of Tennessee

Policy

Reimbursement Policy

Metabolite Markers of Thiopurines Testing

I. Policy Description

Thiopurines are a class of purine antimetabolite immunomodulators with diverse clinical applications in treatment of autoimmune disorders, transplant rejection, and acute lymphoblastic leukemia (Belmont, 2024). 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, patient response varies considerably between individuals, both in achieving therapeutic drug levels as well as in developing adverse reactions (Bradford & Shih, 2011).

Please note that this policy discusses the monitoring of thiopurine metabolite levels in individuals. For guidance on pharmacogenetic testing prior to therapy, please refer to AHS-M2021 Pharmacogenetic Testing.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) One-time phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) **MEETS COVERAGE CRITERIA** for a**ny** of the following situations:
   a) Prior to initiating treatment with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG).
   b) For individuals on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction.
2) For individuals with inflammatory bowel disease, monitoring of thiopurine metabolite levels **MEETS COVERAGE CRITERIA** for **any** of 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).
3) For individuals with acute lymphoblastic leukemia, monitoring of thiopurine metabolite levels **MEETS COVERAGE CRITERIA** for **any** of the following situations:
   a) For individuals showing signs of a lack of myelosuppression while on therapy.
   b) For individuals who do not tolerate thiopurines.

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The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

4) For all other situations not addressed above, phenotypic analysis of the enzyme TPMT **DOES NOT MEET COVERAGE CRITERIA**.
5) For all other situations not addressed above, analysis of the metabolite markers of azathioprine and 6-mercaptopurine, including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), **DOES NOT MEET COVERAGE CRITERIA**.

III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
80299	Quantitation of therapeutic drug, not elsewhere specified
82657	Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen
84433	Thiopurine S-methyltransferase (TPMT)

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

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