

Evidence Based Guideline

Pharmacogenomic and Metabolite Markers for Treatment with Thiopurines

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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.

Azathioprine, which is a prodrug of mercaptopurine (6-MP), is considered an effective immunosuppressive treatment of inflammatory bowel disease, particularly in patients with corticosteroid-resistant disease. For example, in the course of 1 year, 50% of patients with Crohn's disease will require treatment with corticosteroids; of these, 50% will either be corticosteroid resistant or corticosteroid dependent, and thus candidates for immunosuppressive therapy. Azathioprine therapy eliminates the need for corticosteroids in about 75% of patients; azathioprine is also considered an effective therapy for fistulizing disease. Results of a recent randomized clinical trial of children with Crohn's disease suggest that compared to prednisone alone, inclusion of azathioprine with prednisone at the time of initial diagnosis is associated with improved maintenance of remission while simultaneously decreasing the dose of prednisone.

However, the use of azathioprine 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. Long-term drug use has been associated with neoplasia. Due to these side effects it is estimated that less than 5% of patients with Crohn's disease ever receive azathioprine.

Pharmacogenomics

Azathioprine is 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 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.)

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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.

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 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 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 recently 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.

Prometheus is a commercial laboratory that offers pharmacogenomic and metabolite testing for those undergoing azathioprine therapy. The tests are referred to as Pro-Predict Rx TPMT and Pro-Predict Rx 6MP, respectively. Other laboratories that offer TPMT genotyping include Quest (TPMT Genotype) and Specialty Laboratories (TPMT GenoTypR™).

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

Evidence Based Guideline for pharmacogenomic and metabolite markers for treatment with thiopurines

One-time genotypic or phenotypic analysis of the TPMT *thiopurine methyltransferase* may be recommended 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.

Medical Evidence regarding pharmacogenomic and metabolite markers for treatment with thiopurines indicates it is not recommended in the following situations

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 and is not recommended.

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.

Billing/Coding/Physician Documentation Information

This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee

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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 codes: There are no specific CPT codes for genotypic or phenotypic analysis of the TPMT gene or for metabolite markers of azathioprine, mercaptopurine (6-MP) or thioguanine.

According to the laboratories offering this testing, a combination of the CPT codes listed below may be used to code for this test (for example, Prometheus uses 83891, 83898 x3; 83896 x6; 83912):

83890, 83891, 83892, 83896, 83898, 83900, 83909, 83912, 83914

There is a CPT genetic testing modifier that is specific to TPMT: -9A

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.19, 9/10/09

Policy Implementation/Update Information

5/10/11 New Evidence Based Guideline issued. One-time genotypic or phenotypic analysis of the TPMT *thiopurine methyltransferase* may be recommended 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. 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 and is not recommended. Specialty Matched Consultant Advisory Panel review 4/27/11. (adn)

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