

Policy: MP311

Section: Medical Benefit Policy

Subject: Genotyping or Phenotyping for Thiopurine Methyltransferase

Applicable Lines of Business

Commercial	X	CHIP	X
Medicare	X	ACA	X
Medicaid	X		

I. Policy: Genotyping or Phenotyping for Thiopurine Methyltransferase

II. Purpose/Objective:

To provide a policy of coverage regarding Genotyping or Phenotyping for Thiopurine Methyltransferase

III. Responsibility:

- A. Medical Directors
- B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.

- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

DESCRIPTION:

Thiopurine drugs are used to treat patients with leukemia, rheumatic disease, inflammatory bowel disease, or solid organ transplant. To be effective, those drugs require conversion to thioguanine nucleotides. That process can be blocked by methylation or oxidation. The potential for methylation depends on thiopurine methyltransferase (TPMT) activity, which varies among individuals. Approximately 90% have normal activity, 10% have intermediate activity, and 0.3% have low or no detectable activity. In patients who have reduced TPMT activity and who are receiving standard thiopurine doses, thioguanine nucleotides can accumulate, resulting in myelosuppression. In those patients, dosage reduction can minimize toxicity.

INDICATIONS:

One-time genotypic or phenotypic analysis of the enzyme TPMT and nudix hydrolase (NUDT15) enzyme is considered medically necessary in members who are:

- considering initiation of therapy with azathioprine, mercaptopurine, or thioguanine; or
- on thiopurine therapy with abnormal complete blood count results that do not respond to dose reduction; or
- on thiopurine therapy with elevated liver biochemical tests, or clinical or laboratory evidence of myelosuppression and no previous diagnostic TPMT genotyping

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

LIMITATIONS:

- TPMT testing should not substitute for CBC monitoring in members receiving thiopurines.
- Accurate phenotyping results are not possible in patients who received recent blood transfusions. A period of at least 6 weeks should have elapsed since the transfusion before TPMT phenotyping is performed.
- 6-mercaptopurine metabolite testing during treatment is considered appropriate in members who previously developed leukopenia or elevated liver biochemical tests while taking 6-mercaptopurine or azathioprine

EXCLUSIONS:

Genotypic and/or phenotypic analysis of the enzyme TPMT is considered experimental, investigational or unproven and **NOT COVERED** in all other situations.

Analysis of the metabolite markers as routine monitoring of azathioprine and mercaptopurine is considered experimental, investigational or unproven and **NOT COVERED**. Routine monitoring should consist of complete blood count (CBC) and liver function tests as well as clinical status.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

CODING ASSOCIATED WITH:

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements

- 81401 Molecular pathology procedure, level 2
- 82542 Column chromatography, includes mass spectrometry, if performed
- 82657 Enzyme activity in blood cells, cultured cells or tissue, not elsewhere specified, nonradioactive substrate, each Specimen
- 81335 TPMT (thiopurine S-methyltransferase, gene analysis, common variants
- 84433 Thiopurine S-methyltransferase (TPMT)

- 0034U TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (eg, thiopurine metabolism), gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
- 0169U NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants
- 0286U CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants

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LINE OF BUSINESS:

Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

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- Yang SK, Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. *Nat Genet.* Sep 2014;46(9):1017-20.
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This policy will be revised as necessary and reviewed no less than annually.

Devised: 8/16

Revised: 9/23 (add indication and NUDT15 testing)

Reviewed: 8/17, 8/18, 9/19, 9/20, 9/21, 9/22

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.