

Rheumatoid Arthritis: Biologic Markers and Pharmacologic Assessment



INDEPENDENT CARE HEALTH PLAN

Effective Date: 01/01/2024

Revision Date: Click or tap to enter a date.

Review Date: Click or tap to enter a date.

Policy Number: WI.PA-1201

Line of Business: Medicare

Medicare Advantage Medical Coverage Policy

Table of Contents

[Related Medical/Pharmacy Coverage Policies](#)

[Related Documents](#)

[Description](#)

[Coverage Determination](#)

[Coverage Limitations](#)

[Coding Information](#)

[References](#)

[Change Summary](#)

Disclaimer

The Coverage Summaries are reviewed by the iCare Medicare Utilization Management Committee. Policies in this document may be modified by a member's coverage document. Clinical policy is not intended to preempt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test, or procedure over another. Clinical technology is constantly evolving, and we reserve the right to review and update this policy periodically. References to CPT® codes or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee of claims payment. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any shape or form or by any means, electronic, mechanical, photocopying or otherwise, without permission from iCare.

Related Medicare Advantage Medical/Pharmacy Coverage Policies

For information regarding adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi and Simponi Aria) and infliximab (Remicade), methotrexate please refer to the applicable Pharmacy Coverage Policies.

Related Documents

Please refer to [CMS website](#) for the most current applicable National Coverage Determination (NCD)/Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

Type	Title	ID Number	Jurisdiction Medicare Administrative Contractors (MACs)	Applicable States/Territories
------	-------	-----------	---	-------------------------------

LCD	Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis	L39481	J5, J8 - Wisconsin Physicians Service Insurance Corporation	IA, IN, KS, MI, MO, NE
LCD	Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis	L39427	J15 - CGS Administrators, LLC	KY, OH
LCD	Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis	L39467	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
LCD	Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis	L39469	JF - Noridian Healthcare Solutions, LLC	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
LCD	Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis	L39424	JJ, JM - Palmetto GBA	AL, GA, NC, SC, TN, VA, WV
LCD	Molecular Pathology Procedures	L34519	JN - First Coast Service Options, Inc.	FL, Puerto Rico, Virgin Islands

Description

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that causes deterioration of the joints, inflammation, loss of mobility, pain and stiffness. RA affects multiple joints, most commonly the hands, wrists and other joints such as the elbows, feet, hips, knees, neck and shoulders.

Common laboratory tests used to diagnose and monitor treatment for RA include, but may not be limited to, anti-citrullinated peptide antibodies (anti- CCP or ACPA), C reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and serum IgM rheumatoid factor.

Testing has been developed or is in development to assist in diagnosing and guiding treatment decisions in RA which include, but may not be limited to, presence of autoantibodies to carbamylated proteins (eg, Avise Anti-CarP) and panel testing for RA (eg, RheumAssure) that evaluates many common tests (eg, RF, CCP and 14-3-3 eta) associated with RA simultaneously and have been proposed to aid in the diagnosis of RA.

Methotrexate (MTX), a disease modifying antirheumatic drug (DMARD), is known as the gold standard therapy for long term management in the treatment of RA alone or in combination with other medications (eg, hydroxychloroquine sulfate [Plaquenil]). Drug level testing (eg, Avise HCQ and Avise MTX) has been purported to determine how an individual metabolizes the drug and to guide dosing. Tumor necrosis factor (TNF-alpha) inhibitors, such as adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel),

golimumab (Simponi and Simponi Aria) and infliximab (Remicade), are pharmacotherapeutic agents used for the treatment of many inflammatory conditions, including RA.

Lab testing has been developed to try to identify the serum drug concentration and development of antibodies to tumor necrosis factor-alpha inhibitor (TNFi). Results may be associated with allergic reaction, determining dosage, loss of drug efficacy (eg, Anser ADA and Anser IFX). However, most of these have not been studied in the management of RA.

A molecular signature test to predict response to TNFi therapies (eg, PrismRA) integrates 10 ribonucleic acid single nucleotide polymorphisms (RNA SNPs), 8 RNA transcripts, 2 serum proteins (CRP, anti-cyclic citrullinated protein) and 3 clinical features (sex, body mass index, patient disease assessment).

RA disease activity multianalyte assay (eg, Vectra DA) measures concentrations of 12 serum proteins purportedly associated with RA disease activity. These concentrations are then applied in an algorithm to estimate a disease activity score. The panel measures the following proteins: CRP, epidermal growth factor (EGF), interleukin 6 (IL-6), leptin, matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 3 (MMP-3), resistin, serum amyloid (SAA), tumor necrosis factor receptor, type 1 (TNF-R1), vascular cell adhesion molecule 1 (VCAM-1), vascular endothelial growth factor A (VEGF-A) and YKL-40.

Coverage Determination

iCare follows the CMS requirement that only allows coverage and payment for services that are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.

Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS “reasonable and necessary” criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary’s specific medical problem.

For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the [MolDX program](#) and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare’s reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:

Molecular Biomarker Testing to guide targeted therapy selection in RA will be considered medically reasonable and necessary when the following requirements are met:

- Individual is at least 18 years of age with a confirmed diagnosis of moderately to severely active RA; **AND**

- Individual has a history of failure, contraindication, or intolerance to at least one first-line therapy for the treatment of RA (eg, conventional synthetic DMARDs [csDMARDs]) despite adequate dosing; **AND**
- Individual has not initiated a biologic or targeted synthetic therapy (b/tDMARD) for RA (eg, TNFi, Janus Kinase [JAK] inhibitor) **OR** has initiated b/tDMARD therapy and is being considered for an alternate class of targeted therapies as a result of failure, contraindication, or intolerance to the initial targeted therapy despite adequate dosing; **AND**
- The test predicts response and/or non-response to at least one class of targeted or biologic therapies for RA according to multiple validated response/remission criteria:
 - Accuracy that exceeds that which can be obtained from the combination of existing clinical and other data; **AND**
 - Demonstrated reproducibility across clinical study cohorts; **AND**
- Testing using molecular biomarkers has not been previously performed for predictive therapy selection in RA; **AND**
- If the test relies on an algorithm, the algorithm must be validated in a cohort that is not a development cohort for the algorithm; **AND**
- The lab providing the test is responsible for clearly indicating to treating physicians the population and indication(s) for test use; **AND**
- If applicable, performance characteristics are equivalent or superior to the average performance of other similar tests (for the same intended use) evaluated by this contractor upon successful completion of a technical assessment

*Since the clinical utility of predictive testing is largely dependent upon consensus-based management recommendations, this policy is subject to change pending changes in the literature and in consensus guidelines.

**New tests that become available with significantly improved performance may render older tests no longer compliant with this policy.

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

Coverage Limitations

[US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage](#)

The following tests may not be considered a benefit (statutory exclusion)¹⁶:

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law; **OR**
- Tests that confirm a diagnosis or known information; **OR**
- Tests to determine risk for developing a disease or condition; **OR**
- Tests performed to measure the quality of a process; **OR**
- Tests without diagnosis specific indications; **OR**
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial

These treatments and services fall within the Medicare program's statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program's statutory exclusion at 1862(a)(12), which prohibits payment.

The following **services/items** will not be considered medically reasonable and necessary:

- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the [MoIDX Program](#); **OR**
- 14-3-3 eta protein; **OR**
- HLA typing in RA (81376); **OR**
- Levels of antibodies to adalimumab or infliximab (eg, Anser ADA and Anser IFX); **OR**
- Levels of hydroxychloroquine (eg, Avise HCQ); **OR**
- Levels of methotrexate polyglutamates (eg, Avise MTX); **OR**
- Panels for RA unless ALL components in the panel are relevant to the personal history of the individual being tested⁸ eg, RheumAssure; **OR**
- Presence of autoantibodies to carbamylated proteins (eg, Avise Anti-CarP)

A review of the current medical literature shows that the evidence is insufficient to determine that this service is standard medical treatment for these indications. There remains an absence of randomized blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of this service in clinical management for these indications.

Summary of Evidence

14-3-3 eta protein

Serum 14-3-3 eta may be helpful diagnostically in RA as some data suggest that it may have similar sensitivity and specificity to RF and ACPA in distinguishing patients with RA from osteoarthritis, other autoimmune disorders, and healthy controls. However, in a cohort of patients with arthralgia, preselected for ACPA and/or RF positivity, the added predictive value of 14-3-3 eta could not be established.¹⁷

HLA typing in RA

Evidence indicates genetic markers are not useful for diagnosis or screening of RA. Although certain HLA alleles are strongly associated with severe RA, these alleles are common in the normal carriage population. Knowledge of a patient's HLA status and other genetic markers may be useful with further developments in diagnosis and screening, in estimating prognosis, and in predicting the response to specific therapies, but a role for HLA testing in RA outside the research setting has not been established.²¹

Levels of antibodies to adalimumab, infliximab or drug concentration of hydroxychloroquine, methotrexate polyglutamates in the treatment of RA

Limited evidence suggests in selected patients suspected of inadequate adherence to therapy, it is reasonable to perform measurement of MTX polyglutamates in those patients in whom this information would change the treatment strategy.¹⁷

No additional recommendations from professional organizations or the US Food & Drug Administration (FDA) prescribing information.

Autoantibodies to carbamylated proteins (eg, Avise Anti-CarP)

The identification of both ACPAs and anti-carbamylated protein antibodies (anti-CarP Abs) has greatly facilitated approaches toward RA, especially in the fields of early diagnosis and prognosis prediction of the disease. Although these antibodies share many common features and can function synergistically to promote disease progression, they differ mechanistically and have unique clinical relevance. The current evidence suggests a synergic effect of RF and ACPA in predicting the development of RA and an erosive phenotype, controversies exist regarding the additive value of anti-CarP Abs.²⁵

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
--------------	-------------	----------

80145	Adalimumab	
80230	Infliximab	
81376	HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each	
81479	Unlisted molecular pathology procedure	
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score	
81599	Unlisted multianalyte assay with algorithmic analysis	
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified	
84999	Unlisted chemistry procedure	
85651	Sedimentation rate, erythrocyte; non-automated	
85652	Sedimentation rate, erythrocyte; automated	
86038	Antinuclear antibodies (ANA);	
86140	C-reactive protein;	
86141	C-reactive protein; high sensitivity (hsCRP)	
86200	Cyclic citrullinated peptide (CCP), antibody	
86430	Rheumatoid factor; qualitative	
86431	Rheumatoid factor; quantitative	
CPT® Category III Code(s)	Description	Comments
No code(s) identified		
HCPCS Code(s)	Description	Comments
No code(s) identified		

References

1. American College of Rheumatology (ACR). 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. <https://www.rheumatology.org>. Published May 2012. Accessed June 23, 2023.
2. American College of Rheumatology (ACR). 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. <https://www.rheumatology.org>. Published 2021. Accessed June 23, 2023.

3. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MoIDX: Molecular biomarker testing to guide targeted therapy selection in rheumatoid arthritis (L39424). <https://www.cms.gov>. Published October 15, 2023. Accessed October 11, 2023.
4. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MoIDX: Molecular biomarker testing to guide targeted therapy selection in rheumatoid arthritis (L39427). <https://www.cms.gov>. Published October 15, 2023. Accessed October 11, 2023.
5. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MoIDX: Molecular biomarker testing to guide targeted therapy selection in rheumatoid arthritis (L39467). <https://www.cms.gov>. Published October 15, 2023. Accessed October 11, 2023.
6. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MoIDX: Molecular biomarker testing to guide targeted therapy selection in rheumatoid arthritis (L39469). <https://www.cms.gov>. Published October 15, 2023. Accessed October 11, 2023.
7. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MoIDX: Molecular biomarker testing to guide targeted therapy selection in rheumatoid arthritis (L39481). <https://www.cms.gov>. Published October 15, 2023. Accessed October 11, 2023.
8. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Molecular Pathology Procedures (L34519). <https://www.cms.gov>. Published October 1, 2015. Accessed October 27, 2023.
9. ClinicalKey. Clinical Overview. Rheumatoid arthritis. <https://www.clinicalkey.com>. Updated March 20, 2023. Accessed June 26, 2023.
10. ECRI Institute. ECRIgene Genetic Test Assessment. PrismRA (Scipher Medicine Corp.) for guiding treatment decisions in patients with rheumatoid arthritis. <https://www.ecri.org>. Published November 2021. Accessed June 19, 2023.
11. ECRI Institute. ECRIgene Genetic Test Assessment. Vectra (Labcorp) for assessing prognosis and monitoring rheumatoid arthritis. <https://www.ecri.org>. Published August 24, 2022. Accessed June 19, 2023.
12. Hayes, Inc. Health Technology Brief (ARCHIVED). Vectra DA test (Crescendo Bioscience) for management of patients with rheumatoid arthritis. <https://evidence.hayesinc.com>. Published January 25, 2018. Updated March 14, 2022. Accessed June 19, 2023.
13. Hayes, Inc. Molecular Test Assessment. PrismRA (Scipher Medicine). <https://evidence.hayesinc.com>. Published April 22, 2022. Accessed June 19, 2023.
14. Heemst J, Trouw L, Nogueira L, et al. An investigation of the added value of an ACPA multiplex assay in an early rheumatoid arthritis setting. *Arthritis Res Ther*. 2015;17:276. <https://www.ncbi.nlm.nih.gov/pmc>. Accessed June 23, 2023.

15. Merck Manual: Professional Version. Rheumatoid arthritis (RA). <https://www.merckmanuals.com>. Updated November 2022. Accessed June 26, 2023.
16. Palmetto GBA. Molecular diagnostic program (MolDX®): coverage, coding, and pricing standards and requirements (M00106). <https://www.palmettogba.com/MolDx>. Published December 2019. Accessed September 27, 2023.
17. UpToDate, Inc. Biologic markers in the diagnosis and assessment of rheumatoid arthritis. <https://www.uptodate.com>. Updated May 2023. Accessed June 23, 2023.
18. UpToDate, Inc. Clinical significance of antinuclear antibody staining patterns and associated autoantibodies. <https://www.uptodate.com>. Updated May 2023. Accessed June 21, 2023. 12.
19. UpToDate, Inc. Diagnosis and differential diagnosis of rheumatoid arthritis. <https://www.uptodate.com>. Updated May 2023. Accessed June 21, 2023. 13.
20. UpToDate, Inc. General principles and overview of management of rheumatoid arthritis in adults. <https://www.uptodate.com>. Updated May 2023. Accessed June 21, 2023. 14.
21. UpToDate, Inc. HLA and other susceptibility genes in rheumatoid arthritis. <https://www.uptodate.com>. Updated May 2023. Accessed June 21, 2023.
22. UpToDate, Inc. Investigational biologic markers in the diagnosis and assessment of rheumatoid arthritis. <https://www.uptodate.com>. Updated May 2023. Accessed June 21, 2023.
23. UpToDate, Inc. Tumor necrosis factor-alpha inhibitors: induction of antibodies, autoantibodies, and autoimmune diseases. <https://www.uptodate.com>. Updated May 2023. Accessed June 21, 2023.
24. UpToDate, Inc. Use of methotrexate in the treatment of rheumatoid arthritis. <https://www.uptodate.com>. Updated May 2023. Accessed June 21, 2023.
25. Wu C, Yang H, Luo S, Lai J. From rheumatoid factor to anti-citrullinated protein antibodies and anti-carbamylated protein antibodies for diagnosis and prognosis prediction in patients with rheumatoid arthritis. *Int J Mol Sci.* 2021;22(2):686. <https://www.ncbi.nlm.nih.gov/pmc>. Accessed June 23, 2023.

Change Summary

- Click or tap to enter a date. New Policy.