Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MP311

Section: Medical Benefit Policy

Subject: Genotyping or Phenotyping for Thiopurine Methyltransferase

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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

Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

(i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
(ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
(iii) The service or benefit 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 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

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 azothiaprine

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.

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
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

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.**

REFERENCES:

Donnan JR, Ungar WJ, Mathews M, Rahman P. Systematic review of thiopurine methyltransferase genotype and enzymatic testing strategies. Ther Drug Monit. 2011 Apr;33(2):192-9

Bradford K, Shih D. Optimizing 6-mercaptopurine and azathioprine therapy in the management of inflammatory bowel disease. World J Gastroenterol. 2011 Oct;17(37):4166-4173

MacDermott RP. 6-mercaptopurine (6-MP) metabolite monitoring and TPMT testing in the treatment of inflammatory bowel disease with 6-MP or azathioprine. UptoDate. July 2016

Benkov K, Lu Y, Patel A, et al. Role of thiopurine metabolite testing and thiopurine methyltransferase determination in pediatric IBD. J Pediatr Gastroenterol Nutr. Mar 2013;56(3):333-340.

Gisbert JP, Nino P, Rodrigo L, et al. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. Am J Gastroenterol. Dec 2006;101(12):2769-2776.

Gisbert JP, Luna M, Mate J, et al. Choice of azathioprine or 6-mercaptopurine dose based on thiopurine methyltransferase (TPMT) activity to avoid myelosuppression. A prospective study. Hepatogastroenterology. May-Jun 2006;53(69):399-404.

Newman WG, Payne K, Tricker K, et al. A pragmatic randomized controlled trial of thiopurine methyltransferase genotyping prior to azathioprine treatment: the TARGET study. Pharmacogenomics. Jun 2011;12(6):815-826.

Liu YP, Wu HY, Yang X, et al. Association between thiopurine S-methyltransferase polymorphisms and thiopurine-induced adverse drug reactions in patients with inflammatory bowel disease: a meta-analysis. PLoS One. 2015;10(3):e0121745.

Booth RA, Ansari MT, Loit E, et al. Assessment of thiopurine S-methyltransferase activity in patients prescribed thiopurines: a systematic review. Ann Intern Med. Jun 21 2011;154(12):814-823, W-295-818.

Hindorf U, Appell ML. Genotyping should be considered the primary choice for pre-treatment evaluation of thiopurine methyltransferase function. J Crohns Colitis. Dec 13 2011.

Coenen MJ, et al. Identification of patients with variants in TPMT and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. Gastroenterology 2015 Oct;149(4):907-17.

This policy will be revised as necessary and reviewed no less than annually.

Devised: 8/16

Revised:

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