levels correlate with therapeutic efficacy and toxicity, whether measurement in individual patients can improve their individual long-term outcomes has not been established. There is wide range of response and toxicity across this range of 6-TG levels (Cuffari et al., 1996; Dubinsky et al., 2000), substantial variation (up to five fold) between measurements in individual patients (Wright et al., 2004), and the predictive value of metabolite levels in individual patients is low (Cuffari et al., 1996; Goldenberg et al., 2004). Furthermore, 6-MMP levels are not a highly accurate predictor of toxicity in individual patients (Shaye et al., 2007) and adverse can occur unrelated to elevated levels (Cuffari et al., 1996). However, retrospective study did find that using the results of metabolite testing to direct treatment was associated with improved clinical outcomes (Askanase et al., 2009; Haines et al., 2011; MacDermott, 2017).

Two enzymes are responsible for catalyzing these reactions: thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase. TPMT enzyme activity is a major factor determining AZA and 6-MP metabolism, and therefore 6-TG and 6-MMP levels. The majority of
the population have wild type TMPT and normal enzyme activity, while 11 percent are heterozygous and have corresponding low TPMT enzyme activity, and 0.3 percent (1 in 300) have negligible activity (Lennard, Gibson, Nicole, & Lilleyman, 1993; Lennard, Van Loon, & Weinshilboum, 1989). Intermediate and normal metabolizers can have up to a threefold difference in initial target doses of AZA and 6-MP to achieve therapeutic 6-TG concentrations (Gardiner, Gearry, Begg, Zhang, & Barclay, 2008). Measurement of TPMT genotypes and/or TPMT enzyme activity before instituting AZA or 6-MP may help prevent toxicity by identifying individuals with low or absent TPMT enzyme activity (Black et al., 1998; Cuffari, Dassopoulos, Turnbough, Thompson, & Bayless, 2004; Dubinsky et al., 2005; Gisbert, Nino, Rodrigo, Cara, & Guijarro, 2006; Lennard et al., 1993; Lennard et al., 1989), and conversely, identify those with higher than average TPMT activity who may remain refractory to conventional dosages (Cuffari et al., 2004). Dosing strategies involving such testing may be cost-effective (Cuffari et al., 2004; Dubinsky et al., 2005; Winter et al., 2004). However, prediction of toxicity is not consistently reliable, other genes are also likely to play a role in determining toxicity, such as glutathione-S-transferase (Stocco et al., 2007) and drug interactions must be taken into account (Dewit, Vanheuverzwyn, Desager, & Horsmans, 2002; Gilissen et al., 2005; Szumlanski & Weinshilboum, 1995). Thus, even though TPMT testing is recommended (Lichtenstein, 2004; Relling et al., 2013; Relling et al., 2011), a complete blood count (CBC), and also liver function tests, must still be obtained (Belmont, 2017; MacDermott, 2017).

Newman et al (2011) conducted a randomized controlled trial to assess whether TPMT genotyping prior to azathioprine reduces adverse drug reactions. 333 participants were randomized 1:1 to undergo TPMT genotyping prior to azathioprine or to commence treatment without genotyping. Data were available for 322 of 333 (97 percent) patients at four months. At four months, a total of 91 of 322 (28 percent) patients had stopped taking AZA because of an adverse drug reaction, 47 of 163 (29 percent) in the genotyping group and 44 of 159 (28 percent) in the non-genotyping group. The single individual with TPMT variant homozygosity experienced severe neutropenia. The authors concluded that “individuals with TPMT variant homozygosity are at high risk of severe neutropenia, whereas TPMT heterozygotes are not at increased risk of ADRs at standard doses of azathioprine.”

Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

The 2016 NCCN guidelines on Acute Lymphoblastic Leukemia recommended that “for patients receiving mercaptopurine (6-MP), consider testing for TPMT gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP” (NCCN, 2016).

Bressler et al (2015) published clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis on behalf of the Toronto Ulcerative Colitis Consensus Group, which reaffirmed recommendations from the American College of Gastroenterology, Practice Parameters Committee (Kornbluth & Sachar, 2010) for thiopurine therapy (Bressler et al., 2015) The authors stated that “Because thiopurines are metabolized by TPMT, which may be absent or present in
low levels in some patients, a TPMT assay is necessary before initiation of treatment to identify patients at risk for severe dose-dependent myelosuppression. In addition, higher levels of the thiopurine metabolite 6-thioguanine nucleotide have been correlated with clinical remission rates; therefore, thiopurine metabolite levels may be helpful to guide therapy. Note that TPMT testing does not replace the need for mandatory monitoring of complete blood cell count.

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

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

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 (A-I).” 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.

In 2006, the American Gastroenterological Association (AGA) released a position statement that included the following recommendations for AZA/6-MP use (Lichtenstein et al, 2006):

- “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)”.

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- “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.”

American College of Gastroenterology

The ACG published guidelines (Feuerstein, Nguyen, Kupfer, Falck-Ytter, & Singh, 2017) on Therapeutic Drug Monitoring in Inflammatory Bowel Disease which recommend:

In adult patients with IBD being started on thiopurines, the AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing.

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

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 80299, 81335, 82657

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Policy Implementation/Update Information

For Policy Titled: Pharmacogenomic and Metabolite Markers for Thiopurines

1/1/2019 New policy developed. BCBSNC will provide coverage for pharmacogenomics and metabolite markers for thiopurine when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

For Policy Titled: Metabolite Markers of Thiopurines

12/10/2019 Reviewed by Avalon 3rd Quarter 2019 CAB. Policy retitled. Removed “pharmacogenomics” from the Policy Statement. Added “Monitoring of thiopurine metabolite levels in individuals with acute lymphoblastic leukemia is considered medically necessary”, along with corresponding a. and b. to the When Covered section. Removed “genotyping” from both When Covered and When Not Covered sections. Code table removed from Billing/Coding section. Medical Director review 11/2019. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.