# Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/23**

## Title: Methotrexate (MTX) Polyglutamate Testing To Measure Response To Methotrexate Therapy

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## Description/Background

Arthritis is a general term that refers to inflammation in a joint. Joint inflammation is characterized by redness, warmth, swelling and pain within the joint. Rheumatoid arthritis (RA) is a type of chronic arthritis that typically occurs in joints on both sides of the body (such as hands, wrists or knees). This symmetry helps distinguish rheumatoid arthritis from other types of arthritis. In addition to affecting the joints, rheumatoid arthritis may occasionally affect the skin, eyes, lungs, heart, blood or nerves. RA joint symptoms may develop gradually over several years in some persons but it others rheumatoid arthritis may progress rapidly. Other people may have rheumatoid arthritis for a limited period of time and then enter a period of remission.

Rheumatoid arthritis affects about 1% of the U.S. population. Although it is two to three times more common in women than in men, men tend to be more severely affected when they get it. It usually occurs in middle age, but young children and the elderly also can develop rheumatoid arthritis.

One of the standard treatments for rheumatoid arthritis is methotrexate, a drug that interferes with the folic acid production, which is essential for the production and maintenance of DNA, the genetic backbone of all the cells of the body. Methotrexate was developed in the 1940s as a treatment for leukemia. The first attempt to use it again RA was reported in 1951. In the 1970s methotrexate was considered to be and experimental treatment for rheumatoid arthritis. It is not known exactly how methotrexate works in rheumatoid arthritis, but it can reduce inflammation and slow the progression of the disease. Methotrexate is considered a disease-modifying antirheumatic drug (DMARD). DMARDs are also called immunosuppressive drugs or slow-acting antirheumatic drugs (SAARDs).

Initially, methotrexate was reserved for patients who did not respond to other therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) or by one of the other disease-modifying anti-rheumatic drugs such as gold, penicillamine or Plaquenil. Over the course of time, the trend for treatment of rheumatoid arthritis evolved toward more early, aggressive treatment of RA. MTX is

favored as a treatment for RA due to its relatively low cost and long history of effective symptom relief. Methotrexate has thus become the gold standard treatment for patients who have moderate to severe rheumatoid arthritis with pain, stiffness, swelling and fatigue.

Unfortunately, not all patients with RA respond favorably to treatment with methotrexate. It is well recognized that response to DMARDs is variable. It has been estimated that, in clinical practice, only around 50% of patients respond adequately to any one traditional DMARD even in the short term. Moreover, a substantial number of patients have to stop DMARD therapy because of side effects before they have had a chance to respond.

The benefits of MTX are generally noticeable six to eight weeks after the first dose is taken, but it can take many more months before the full benefits are experienced. The Avise MTX test is a proprietary test that measures the level of methotrexate (MTX) polyglutamates, the active metabolites of methotrexate. Use of the Avise MTX test has been suggested for patients that have been taking MTX for at least three months and have not obtained significant relief from their RA symptoms. The theory is that measuring the level of methotrexate polyglutamates, the active metabolites of MTX, can help the physician determine if the patient is a partial or nonresponder to methotrexate therapy, and whether or not the patient would benefit from continued MTX dose escalation or a complete change in therapy.

The Avise MTX assay was developed to support dose optimization and therapeutic decision making for patients diagnosed with RA on MTX. The assay is designed to help dose the MTX to higher and safer levels for patients with RA or similar diseases that respond to the drug methotrexate. However, although some studies have suggested that the levels of the polyglutamate MTX metabolites can be used to direct MTX treatment, this approach is not generally recommended. There is no evidence to indicate that the measurement of methotrexate levels has any clinically relevant impact on the patient's treatment and outcomes.

The ARK Methotrexate Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of methotrexate in human serum or plasma on automated clinical chemistry analyzers. The measurements obtained are intended to be used in monitoring levels of methotrexate to ensure appropriate therapy.

The TDx/TDxFlx Methotrexate II assay is a reagent system also used for the quantitative measurement of methotrexate in serum or plasma through the use of Fluorescence Polarization Immunoassay (FPIA) technology.

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## Medical Policy Statement

The clinical utility of methotrexate polyglutamate testing has not been demonstrated. The peer reviewed medical literature has not yet shown that this laboratory test has sufficient diagnostic accuracy to provide clinically relevant information for the management of patients with rheumatoid arthritis. There is no evidence to indicate that the measurement of methotrexate levels has any clinically relevant impact on the patient's treatment and outcomes. Therefore, methotrexate polyglutamate testing is considered experimental/investigational.

## Inclusionary and Exclusionary Guidelines

N/A

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## CPT/HCPCS Level II Codes and Description *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

### *Established codes:*

N/A

### *Other codes (investigational, not medically necessary, etc.):*

84999 80204

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## Rationale

Until recently, the mechanism by which MTX helps control symptoms of RA was unclear. Recent studies have focused on the role of intracellular adenosine, which accumulates as a result of MTX therapy. Because MTX polyglutamates (metabolic breakdown products) also accumulate, a possible relationship between polyglutamate levels and clinical effectiveness of MTX therapy has been sought.

In 2005, a clinical trial by Dolezalova on 30 patients showed that there is no relationship between effective MTX dose represented by EMTX (adenosine and MTX-polyglutamate concentrations in erythrocytes) on blood adenosine concentration in juvenile idiopathic arthritis patients. If MTX anti-inflammatory action is mediated by adenosine, it is likely that local release of adenosine at inflamed tissues is responsible for its action, which may not be reflected by sustained increase of its blood concentration.[14]

In 2006, Dervieux et al evaluated the contribution of metabolites (methotrexate [MTX] and folate polyglutamate [PG] levels) and pharmacogenetic biomarkers in the folate pathway to the effects of MTX in patients with rheumatoid arthritis (RA) not previously treated with this antifolate. Forty-eight adult patients who had not been treated with methotrexate were enrolled in a prospective study. MTX was started at 7.5 mg/week and increased every 4 to 6 weeks until a therapeutic response was achieved. Response was measured using the Disease Activity Score in 28 joints (DAS28). Red blood cell (RBC) MTX and folate PG levels were measured with 9 common polymorphisms in the folate pathway. After 6 months of therapy, the median weekly MTX dosage was 17.5 mg and the median decrease in the DAS score was 2.0. Patients with a lesser decrease in the DAS28 (fewer improvements) had lower RBC MTXPG levels ($P < 0.05$) despite the higher MTX dose administered ($P < 0.05$). RBC folate PG levels decreased significantly during treatment, and a lesser decrease in RBC folate PGs was associated with a lesser decrease in the DAS28 ($P < 0.05$). RBC MTXPG levels could be a useful means by which to monitor therapy. The genetic associations presented generate hypotheses, and confirmation in independent cohorts is warranted.[10]

A study presented by Stamp et al in 2010 reported on a series of 192 patients receiving oral methotrexate. Disease activity was assessed based on physical symptoms such as joint swelling, the C-reactive protein level and the DAS28 scores. In addition, a standardized questionnaire regarding common MTX adverse effects was completed. The results showed that the MTX dosage was significantly higher in patients in whom the swollen joint count and DAS28 scores were higher. After correction for age, the estimated glomerular filtration rate, and the MTX dosage, the association remained significant for methotrexate glutamates. RBC folate concentrations were significantly higher in the group with high disease activity. There was no association between any MTX polyglutamate concentration and adverse effects. The results of this study did not show a relationship between the MTX concentration and reduced disease activity. Prospective studies will be important to determine whether there is a role for measuring MTXGlu concentrations in patients receiving long-term treatment with MTX.[24]

In 2011, Becker et al. reported on a study of patients with juvenile idiopathic arthritis who were receiving stable doses of methotrexate at a tertiary care children's hospital. After informed consent was obtained from the 104 patients with JIA, blood was withdrawn during routine MTX-screening laboratory testing. Clinical data were collected by chart review. Genotyping for 34 single-nucleotide polymorphisms (SNPs) in 18 genes within the MTX metabolic pathway was performed. An ion-pair chromatographic procedure with mass spectrometric detection was used to measure MTXGlu. Analysis and genotyping of MTXGlu was completed in the 104 patients. K-means clustering resulted in 3 distinct patterns of MTX polyglutamation. Cluster 1 had low red blood cell (RBC) MTXGlu concentrations, cluster 2 had moderately high RBC MTXGlu1 _ 2 concentrations, and cluster 3 had high concentrations of MTXGlu, specifically MTXGlu3–5. SNPs in the purine and pyrimidine synthesis pathways, as well as the adenosine pathway, were significantly associated with cluster subtype. The cluster with high concentrations of MTXGlu3–5 was associated with elevated liver enzyme levels on liver function tests (LFTs), and there were higher concentrations of MTXGlu3–5 in children who reported gastrointestinal side effects and had abnormal findings on LFTs. No association was noted between MTXGlu and active arthritis. MTXGlu remains a potentially useful tool for determining outcomes in patients with JIA being treated with MTX. The genetic predictors of MTXGlu variability may also contribute to a better understanding of the intracellular biotransformation of MTX in these patients.[3]

In 2013, Bulatovic et al studied the association of erythrocyte methotrexate polyglutamates (MTX-PG) with disease activity and adverse effects in a prospective juvenile idiopathic arthritis (JIA) cohort. One hundred and thirteen JIA patients were followed from MTX start until 12 months. Erythrocyte MTX-PGs with 1-5 glutamate residues were measured at 3 months with tandem mass spectrometry. The outcomes were Juvenile Arthritis Disease Activity Score (JADAS)-27 and adverse effects. To determine associations of MTX-PGs with JADAS-27 at 3 months and during 1 year of MTX treatment, linear regression and linear mixed-model analyses were used. To determine associations of MTX-PGs with adverse effects during 1 year of MTX treatment, logistic regression was used. Analyses were corrected for JADAS-27 at baseline and co-medication. Median JADAS-27 decreased from 12.7 (IQR: 7.8-18.2) at baseline to 2.9 (IQR: 0.1-6.5) at 12 months. Higher concentrations of MTX-PG3 (β: -0.006, p=0.005), MTX-PG4 (β: -0.015, p=0.004), MTX-PG5 (β: -0.051, p=0.011) and MTX-PG3-5 (β: -0.004, p=0.003) were associated with lower disease activity at 3 months. Higher concentrations of MTX-PG3 (β: -0.005, p=0.028), MTX-PG4 (β: -0.014, p=0.014), MTX-PG5 (β: -0.049, p=0.023) and MTX-PG3-5 (β: -0.004, p=0.018) were associated with lower disease activity over 1 year. None of the MTX-PGs was associated with adverse effects. Conclusions: In the first prospective study in JIA, long-chain

MTX-PGs were associated with lower JADAS-27 at 3 months and during 1 year of MTX treatment. Erythrocyte MTX-PG could be a plausible candidate for therapeutic drug monitoring of MTX in JIA.[4]

A 2014 article by Calasan et al reported on a study that was done to determine association of erythrocyte methotrexate polyglutamates (MTX-PG) with disease activity and adverse effects in a prospective juvenile idiopathic arthritis (JIA) cohort. One hundred and thirteen JIA patients were followed from MTX start until 12 months. Erythrocyte MTX-PGs with 1-5 glutamate residues were measured at 3 months with tandem mass spectrometry. The outcomes were Juvenile Arthritis Disease Activity Score (JADAS)-27 and adverse effects. To determine associations of MTX-PGs with JADAS-27 at 3 months and during 1 year of MTX treatment, linear regression and linear mixed-model analyses were used. To determine associations of MTX-PGs with adverse effects during 1 year of MTX treatment, logistic regression was used. Analyses were corrected for JADAS-27 at baseline and co-medication. The results showed that median JADAS-27 decreased from 12.7 (IQR: 7.8-18.2) at baseline to 2.9 (IQR: 0.1-6.5) at 12 months. Higher concentrations of MTX-PG3 (β: -0.006, p=0.005), MTX-PG4 (β: -0.015, p=0.004), MTX-PG5 (β: -0.051, p=0.011) and MTX-PG3-5 (β: -0.004, p=0.003) were associated with lower disease activity at 3 months. Higher concentrations of MTX-PG3 (β: -0.005, p=0.028), MTX-PG4 (β: -0.014, p=0.014), MTX-PG5 (β: -0.049, p=0.023) and MTX-PG3-5 (β: -0.004, p=0.018) were associated with lower disease activity over 1 year. None of the MTX-PGs was associated with adverse effects. The authors concluded that erythrocyte MTX-PG could be a plausible candidate for therapeutic drug monitoring of MTX in JIA, since, in this study, for JIA patients, long-chain MTX-PGs were associated with lower JADAS-27 at 3 months and during 1 year of MTX treatment.[5]

In 2015, Mohamed et al performed a systemic literature review to identify all studies that had reported an association between red blood cell methotrexate polyglutamate concentration and disease activity or adverse drug reactions in users of methotrexate for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis or psoriatic arthritis. No randomised controlled trials were identified. Thirteen studies (ten in patients with rheumatoid arthritis and three in patients with juvenile idiopathic arthritis) were identified. All studies evaluated an association between red blood cell methotrexate polyglutamate concentration and response to treatment, and eight evaluated an association with toxicity. Eight studies identified lower disease activity with at least one higher red blood cell methotrexate polyglutamate concentration, although there was at least moderate potential for bias in all of these studies. Relatively large increases in concentration appeared to be required to produce a meaningful reduction in disease activity. Only one study identified an association between red blood cell methotrexate polyglutamate concentration and methotrexate-induced side effects, although studies were likely underpowered to detect this type of association. According to the authors, the manner in which data were presented in the included studies had many limitations that hampered its conclusive assessment, but red blood cell methotrexate polyglutamate concentrations appear to be a potentially useful guide to treatment in patients with inflammatory arthropathies, but the specific polyglutamate that should be monitored and how monitoring could be integrated into treat-to-target approaches should be clarified before it can be routinely implemented.[20]

**SUMMARY OF EVIDENCE**
The value of RBC MTX polyglutamates as a predictor of response and adverse events to low dose MTX therapy in patients with RA remains unclear because of the conflicting data in the literature, and many important questions remain unanswered. Large, longitudinal prospective studies are needed to examine the relationship between MTX polyglutamate levels, folate polyglutamate concentrations, and treatment response and side effects of low dose MTX therapy. No studies addressed the clinical utility of measuring methotrexate polyglutamate levels to aid in dosage optimization for rheumatoid arthritis patients. Therefore, there is insufficient evidence to determine the clinical utility of measuring methotrexate polyglutamate levels to aid in dosage optimization for rheumatoid arthritis patients.

**Ongoing and Unpublished Clinical Trials**
There are no current clinical trials on ClinicalTrials.com that might influence this review.

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## Government Regulations
### National:
Local Coverage Article: MolDX: Avise PG Assay (A55144), effective 10/01/2020. Retired on 12/30/2021.

The **AVISE** PG Assay, developed to support dose optimization and therapeutic decision making for patients diagnosed with rheumatoid arthritis (RA) on methotrexate ("MTX"), has been assigned a unique identifier. To bill an **AVISE** PG service, please provide the following claim information:

- CPT code 84999 – Unlisted Chemistry Procedure
- Enter “1” in the Days/Unit field
- Select the appropriate ICD-10-CM diagnosis
- Labs may either use the SV101-7 or SV202-7 (preferred) or the NTE field to submit this required information.
- Enter the appropriate DEX Z-Code™ identifier in the comment/narrative field for the following Part B claim field/types:
    - Loop 2400 or SV101-7 for the 5010A1 837P
    - Box 19 for paper claim
- Enter the appropriate DEX Z-Code™ identifier in the comment/narrative field for the following Part A claim field/types:
    - Block 80 for the UB04 claim form
    - Line SV202-7 for the 837I electronic claim

Note: The DEX Z-code™ identifier is required in addition to the appropriate disease/syndrome code.

### Local:
There is no WPS LCD on this topic.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicaid Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

## Related Policies

- Genetic Testing for HLA-B 1502 Before Initiating Carbamazepine Therapy
- Genetic Testing for Warfarin Dosing
- Interferon Antibody Testing In The Treatment Of Multiple Sclerosis
- Multi-Biomarker Disease Activity (MBDA) Laboratory Testing (e.g., Vectra DA Blood Test) for Rheumatoid Arthritis
- Myeloperoxidase (MPO) Immunoassay
- Pharmacogenomic and Metabolite Markers for Patients with Inflammatory Bowel Disease (IBD) Who Have Been Treated with Azathioprine (6-MP)

## References


1. ARK Diagnostics, Inc. 510(k) Summary K111904. Available at < https://www.accessdata.fda.gov/cdrh_docs/pdf11/K111904.pdf > (accessed February 2021).
2. Avise MTX product information, < http://www.exagen.com/wp-content/uploads/AVISE_MTX_Sample_Test_Report.pdf > (accessed February 2021).
3. Becker ML, Gaedigk R, van Haandel L, Thomas B, Lasky A, Hoeltzel M, Dai H, Stobaugh J, Leeder JS. The Effect of Genotype on Methotrexate Polyglutamate. Arthritis & Rheumatism. Vol. 63, No. 1, January 2011, pp 276–285
4. Bulatovic Calasan M, den Boer E, de Rotte MC, Vastert SJ, Kamphuis S, de Jonge R, Wulffraat NM. Methotrexate polyglutamates in erythrocytes are associated with lower disease activity in juvenile idiopathic arthritis patients. Ann Rheum Dis. 2013 Nov 28. Doi: 10.1136/annrheumdis-2013-203723. [Epub ahead of print]
5. Ćalasan MB, den Boer E, de Rotte MC, Vastert SJ, Kamphuis S, de Jonge R, Wulffraat NM. Methotrexate polyglutamates in erythrocytes are associated with lower disease activity in juvenile idiopathic arthritis patients. Ann Rheum Dis. 2015 Feb;74(2):402-7.
6. Chan, Edwin S. L. and Bruce N. Cronstein. Molecular action of methotrexate in inflammatory diseases. Arthritis Research. Volume 4, Number 4. November 27, 2001, pp. 266-273.
7. Dalrymple, J. M., et al., Pharmacokinetics of oral methotrexate in patients with rheumatoid arthritis. Arthritis Rheum, Volume 58, Number 11, November 1, 2008, pp, 3299-3308.
8. Danila M, Hughes L, Brown E, et al. Measurement of erythrocyte methotrexate polyglutamate levels: ready for clinical use in rheumatoid arthritis? Current Rheumatol Rep. 2010 Jul;12:342-347.
9. de Rotte MC, den Boer E, de Jong PH, Pluijm SM, Bulatovic Calasan M, Weel AE, Huisman AM, Gerards AH, van Schaeybroeck B, Wulffraat NM, Lindemans J, Hazes JM, de Jonge R. Methotrexate polyglutamates in erythrocytes are associated with lower disease activity in patients with rheumatoid arthritis. Ann Rheum Dis. 2013 Dec 5. Doi: 10.1136/annrheumdis-2013-203725. [Epub ahead of print]
10. Dervieux T, Furst D, Orentas Lein D, Capps R, Smith K, Walsh M, Kremer J. Polyglutamation of Methotrexate With Common Polymorphisms in Reduced Folate Carrier, Aminoimidazole Carboxamide Ribonucleotide Transformylase, and Thymidylate Synthase Are Associated

With Methotrexate Effects in Rheumatoid Arthritis. Arthritis & Rheumatism. Volume 50, Issue 9, Article first published online: 9 SEP 2004.
11. Dervieux T, Greenstein N, Kremer J. Pharmacogenomic and metabolic biomarkers in the folate pathway and their association with methotrexate effects during dosage escalation in rheumatoid arthritis. Arthritis Rheum . 2006 Oct;54(10):3095-103.
12. Dervieux t, Furst D, Orenta D, et al. Polyglutamation of Methotrexate With Common Polymorphisms in Reduced Folate Carrier, Aminoimidazole Carboxamide Ribonucleotide Transformylase, and Thymidylate Synthase Are Associated With Methotrexate Effects in Rheumatoid Arthritis. Arthritis & Rheumatism. Vol. 50, No. 9, September 2004, pp 2766–2774.
13. Dervieux, T, et al. Pharmacogenetic and metabolite measurements are associated with clinical status in patients with rheumatoid arthritis treated with methotrexate: results of a multi-centered cross sectional observational study. Ann Rheum Dis, Volume 64, Number 8, August 2005, pp, 1180–1185.
14. Dolezalova, P., et al. Adenosine and methotrexate polyglutamate concentrations in patients with juvenile arthritis. Rheumatology. Volume 44, 2005, pp. 74-79.
15. Fathi, Nihal H., et al. Longitudinal Measurement of Methotrexate Liver Concentrations Does Not Correlate with Liver Damage, Clinical Efficacy, or Toxicity During a 3.5 Year Double Blind Study in Rheumatoid Arthritis. The Journal of Rheumatology, Volume 29, Number 10, 2002, pp. 2092-2098.
16. Goodman S. Measuring methotrexate polyglutamates. Clin Exp Rheumatol. 2010 Jul;28(61):S24-S26.
17. Halilova KI, Brown EE, Morgan SL, Bridges SL Jr, Hwang MH, Arnett DK, Danila MI. Markers of Treatment Response to Methotrexate in Rheumatoid Arthritis: Where Do We Stand? International Journal of Rheumatology. Volume 2012, Article ID 978396, 7 pages.
18. Hayashi, H., et al. Application of fluorescence polarization immunoassay for determination of methotrexate-polyglutamates in rheumatoid arthritis patients. Tohoku J Exp Med, Volume 215, Number 1, May 1, 2008, pp. 95-101.
19. Hroch, M., et al. An improved high-performance liquid chromatography method for quantification of methotrexate polyglutamates in red blood cells of children with juvenile idiopathic arthritis. Biopharm Drug Dispos, Volume 30, Number 3, April 1, 2009, pp. 138-148.
20. Mohamed HJ, Sorich MJ, Kowalski SM, McKinnon R, Proudman SM, Cleland L, Wiese MD. The role and utility of measuring red blood cell methotrexate polyglutamate concentrations in inflammatory arthropathies-a systematic review. Eur J Clin Pharmacol. 2015 Apr;71(4):411-23.
21. Rahman, S, Siegfried, Flanagan K and Armbrecht, ES. The validity of methotrexate polyglutamate assay in treating pediatric skin conditions. J Clin Exp Dermatol Res 2013. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum, Volume 50, Number 7, July 1, 2004, pp. 2191-2201.
22. Stamp L, O'Donnell J, Chapman P, et al. Methotrexate polyglutamate concentrations are not associated with disease control in rheumatoid arthritis patients receiving long-term methotrexate therapy. Arthritis Rheum. 2010 February;62(2):359-368.
23. Takahashi C, Kaneko Y, Okano Y, et al. Association of erythrocyte methotrexate-polyglutamate levels with the efficacy and hepatotoxicity of methotrexate in patients with rheumatoid arthritis: a 76-week prospective study. RMD Open. 2017 Jan 3;3(1)e000363..

*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2023, the date the research was completed.*

## Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 11/1/09 | 9/10/09 | 8/18/09 | Joint policy established |
| 3/1/12 | 12/13/11 | 12/21/11 | Routine maintenance; references updated |
| 7/1/14 | 4/10/14 | 4/15/14 | Routine maintenance; changed name of Avise PG to Avise MTX. No change in status. |
| 7/1/15 | 4/21/15 | 5/8/15 | Policy updated to reflect status change for **BCNA** members only; test is covered for BCNA members who meet patient selection criteria. Still considered EI for commercial members. |
| 7/1/16 | 4/19/16 | 4/19/16 | Routine maintenance |
| 7/1/17 | 4/18/17 | 4/18/17 | Routine maintenance |
| 7/1/18 | 4/17/18 | 4/17/18 | Routine policy maintenance. No change in policy status. |
| 7/1/19 | 4/16/19 | | Routine policy maintenance. No change in policy status. |
| 7/1/20 | 4/14/20 | | Routine policy maintenance. No change in policy status. |
| 7/1/21 | 4/20/21 | | Routine policy maintenance. No new literature available. Code 80204 added as E/I. |
| 7/1/22 | 4/19/22 | | Routine policy maintenance, no change in policy status. |
| 7/1/23 | 4/18/23 | | Routine policy maintenance, no change in policy status. Vendor managed: N/A. (ds) |

Next Review Date: 2nd Qtr., 2024

# BLUE CARE NETWORK BENEFIT COVERAGE
# POLICY: METHOTREXATE (MTX) POLYGLUTAMATE TESTING TO MEASURE RESPONSE TO METHOTREXATE THERAPY

## I. Coverage Determination:

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| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | Not covered for commercial members. |
| **BCNA (Medicare Advantage)** | See Government Regulations section. |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.