MEDICAL POLICY

POLICY TITLE	PHARMACOGENOMIC AND METABOLITE MARKERS FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE TREATED WITH THIOPURINES
POLICY NUMBER	MP-2.218

Original Issue Date (Created):	**7/1/2002**
Most Recent Review Date (Revised):	**5/12/2020**
Effective Date:	**8/1/2020**

I. POLICY

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

Analysis of the metabolite markers of azathioprine and 6-mercaptopurine, including 6-MMP and 6-TG, may be considered **medically necessary** to optimizing the therapeutic response to 6-MP (azathioprine, Imuran®) if the therapeutic response is not reached with standard dosing.

Monitoring of thiopurine metabolite levels in individuals with inflammatory bowel disease may be considered **medically necessary** for the following indications:

- To measure blood levels in individuals suspected of having toxic responses to AZA and/or 6-MP (e.g., hepatotoxicity or myelotoxicity);
- To measure drug levels in individuals who have not responded to therapy (e.g., persistent
- fever, further weight loss, and bloody diarrhea).

Genotypic and/or phenotypic analysis of the enzyme TPMT is considered **investigational** in all other situations. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

Thiopurine methyltransferase (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. Alternate 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. Genotyping and phenotyping of TPMT would only need to be performed once.

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II. PRODUCT VARIATIONS TOP

This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO: Refer to FEP Medical Policy Manual MP-2.04.19, Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND TOP

Thiopurines

Thiopurines or purine analogues **ARE** immunomodulators. They include azathioprine (AZA; Imuran), mercaptopurine (6-MP; Purinethol), and thioguanine (6-TG; Tabloid). Thiopurines are used to treat malignancies, rheumatic diseases, dermatologic conditions, and irritable bowel disease (IBD), and are used in solid organ transplantation. They are considered an effective immunosuppressive treatment of IBD, particularly in patients with corticosteroid-resistant disease. However, use of thiopurines 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.

Pharmacogenomics

Thiopurines are converted to 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 thiopurine methyltransferase (TPMT). TPMT also converts 6-MP into an inactive metabolite, 6-methyl-mercaptopurine. 6-TGNs 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 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 IMPDH 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 3 distinct *TPMT* mutations and has permitted the development of *TPMT* genotyping based on a polymerase chain reaction. 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). Genetic analysis has been explored as a technique to identify patients at risk for myelotoxicity; those 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. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in erythrocytes and can also be informative. Caution must be taken with phenotyping, because 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 at increased risk of developing severe, life-threatening myelotoxicity.

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-MMRP) 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 multiple times during the course of the disease to aid in determining initial dose and to evaluate ongoing dosing.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Several thiopurine genotype, phenotype, and metabolite tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA 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; Madison, NJ), ARUP Laboratories (TPMT D; 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).

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IV. RATIONALE

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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. vs 7. i.e., 0. 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. 2. vs 22. 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.

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V. DEFINITIONS

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CROHN'S DISEASE is a chronic inflammatory bowel disease of unknown origin, usually affecting the ileum, the colon, or another part of the gastrointestinal tract.

IMMUNOSUPPRESSIVE refers to any treatment used to block abnormal or excessive immune responses.
METABOLITE refers to any product of metabolism.
NEOPLASIA is the development of neoplasms that are new and abnormal formations of tissue such as tumors or growths.
PHARMACOGENOMIC refers to the study of the effects of genetic differences among people and the impact these differences have on the uptake, effectiveness, toxicity, and metabolism of drugs.
THIOPURINE METHYLTRANSFERASE ENZYME (TPMT) is an enzyme that is active in the metabolism of azathioprine in the body.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes®								
80299	81335	82542	82657					

ICD-10-CM Diagnosis Code	Description
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication

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ICD-10-CM Diagnosis Code	Description
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess
K51.218	Ulcerative (chronic) proctitis with other complication
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.40	Inflammatory polyps of colon without complications
K51.411	Inflammatory polyps of colon with rectal bleeding
K51.412	Inflammatory polyps of colon with intestinal obstruction
K51.413	Inflammatory polyps of colon with fistula
K51.414	Inflammatory polyps of colon with abscess
K51.418	Inflammatory polyps of colon with other complication
K51.50	Left sided colitis without complications
K51.511	Left sided colitis with rectal bleeding
K51.512	Left sided colitis with intestinal obstruction
K51.513	Left sided colitis with fistula
K51.514	Left sided colitis with abscess
K51.518	Left sided colitis with other complication
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.218	**3/25/03 CAC**
	1/25/05 CAC
	02/28/06 CAC Consensus review
	2/27/07 CAC
	1/29/08 CAC Consensus review
	5/26/09 CAC
	11/30/10 CAC Minor revision. Policy title changed – azathioprine (6-MP) taken out, replaced with "Thiopurines". Medical necessity indication clarified regarding TPMT testing; Changed to "One-time genotypic OR phenotypic testing"; "or in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction" as medically necessary.
	4/24/12 CAC Consensus review. References updated. The word "enzyme" added to first policy statement for clarification. FEP variation added. Background updated. Deleted any information related to benefits. This information is covered under Heading V "Benefit Variations."
	04/02/2013 Admin update. Deleted codes removed from policy
	7/24/13 Admin update. Coding review complete
	9/24/13 CAC Consensus review. References updated. No change to policy statements. Added policy guidelines adopted from BCBSA.
	9/30/14 CAC Consensus review. References updated. Clarification statement added that genotypic and/or phenotypic analysis of the enzyme TPMT is considered investigational in all other situations. Rationale added.

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	9/29/15 CAC Consensus review. No change to policy statements. References and rationale updated. Coding was reviewed.
	1/20/16 Administrative update. 2016 coding code update, 82491 end dated and cross-walked to 82542.
	9/27/16 CAC Consensus review. No change to policy statements. Coding reviewed. Variation reformatting.
	1/1/18Admin Update: Added new code 81335 and removed 81401; effective 1/1/18
	11/28/17 CAC Consensus review. Policy statements unchanged. Description/Background, Rationale and Reference sections updated. Appendix added. Coding reviewed. Code 82657 added. Unlisted codes removed. **Effective 2/1/18.**
	8/20/18 Consensus review. No change to the policy statements. Background and references updated. Rationale revised. Appendix removed**.**
	6/3/2019 Consensus review. Policy statement unchanged. References updated**.**
	5/12/2020 Consensus Review. Policy Statement unchanged. References checked and updated. Coding checked with no changes.

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