KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
AVISE MTX Test for Measuring Methotrexate Polyglutamate Levels

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***AVISE MTX Test for Measuring Methotrexate Polyglutamate Levels***" for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Rheumatoid arthritis is a chronic, systemic, inflammatory disorder that affects approximately 0.5–1% of the Western population. If left untreated, this disease can result in permanent joint damage (Binker 2010). Evidence from recent studies suggests that achieving early control of rheumatoid arthritis minimizes joint destruction and increases long-term disease control.

Methotrexate is one of the most effective and commonly prescribed drugs for the treatment of rheumatoid arthritis. Although methotrexate is effective, it is not without side effects. Side effects of methotrexate include gastrointestinal disturbance, mucositis, fatigue, alopecia, elevated serum transaminase levels, and bone marrow toxicity. Frequent blood tests are required to monitor for the development of these adverse effects. Additionally, patient response to methotrexate, both in terms of efficacy and toxicity is highly variable. It is estimated that approximately 30–40% of patients with rheumatoid arthritis taking methotrexate do not adequately respond to treatment (Danilia 2010, Goodman 2010). Currently, there is no reliable means of predicting patient response to methotrexate.

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After administration and absorption, serum methotrexate levels fall rapidly as it is actively transported into a variety of cells. In the cells, up to six additional glutamate residues are added, converting methotrexate into the more stable polyglutamate form. Methotrexate polyglutamate can be converted back to methotrexate to permit efflux from the cell. The therapeutic effect of methotrexate depends on its conversion to methotrexate polyglutamate. It has been suggested that if methotrexate polyglutamate levels were associated with adverse events or therapeutic response then knowledge of these levels could be used to help optimize methotrexate therapy in rheumatoid arthritis (Binker 2010, Danilia 2010, Goodman 2010).The Avise PG test (Cypress Bioscience, San Diego, CA) measures methotrexate polyglutamate levels and was developed to aid in dosage optimization for rheumatoid arthritis patients who have been on methotrexate for at least three months. Results of the Avise PG test are reported as therapeutic (> 60 nmol/L), intermediate (20-60 nmol/L), and subtherapeutic (< 20 nmol/L).

Medical Technology Assessment Committee (MTAC)

Avise PG Test for Measuring Methotrexate Polyglutamate Levels

06/20/2011: MTAC REVIEW

Evidence Conclusion: Analytic validity - There are a variety of rapid, sensitive, and accurate methods for the detection of methotrexate polyglutamate (Dervieux 2003, Li 2007). Clinical validity - Two cross-sectional studies that examined the association between methotrexate polyglutamate levels and disease activity were selected for review. The first study included 192 subjects with rheumatoid arthritis who had been taking methotrexate for at least 3 months and had a stable dose for at least a month prior to study entry. Before adjusting for confounding factors results suggest that higher disease activity, measured using the swollen joint count (SJC), the physician's global assessment, the physician's assessment of response to methotrexate, the Disease Activity Score in 28 joints (DAS28), the Clinical Disease Activity Index (CDAI), and the Simplified Disease Activity Index (SDAI), was associated with higher MTX PG concentrations (MTX PG_4, MTX PG_5, MTX PG_{1-5}, and MTX PG_{3-5}). After adjusting for confounding factors, patients with higher disease activity measured using TJC, SJC, and DAS28 still had higher MTX PG_5 concentrations. There was no association between methotrexate polyglutamate concentration and adverse events (Stamp 2010). Two other studies also failed to find an association between methotrexate polyglutamate concentration and adverse events (Dervieux 2006, Angelis-Stoforidis 1999). The second study included 226 subjects with rheumatoid arthritis who had been taking methotrexate for at least 3 months. After controlling for confounding factors, low methotrexate polyglutamate levels were associated with poor clinical status (high number of tender and swollen joints, physician's assessment of disease activity, and the modified Health Assessment Questionnaire) (Dervieux 2005). The same group of authors also conducted two other studies that examined the relationship between methotrexate polyglutamate levels and clinical status. Both of these studies along with two other observational studies also found that low methotrexate polyglutamate levels were associated with poor clinical status (Angelis-Stoforidis 1999, Dervieux 2004, Dervieux 2006, Hornung 2008).
Clinical utility -
No studies were identified that addressed the clinical utility of measuring methotrexate polyglutamate levels to aid in dosage optimization for rheumatoid arthritis patients.
Conclusion: Analytic validity: There are a variety of rapid, sensitive, and accurate methods for the detection of methotrexate polyglutamate. Clinical validity: Several observational studies have investigated the association between methotrexate polyglutamate levels and clinical status. While the majority of these studies found that low methotrexate polyglutamate levels were associated with poor clinical response, not all studies have found this association. Clinical utility: There is insufficient evidence to determine the clinical utility of measuring methotrexate polyglutamate levels to aid in dosage optimization for rheumatoid arthritis patients.
Articles: Two studies were identified that address analytic validity. Several observational studies were identified that examined the relationship between methotrexate polyglutamate levels and clinical status (clinical validity). Two of the larger studies were selected for review. No studies were identified that addressed the clinical utility of measuring methotrexate polyglutamate to aid in dosage optimization for rheumatoid arthritis patients. The following studies were critically appraised: Stamp LK, O'Donnell JL, Chapman PT, et al. Methotrexate polyglutamate concentrations are not associated with disease control in rheumatoid arthritis patients receiving long-term methotrexate therapy. *Arthritis Rheum 2010;* 62:359-638. See Evidence Table. Dervieux T, Frust D, Lein DO, et al. Pharmacogenetic and metabolite measurements are associated with clinical status in patient's rheumatoid arthritis treated with methotrexate: results of a multicentered cross sectional observational study. *Ann Rheum Dis 2005;* 64:1180-1185. See Evidence Table**.**

The use of Avise PG test for measuring methotrexate polyglutamate levels does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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Applicable Codes

Considered Not Covered:

CPT® Codes	Description
84999	Unlisted chemistry procedure
ICD-10 Codes	**Description**
M05.60-M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70-M05.79	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80-M05.89	Other rheumatoid arthritis with rheumatoid factor
M06.00-M06.09	Rheumatoid arthritis without rheumatoid factor

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Creation Date	Review Dates	Date Last Revised
07/05/2011	07/05/2011[MDCRPC], 07/03/2012[MDCRPC] ,05/07/2013 [MDCRPC] ,03/04/2014 [MPC], 01/06/2015 [MPC], 11/03/2015 [MPC], 09/06/2016[MPC], 07/11/2017[MPC], 05/01/2018[MPC], 05/07/2019[MPC], 05/05/2020[MPC], 05/04/2021[MPC], 05/03/2022[MPC], 05/02/2023[MPC]	05/05/2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
05/05/2020	Added CPT code 84999 and rheumatoid arthritis ICD-10 codes M05.60-M06.09
05/06/2022	Medicare retired LCA A54378 Billing and Coding: MolDX: Avise PG Assay

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