Protocol

Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines

(20419)

Medical Benefit		**Effective Date**: 01/01/15	**Next Review Date**: 11/20
Preauthorization	Yes	**Review Dates**: 04/07, 09/08, 05/09, 03/10, 03/11, 03/12, 03/13, 03/14, 11/14, 11/15, 11/16, 11/17, 11/18, 11/19	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are treated with thiopurines	Interventions of interest are: • Thiopurine methyltransferase genotype analysis	Comparators of interest are: • Standard management without genotype analysis	Relevant outcomes include: • Symptoms • Morbid events • Change in disease status
Individuals: • Who are treated with thiopurines	Interventions of interest are: • Thiopurine methyltransferase phenotype analysis	Comparators of interest are: • Standard management without phenotype analysis	Relevant outcomes include: • Symptoms • Morbid events • Change in disease status
Individuals: • Who are treated with thiopurines	Interventions of interest are: • Azathioprine and/or 6-mercaptoprine metabolites analysis	Comparators of interest are: • Standard management without metabolite analysis	Relevant outcomes include: • Symptoms • Morbid events • Change in disease status

DESCRIPTION

The thiopurine class of drugs-which include azathioprine (a pro-drug for mercaptopurine), mercaptopurine, and thioguanine-are used to treat a variety of diseases; however, it is recommended the use of thiopurines be limited due to a high rate of drug toxicity. Mercaptopurine and thioguanine are directly metabolized by the thiopurine S-methyltransferase (TPMT) enzyme. Susceptibility to drug toxicity is linked to the level of TPMT activity. The variation in TPMT activity has been related to three distinct TPMT variants. Pharmacogenomic analysis of TPMT status is proposed to identify patients at risk of thiopurine drug toxicity and adjust medication doses accordingly; measurement of metabolite markers has also been proposed.

SUMMARY OF EVIDENCE

For individuals who are treated with thiopurines who receive TPMT genotype analysis or TPMT phenotype analysis, the evidence includes studies of diagnostic performance, systematic reviews, and randomized controlled trials. Relevant outcomes are symptoms, morbid events, and change in disease status. A large number of studies have assessed the diagnostic performance of TPMT genotyping and phenotyping tests. The most recent meta-analysis reported genotyping sensitivity and specificity of 90% and 100%, respectively, and a phenotyping sensi-

tivity and specificity of 76% and 99%, respectively, for identifying patients with subnormal enzymatic activity. Three randomized controlled trials (total N=1145 patients) have compared TPMT genotype/phenotype testing with no testing and empirical weight-based thiopurine dosing. There were no significant differences in the incidence of hematologic adverse events, treatment discontinuation rates, or clinical remission rates. However, secondary analysis of a small number of individuals who had intermediate enzymatic activity (a heterozygous genotype) or a low enzymatic activity (a homozygous genotype) showed that TPMT testing to guide dosing was associated with statistically significant risk reduction in hematologic adverse events with a wide margin of error. In summary, 200 patients would have to be genotyped to avoid one episode of a hematologic adverse drug reaction (7.4% vs. 7.9%; i.e., 0.5% risk difference). The number needed to treat to avoid one episode of a hematologic adverse drug reaction would be five for at-risk individuals (risk difference in patients with a genetic variant, 20.3%; 2.6% vs. 22.9%). In addition, a small, inadequately powered randomized controlled trial, which assessed phenotype TPMT testing, found no difference in treatment discontinuation rates due to adverse drug reactions between the two arms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are treated with thiopurines who receive azathioprine and/or 6-mercaptoprine metabolite analysis, the evidence includes a systematic review as well as prospective and retrospective studies. Relevant outcomes are symptoms, morbid events, and change in disease status. The systematic review, which assessed the diagnostic accuracy of metabolite testing, reported that the ability of the metabolite tests to predict clinical outcomes and toxicity was inconsistent across studies. There is insufficient evidence from prospective studies to determine whether knowledge of metabolite marker status will lead to improved outcomes (primarily improved disease control and/or less adverse drug events). Findings from studies evaluating the association between metabolite markers and clinical remission are mixed, and no prospective comparative trials have compared health outcomes in patients managed using metabolite markers with current approaches to care. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

One-time genotypic **or** phenotypic analysis of the thiopurine methyltransferase (TPMT) enzyme 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 results that do not respond to dose reduction.

Genotypic and/or phenotypic analysis of the TPMT enzyme is considered **investigational** in all other situations.

Analysis of the metabolite markers AZA and 6-MP, including 6-methyl-mercaptopurine ribonucleotides and 6-thioguanine nucleotides, is considered **investigational**.

POLICY GUIDELINES

TPMT testing cannot 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. Alternative therapies may need to be considered for patients who have low or absent TPMT activity (homozygous for nonfunctional alleles). Accurate phenotyping results are not possible in patients who received recent blood transfusions. TPMT genotyping and phenotyping would only need to be performed once.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend

formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BACKGROUND

THIOPURINES

Thiopurines or purine analogues are immunomodulators. They include azathioprine (Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, and inflammatory bowel disease, and are used in solid organ transplantation. They are considered an effective immunosuppressive treatment of inflammatory bowel disease, particularly in patients with corticosteroid-resistant disease. However, the use of thiopurines is limited by both long onset of action (three to four months) and drug toxicities, which include hepatotoxicity, bone marrow suppression, pancreatitis, and allergic reactions.

Pharmacogenomics

Thiopurines are converted to 6-MP in vivo, where it is subsequently metabolized to two active metabolites: either 6-thioguanine nucleotides (6-TGN) by the inosine-5'-monophosphate dehydrogenase enzyme; or to 6-methyl-mercaptopurine ribonucleotides by the thiopurine methyltransferase (TPMT) enzyme. TPMT also converts 6-MP into an inactive metabolite, 6-methyl-mercaptopurine. The 6-TGN metabolites are considered cytotoxic and thus are associated with bone marrow suppression, while the 6-methyl-mercaptopurine ribonucleotides are associated with hepatotoxicity. In population studies, the activity of the TPMT enzyme 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 inosine-5'-monophosphate dehydrogenase pathway with greater accumulation of 6-TGN; these patients are considered at risk for myelotoxicity (i.e., bone marrow suppression).

This variation in TPMT activity has been related to three distinct TPMT variants and has permitted the development of TPMT genotyping using a polymerase chain reaction. For example, patients with high TPMT activity are found to have two normal (wild-type) TPMT alleles; those with intermediate activity are heterozygous (i.e., have a variant on one chromosome), while those with low TPMT activity are homozygous for TPMT variants (i.e., have a variant on both chromosomes). Genetic analysis has been explored as a technique to identify patients at risk for myelotoxicity. Patients with high TPMT activity may be treated with standard doses of thiopurines, patients 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. Phenotyping determines the level of thiopurine nucleotides or TPMT activity in erythrocytes. Caution must be taken with phenotyping, because some coadministered drugs can influence the 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 at increased risk of developing severe, life-threatening myelotoxicity.

The genotypic analysis of the TPMT gene is based on well-established polymerase chain reaction technology to detect three distinct variants. Currently, three alleles (TPMT*2, TPMT*3A, TPMT*3C) account for about 95% of

subjects with reduced TPMT enzyme activity. Subjects homozygous for these alleles are TPMT-deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. A study by Hindorf and Appell (2012) 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 genotyping tests examined the three most common TPMT variants, previously noted. TPMT genotyping identified 6,454 (89.7%) as TPMT wild-type, 704 (9.8%) as TPMT heterozygous, and 37 (0.005%) as TPMT homozygous. The overall agreement between genotyping and phenotyping was 95%. Genotyping alone would have misclassified three (8%) of 37 homozygous patients as heterozygous; these three subjects were found to have uncommon variants. All three had low TPMT activity. The phenotype test would have misclassified four (11%) of 37 of homozygous patients because they had test results above the cutoff level for low TPMT activity (<2.5 U/mL red blood cells).

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 in monitoring intracellular levels of thiopurine metabolites (i.e., 6-TGN, 6-methyl-mercaptopurine ribonucleotides) to predict response and complications, with the ultimate aim of tailoring drug therapy to each patient.

Metabolite markers have been assessed using high-performance liquid chromatography technology. It would be optimal to assess metabolite markers in peripheral leukocytes because they reflect the status of bone marrow precursors. However, it is technically easier to measure metabolites in red blood cells than in leukocytes.

While genotyping and phenotyping of TPMT would only be performed once, metabolite markers might be tested multiple times during the course of the disease to aid in determining the initial dose and in evaluating any ongoing dosing.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Several thiopurine genotype, phenotype, and metabolite tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus, a commercial laboratory, offers thiopurine genotype, phenotype, and metabolite testing for those on 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 Diagnostics (TPMT Genotype); ARUP Laboratories (TPMT DNA); Specialty Laboratories (TPMT GenoTypR™); PreventionGenetics (TPMT Deficiency via the TPMT Gene); Genelex (TPMT); Fulgent Genetics (TPMT); and LabCorp (TPMT enzyme activity and genotyping).

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced

procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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32. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 01/01/2019.