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# ROUTINE TEST MANAGEMENT POLICY – 15.01.009

# Metabolite Markers of Thiopurines Testing

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| Ref. Policy: | G2115 | |
| Effective Date: | Feb. 6, 2026 | RELATED POLICIES: |
| Last Revised: | Oct. 14, 2025 | N/A |
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**Select a hyperlink below to be directed to that section.**



∞ Clicking this icon returns you to the hyperlinks menu above.

## 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.

## Indications

1. One-time phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) is considered **reimbursable** for any 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.

The following are **not reimbursable** due to lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of the individual's illness.

2. For all other situations not addressed above, phenotypic analysis of the enzyme TPMT is **not reimbursable**.

## Coding

| Code | Description |
|---|---|
| **CPT** | |
| 84433 | Thiopurine S-methyltransferase (TPMT) |

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## Related Information

### Table of Terminology

| Term | Definition |
|---|---|
| 6-MMRP | 6-methyl-mercaptopurine ribonucleotides |
| 6-MMP | 6-methyl-mercaptopurine |
| 6-MP | 6-mercaptopurine |
| 6-TG | 6-thioguanine |
| 6-TGN | 6-thioguanine nucleotides |
| ACG | American College of Gastroenterology |
| AGA | American Gastroenterological Association |
| ASC | Acute severe colitis |
| ALL | Acute lymphoblastic leukaemia |
| AZA | Azathioprine |
| BNF | British National Formulary |
| BNFC | British National Formulary for Children |
| BSG | British Society of Gastroenterology |
| CBC | Complete blood count |

| Term | Definition |
|---|---|
| CLIA ’88 | Clinical Laboratory Improvement Amendments Of 1988 |
| CMS | Centers for Medicare and Medicaid Services |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| ECCO | European Crohn's and Colitis Organization |
| ESPGHAN | European Society of Paediatric Gastroenterology, Hepatology and Nutrition |
| FDA | Food and Drug Administration |
| HPLC | High-performance liquid chromatography |
| IBD | Inflammatory bowel disease |
| IVCS | Intravenous corticosteroids |
| LCAs | Local coverage articles |
| LCDs | Local coverage determinations |
| LDTs | Laboratory-developed tests |
| LFTs | Liver function tests |
| NASPGHAN | North American Society for Pediatric Gastroenterology, Hepatology and Nutrition |
| NCCN | National Comprehensive Cancer Network |
| NICE | National Institute for Health and Care Excellence |
| NRH | Nodular regenerative hyperplasia |
| NUDT15 | Nudix hydrolase 15 |
| RBC | Red blood count |
| RCTs | Randomized controlled trials |
| SFR | Steroid-free clinical remission |
| TDM | Therapeutic drug monitoring |
| TIL | Thiopurine-induced leukopenia |
| TPMT | Thiopurine methyltransferase |
| UC | Ulcerative colitis |

## Evidence Review

## Scientific Background

The thiopurine drugs 6-mercaptopurine (6-MP), azathioprine (AZA), and thioguanine remain a mainstay of immunomodulator therapy (Belmont, 2024; Rubin, 2024; Tantisira, 2024). However, several metabolites of these drugs (particularly 6-thioguanine [6-TG] and 6-methylmercaptopurine [6-MMP]) have been associated with harmful side effects, such as lowered therapeutic efficacy, hepatotoxicity, bone marrow toxicity, and more. The management of these toxic metabolites is further complicated by the many polymorphisms (and therefore efficacy in metabolism) of the genes responsible for metabolizing these drugs. Due to these toxic side effects, there has been significant investigation on monitoring of these metabolites to identify the optimal dose of a thiopurine for an individual patient. This process is called therapeutic drug monitoring (TDM) (Rubin, 2024).

Two enzymes are responsible for catalyzing these reactions: thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase. TPMT enzyme activity is a major factor determining AZA and 6-MP metabolism, and therefore 6-TG and 6-MMP levels. The majority of the population has wild type TPMT and normal enzyme activity, while 11% are heterozygous and have corresponding low TPMT enzyme activity, and 0.3% (1 in 300) have negligible activity (Lennard et al., 1993; Lennard et al., 1989; Rubin, 2024). Intermediate and normal metabolizers can have up to a threefold difference in initial target doses of AZA and 6-MP to achieve therapeutic 6-TG concentrations (Gardiner et al., 2008). Measurement of TPMT enzyme activity before instituting AZA or 6-MP may help prevent toxicity by identifying individuals with low or absent TPMT enzyme activity as well as identify those with higher than average TPMT activity who may remain refractory to conventional dosages (Rubin, 2024). Dosing strategies involving such testing may be cost-effective (Cuffari et al., 2004; Dubinsky et al., 2005; Winter et al., 2004). However, prediction of toxicity is not consistently reliable, as other enzymes are also likely to play a role in determining toxicity, such as glutathione-S-transferase (Stocco et al., 2007), and drug interactions must be considered (Dewit et al., 2002; Gilissen et al., 2005; Szumlanski & Weinshilboum, 1995). Thus, even though TPMT testing is recommended, a complete blood count (CBC), and also liver function tests, must still be obtained (Belmont, 2024; Relling et al., 2019).

Another enzyme that may contribute to thiopurine metabolism is nucleoside diphosphate-linked moiety X motif 15, NUDIX 15 (NUDT15). Variants in this enzyme's genotype and subsequent phenotype may lead to drastically reduced tolerance of 6-MP (Tantisira, 2024). Moriyama et al. proposed that NUDT15 variants cause thiopurines' mechanism of action to fail by preventing the thiopurine metabolites' incorporation into DNA. This causes these metabolites to remain active and therefore toxic (Moriyama et al., 2016). The frequency of these NUDT15 variants varies across populations, with the "poor metabolizer" phenotype reaching as high as 1 in 50 in East Asian populations. Despite the data indicating NUDT15's role in thiopurine toxicity, guidelines

for its assessment have not reached a consensus, and expert opinions and practices are mixed (Tantisira, 2024).

Therapeutic drug monitoring (TDM) is the measurement of serum, plasma, or urinary concentrations of a given drug. This can be measured in a variety of ways, including high performance liquid chromatography (HPLC) or mass spectrometry approaches such as GC-MS (Eadie, 2002). TDM is proposed to allow a clinician to identify the "optimal" dose of a drug (such as a thiopurine) for a patient, thereby maximizing therapeutic efficacy and minimizing harmful side effects. Non-TDM approaches typically involve starting at low doses, then adjusting if the patient is tolerating the drug well or poorly, whereas TDM takes a more proactive approach in managing dose (Rubin, 2024). Several studies have attempted to identify standardized ranges of "optimal" metabolite concentrations. For example, the optimal concentration of the 6-TGN metabolite was found to be between 230 and 400 picomoles per 8 x 108 erythrocytes by Dubinsky et al. In that same study, bone marrow toxicity was found to correlate with levels above 400 picomoles per 8 x 108 erythrocytes (Dubinsky et al., 2000). Although there are potential limitations to TDM for thiopurines (such as intra-individual variability, lack of correlation with toxicity for 6-MMP, and so on), TDM used in conjunction with TPMT and NUDT15 assessment may allow clinicians to increase the therapeutic efficacy of thiopurines (Rubin, 2024; Tantisira, 2024).

## Clinical Utility and Validity

Haines et al. (2011) performed a retrospective study of the utility of measuring thiopurine metabolites in "inadequately controlled" inflammatory bowel disease (IBD). A total of 63 patients with IBD were included, and these patients were treated with AZA or 6-mercaptopurine. On weight-based criteria, 50% of patients were underdosed. However, metabolite study suggested that "7 (11%) patients were noncompliant, 18 (29%) were being underdosed, 33 (52%) were refractory to treatment with either appropriate (41%) or elevated (11%) metabolite concentrations, and 6 (10%) had a raised 6-methyl mercaptopurine: 6-thioguanine nucleotide ratio consistent with aberrant thiopurine metabolism". The clinical outcome of 87% of patients improved when the treatment was shifted to a metabolite-based algorithm, whereas 3 of 17 patients improved when the discordant action was taken. The authors concluded that "Thiopurine metabolite testing is a potentially powerful tool for optimizing thiopurine usage in IBD" (Haines et al., 2011).

Lee et al. (2017) evaluated 165 patients undergoing thiopurine treatment for Crohn's Disease. Thiopurine metabolite levels were measured, and both TPMT and NUDT15 were genotyped. The authors found 95 patients responded to treatment whereas 45 did not. The median 6-TGN (the primary metabolite of 6-thioguanine) was significantly higher in responders than nonresponders. At a 6-TGN level of 230 pmol/8 x 108 blood cells, the odds ratio was 4.63 for

responders to nonresponders. NUDT15 variants were also found to be associated with “severe, early, leukopenia” with an average reduction of 88.2% from baseline white blood cell count at four weeks. The authors concluded that their findings “support the role of therapeutic drug monitoring in thiopurine maintenance treatment to optimize thiopurine therapy, especially, for non-responding CD patients” (Lee et al., 2017).

Spencer et al. (2019) compared “standard” and “optimized” thiopurine dosing regimens in 216 pediatric IBD patients. The “optimal” level was decided at “6-TGN >235 pmol/8 × 108 RBC”, and the metabolite levels were correlated between the primary outcome of “steroid-free clinical remission (SFR)”. Both groups were found to have similar initial and six month metabolite levels. SFR was achieved in 74% of the 180 patients on thiopurines at six months. The authors concluded that “steroid-free clinical remission and 6-TGN levels at 6 months were no different between a standardized, fixed dosing strategy and a metabolite-driven, optimized dosing strategy” (Spencer et al., 2019).

Meijer et al. (2017) evaluated the effects of thiopurine metabolites on clinical signs and if patient characteristics affected metabolite generation. A total of 940 “laboratory findings” from 424 patients were examined. 6-TGN (a metabolite of azathioprine [AZA] and mercaptopurine) was found to negatively correlate with RBC count, WBC count, and neutrophil count. However, in patients using 6-thioguanine, those 6-TGN concentrations correlated positively with WBC count. An inverse correlation was observed between age and 6-TGN concentrations in AZA or 6-thioguanine patients, as well as between body mass index and 6-TGN in AZA or mercaptopurine patients. The authors concluded that “thiopurine derivative therapy influenced bone marrow production and the size of red blood cells. Age and body mass index were important pharmacokinetic factors in the generation of 6-TGN” (Meijer et al., 2017).

Estevinho et al. (2017) performed a meta-analysis to “assess the clinical value of 6-thioguanine nucleotide thresholds; and ii] to compare mean 6-thioguanine nucleotide concentrations between patients in clinical remission vs. those with active disease.” A total of 22 records were used in cut-off comparisons and 12 were used in the 6-thioguanine nucleotide mean differences analysis. The authors calculated the global odds ratio for remission in patients with 6-thioguanine nucleotides above predefined thresholds to be 3.95. The authors also found an odds ratio for remission of 2.25 for the 235 pmol/8 x 108 RBC threshold, and an odds ratio of 4.71 for the 250 pmol /8 x 108 RBC threshold. Finally, the authors found a “pooled difference” of 63.37 pmol/8 x 108 RBC between patients in clinical remission and those not in remission. Overall, the authors concluded that the study reinforced the link between and 6-thioguanine nucleotide levels and clinical remission in inflammatory bowel diseases (Estevinho et al., 2017).

Toksvang et al. (2019) performed a meta-analysis focusing on “incidence of hepatotoxicity in patients [with childhood acute lymphoblastic leukaemia, ALL or inflammatory bowel disease, IBD] treated with 6TG [6-thioguanine]”. A total of 42 reports were included, further broken down

into “four randomised controlled trials (RCTs) including 3,993 patients, 20 observational studies including 796 patients, and 18 case reports including 60 patients”. The authors measured hepatotoxicity by “sinusoidal obstruction syndrome”, which occurred in 9-25% of ALL patients in two of the four RCTs at a dosage of 40–60 mg/m2/day. The authors also noted that at a dosage of 23 mg/m2/day, nodular regenerative hyperplasia (NRH) occurred in 14% of IBD patients. At a dosage of 12 mg/m2/day, NRH occurred in 6% of IBD patients, which was noted to be similar to background incidence. The authors therefore concluded that doses at or under 12 mg/m2/day can “probably be considered safe” (Toksvang et al., 2019).

Zhu et al. (2019) evaluated the “predictive sensitivity based on 6TGN [6-thioguanine nucleotide] by subgrouping patients according to their NUDT15 R139C genotypes”. The authors included 411 patients with Crohn’s Disease. Two subgroups of NUDT15 genotypes were created, “CC” (n = 342) and “CT” (n = 65), with the final four patients harboring a TT genotype. Thiopurine-induced leukopenia (Relling et al.) was the primary clinical endpoint measured. The authors found that of the 342 patients with a CC genotype, only 35 developed TIL (10.2%), but of the 65 CT patients, 33 developed TIL (50.2%). All four of the TT patients developed TIL. The authors also found that in both CC and CT genotypes, the median 6TGH level was higher in patients with TIL than patients without TIL (for CC, 474.8 pmol/8 × 108 RBC vs 306.0 pmol/8 × 108 RBC, for CT 291.7 / 8 × 108 RBC vs 217.6/8 × 108 RBC). From this data, the authors calculated the “cut-off” (a threshold to identify an optimal number of cases) of the CT genotype to be 319.2 pmol/8 × 108 RBC and the cut-off for CC to be 411.5 pmol/8 × 108 RBC). Overall, the authors concluded that “The predictive sensitivity of TIL based on 6TGN is dramatically increased after subgrouping according to NUDT15 R139C genotypes. Applying 6TGN cut-off levels to adjust thiopurine therapies based on NUDT15 is strongly recommended” (Zhu et al., 2019).

## Guidelines and Recommendations

### National Comprehensive Cancer Network (NCCN)

In version two of the 2023 guidelines for Pediatric Acute Lymphoblastic Leukemia, the NCCN recommends that “for patients homozygous for normal function TPMT and NUDT15, who do not appear to tolerate thiopurines, consider measuring erythrocyte thiopurine metabolites and/or erythrocyte TPMT activity. Genetic testing may fail to identify rare or previously undiscovered no function alleles.” The NCCN also writes that “genetic testing for no function alleles of TPMT and NUDT15 should be considered prior to the initiation of thiopurine therapy or if excessive toxicity is encountered following treatment with thiopurines” (NCCN, 2024b).

In version one of the 2023 guidelines for Acute Lymphoblastic Leukemia, the NCCN notes that “quantification of 6-MP metabolites can be very useful in determining whether lack of myelosuppression is due to non-adherence or hypermetabolism”.

The 2023 guidelines also state, “for patients receiving 6-MP, consider testing for TPMT gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both TPMT and NUDT15 variant status should be considered, especially for patients of East Asian origin” (NCCN, 2024a).

### Toronto Ulcerative Colitis Consensus Group/American College of Gastroenterology (ACG)

Bressler et al. (2015) published clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis on behalf of the Toronto Ulcerative Colitis Consensus Group, which reaffirmed recommendations from the American College of Gastroenterology, Practice Parameters Committee (Kornbluth & Sachar, 2010) for thiopurine therapy (Bressler et al., 2015). The authors stated that “…a TPMT assay is necessary before initiation of treatment to identify patients at risk for severe dose-dependent myelosuppression…therefore, thiopurine metabolite levels may be helpful to guide therapy. Note that TPMT testing does not replace the need for mandatory monitoring of complete blood cell count” (Bressler et al., 2015).

### American College of Gastroenterology (ACG)

The ACG published a guideline for the “Management of Crohn's Disease in Adults”. Their relevant recommendations include:

“Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence)” (Lichtenstein et al., 2018).

The ACG also published a guideline for ulcerative colitis (Lichtenstein et al.) in adults. Their relevant recommendations include:

“The patient with nonresponse or loss of response to therapy should be assessed with therapeutic drug monitoring to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.”

“There is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission” (Rubin et al., 2019).

### North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Committee

In 2013, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Committee on Inflammatory Bowel Disease published consensus

recommendations on the role of TPMT and thiopurine metabolite testing in pediatric IBD. The recommendations included the following (Benkov et al., 2013):

- "TPMT testing is recommended before initiation of TPs to identify individuals who are homozygote recessive or have extremely low TPMT activity, with the latter having more reliability than the former. (HIGH)"
- "Individuals who are homozygous recessive or have extremely low TPMT activity should avoid use of TPs because of concerns for significant leukopenia. (HIGH)"
- "TPMT testing does not predict all cases of leukopenia and has no value to predict hypersensitivity adverse effects such as pancreatitis. Any potential value to reduce the risk of malignancy has not been studied. All individuals on TPs should have routine monitoring with CBC and WBC count differential to evaluate for leukopenia regardless of TPMT testing results. (HIGH)"
- "Metabolite testing can be used to determine adherence to TP therapy. (HIGH)"
- "Metabolite testing can be used to guide dose increases or modifications in patients with active disease. Consideration would include either increasing the dose, changing therapy or for those with elevated transaminases or an elevated 6-MMP, using adjunctive allopurinol to help raise 6-TG metabolites and suppress formation of 6-MMP. (MODERATE)"
- "Routine and repetitive metabolite testing has little or no role in patients who are doing well and taking an acceptable dose of a TP. (MODERATE)"

### American Gastroenterological Association (Bressler et al.)

In 2017, the AGA published guidelines on Therapeutic Drug Monitoring in Inflammatory Bowel Disease which recommend (Feuerstein et al., 2017):

- "In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes."
- "In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring."

The AGA published an Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases in the same year. In it, they note that IBD patients treated with thiopurines may benefit from reactive TDM to guide treatment changes (Vande Casteele et al., 2017).

In the 2020 AGA guidelines for "Management of Moderate to Severe Ulcerative Colitis", the AGA remarks that "therapeutic drug monitoring to guide the use of biologic therapy has been addressed in separate AGA guidelines". The "separate AGA guidelines" refer to the 2017 edition above (Feuerstein et al., 2020).

## Clinical Pharmacogenetics Implementation Consortium (CPIC)

In their guideline for "Thiopurine Dosing Based on TPMT and NUDT15 Genotypes", CPIC notes that "mercaptopurine and azathioprine are generally used for nonmalignant immunologic disorders, mercaptopurine for lymphoid malignancies, and thioguanine for myeloid leukemias". However, CPIC also writes that "variants in NUDT15 have been identified that strongly influence thiopurine tolerance in patients with acute lymphoblastic leukemia (ALL) and those with inflammatory bowel diseases" (Relling et al., 2019).

In 2020, the authors of this guideline added recommendations for TPMT and NUDT15 indeterminate phenotypes. That update is as follows:

- "For TPMT and NUDT15 indeterminate phenotypes, (i.e. combination of uncertain and/or unknown function alleles):
    - TPMT indeterminate: Consider evaluating TPMT erythrocyte activity to assess TPMT phenotype.
    - NUDT15 indeterminate: If thiopurines are required and NUDT15 status is unknown, monitor closely for toxicity" (CPIC, 2020).

## British Society of Gastroenterology (BSG)

The BSG published "consensus guidelines" on management of inflammatory bowel disease in adults. They recommend checking TPMT status in "all patients considered for thiopurine therapy". They also recommend testing the NUDT15 genotype if "available".

The BSG also writes that thiopurine metabolites should be checked if a patient experiences myelotoxicity as a side effect. Similarly, if a patient demonstrates "newly abnormal LFTs [liver function tests]", thiopurine metabolites should be checked. Also, BSG states that "all IBD patients considered for thiopurine therapy should have assessment of thiopurine methyltransferase (TPMT) status" (Lamb et al., 2019).

Overall, the BSG writes that thiopurine metabolites can be used to "optimize drug dosing" and "suggest that metabolite monitoring may be used for those with inadequate response to therapy or toxicity, but should not be a substitute for routine monitoring blood tests" (Lamb et al., 2019).

## Canadian Association of Gastroenterology (CAG)

The Canadian Association of Gastroenterology published a guideline on "the Medical Management of Pediatric Luminal Crohn's Disease." The guidelines "suggested that testing for TPMT by genotype or enzymatic activity be done prior to initiating thiopurine therapy to guide dosing" (Mack et al., 2019).

An additional guideline for [Adult] Luminal Crohn's Disease specifies "because some patients may have low or absent levels of the enzyme (thiopurine methyltransferase (TPMT) needed to metabolize thiopurines, a TPMT assay should be performed before initiation of treatment to identify patients at risk for severe toxicity" (Panaccione et al., 2018).

### National Institute for Health and Care Excellence (NICE)

NICE released guidelines on Crohn's Disease Management in 2019. In it, they recommend to "Monitor the effects of azathioprine, mercaptopurine, and methotrexate as advised in the British national formulary (BNF) or British national formulary for children (BNFC)" (NICE, 2019).

### European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ECCO and ESPGHAN)

These joint guidelines note that "measuring…6-TG and 6-MMP levels after two to three months, may aid in optimizing thiopurine dosing." Measuring thiopurine metabolites is recommended in the following scenarios:

- In patients with incomplete response on stable thiopurine dosage
- In patients who present with leucopenia or elevated transaminases
- After acute severe colitis (ASC) responsive to intravenous corticosteroids (IVCS)
- When poor compliance is suspected (Turner et al., 2018)

### US 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 US Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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## History

| Date | Comments |
|---|---|
| 11/01/25 | New policy, approved October 14, 2025, effective for dates of service on or after February 6, 2026, following 90-day provider notification. Add to Routine Test Management Policy section. Testing and monitoring phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) is considered reimbursable when criteria in this policy are met. |

determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). 

**Scope**: Medical policies for routine test management are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices and reimbursement methodology. Coverage and reimbursement for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.