BlueCross BlueShield Federal Employee Program.

FEP 2.04.19 Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines

Effective Date: April 15, 2018 **Related Policies:** None

Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines

Description

The thiopurine drugs—which include azathioprine (a pro-drug for mercaptopurine), mercaptopurine, and thioguanine—are used to treat a variety of diseases; however, it is recommended that 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.

FDA 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 in San Diego, 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; Madison, NJ), ARUP Laboratories (TPMT DNA; Salt Lake City, UT), and Specialty Laboratories (TPMT GenoTypR™; Valencia, CA), PreventionGenetics (TPMT Deficiency via the TPMT Gene; Marshfield, WI), Genelex (TPMT; Seattle, WA), and Fulgent Genetics (TPMT; Temple City, CA).

POLICY STATEMENT

One-time genotypic **or** phenotypic analysis of the thiopurine methyltransferase (TPMT) enzyme may be considered **medically necessary** in patients beginning therapy with azathioprine, mercaptopurine, or thioguanine **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 azathioprine and mercaptopurine, including 6-methyl-mercaptopurine ribonucleotides and 6-thioguanine nucleotides, is considered **investigational**.

POLICY GUIDELINES

Thiopurine methyltransferase (*TPMT*) testing cannot substitute for complete blood count monitoring in patients receiving thiopurines. Early drug discontinuation may be considered in patients with abnormal complete blood count 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.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

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 *TMPT* genotyping and phenotyping tests. A meta-analysis found a pooled sensitivity of about 80% and specificity near 100% for identifying patients with subnormal enzymatic activity. Three randomized controlled trials (total N=1145 patients) compared *TPMT* genotype/phenotype testing with no testing and empirical weight-based thiopurine dosing. There was no significant difference in the incidence of hematologic adverse events, treatment discontinuation rates, or clinical remission. However, secondary analysis of a small number of individuals who had intermediate enzymatic activity/heterozygous genotype or homozygous genotype/low enzymatic activity 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 1 episode of a hematologic adverse drug reaction (7.4% vs 7.9%; ie, 0.5% risk difference). The number needed to treat to avoid 1 episode of a hematologic adverse drug reaction would be 5 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 that assessed phenotype *TPMT* testing found no difference in treatment discontinuation rates due to adverse drug reactions between the 2 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 metabolites 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. 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 for 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (v.3.2017) guidelines on acute lymphoblastic leukemia state that testing for thiopurine methyltransferase (*TPMT*) gene variants should be considered for patients receiving mercaptopurine (6-MP)—in particular, patients who develop severe neutropenia on 6-MP.[26]

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

In 2013, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition on inflammatory bowel disease (IBD) published consensus recommendations on the role of the TMPT enzyme and thiopurine metabolite testing in pediatric IBD.[27] Recommendations (high and moderate) included:

1. "TPMT testing is recommended before initiation of TPs [thiopurines] to identify individuals who are homozygous recessive or have extremely low TPMT activity…
2. Individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of TPs because of concerns for significant leucopenia.
3. … All individuals on TPs should have routine monitoring of CBC [complete blood cell] and WBC [white blood cell] counts to evaluate for leucopenia regardless of TPMT testing results.
4. Metabolite testing can be used to determine adherence to TP therapy.
5. Metabolite testing can be used to guide dosing increases or modifications in patients with active disease….
6. Routine and repeat metabolite testing has little or no role in patients who are doing well and taking an acceptable dose of a TP."

British Association of Dermatologists

The 2011 guidelines from the British Association of Dermatologists addressed the safe and effective prescribing of azathioprine for the management of autoimmune and inflammatory skin diseases.[28] The guidelines included the following recommendations on analysis of TMPT activity and azathioprine toxicity:

- "There is strong evidence that baseline testing 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 azathioprine doses.
- TMPT testing only identifies … haematological toxicity, hence the continued need for regular monitoring of blood counts irrespective of TMPT status."

American Gastroenterological Association Institute

Recommendations from a 2017 American Gastroenterological Association Institute guidelines on therapeutic drug monitoring in IBD are summarized in Table 2.[29]

Table 1. Evidence-Based Clinical Guidelines on Therapeutic Drug Monitoring in IBD

Recommendation	SOR	QOE
In adults with IBD being started on thiopurines, AGA suggests routine *TPMT* testing (enzymatic activity or genotype) to guide thiopurine dosing	Conditional	Low
In adults treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes	Conditional	Very low
In adults with quiescent IBD treated with thiopurines, AGA suggests against routine thiopurine metabolite monitoring	Conditional	Very low

AGA: American Gastroenterological Association; IBD: irritable bowel disease; QOE: quality of evidence; SOR: strength of recommendation; *TPMT*: thiopurine methyltransferase.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
December 2012	Update Policy	Policy updated with literature search, References updated, Policy

		statements unchanged.
September 2013	Update Policy	Policy updated with literature search. References 7,9,15 and 20 added; other references renumbered or removed. Policy statements unchanged.
September 2014 September 2015	Update Policy Update Policy	Policy updated with literature review. References 5, 6, and 18 added. Policy statements unchanged. Policy updated with literature review; references 4, 11 and 21 added. Policy statements unchanged.
March 2017	Update Policy	Policy updated with literature review through November 3, 2016; references 6-7 and 14 added. Policy statements unchanged.
March 2018	Update Policy	Policy updated with literature review through September 11, 2017; references 14, 17, and 29 added. Policy statements unchanged.