



GENETIC TESTING: IMMUNE, AUTOIMMUNE, AND RHEUMATOID DISORDERS (REQUIRES PREAUTHORIZATION)

V.72

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DESCRIPTION

Immunodeficiency disorders typically result from the use of a drug or from a long-lasting significant disorder (e.g., cancer), however a subset of immunodeficiency disorders are inherited.

Immunodeficiency disorders impair the immune system's ability to defend the body against foreign substances, such as bacteria, viruses, yeast, and cancer cells. As a result, infections or cancers can develop. Individuals with immunodeficiency can also have an autoimmune disorder, such as rheumatoid arthritis. Molecular biomarker tests have been developed that can predict response (or non-response) to certain medications in RA treatment.

There are two types of immunodeficiency disorders: primary and secondary. Primary disorders are relatively rare and usually present at birth, genetic in origin, and hereditary; however some primary immunodeficiency disorders are not recognized until adulthood. Secondary disorders are more common and generally develop later in life as a result of the use of certain drugs or from conditions such as diabetes or HIV infection.

Dates

Original Effective

09-01-2021

Last Review

08-07-2024

Next Review

08-10-2025



document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert Genetics Platform](#) for a comprehensive list of registered tests.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	
Periodic Fever Syndrome				
Periodic Fever Syndromes Multigene Panel	Periodic Fever Syndromes Panel (Invitae)	81404, 81479	M04.1, R50.9, A68.9	
	Periodic Fever Syndromes Panel (PreventionGenetics, part of Exact Sciences)			
	Periodic Fever Syndromes Panel (7 genes) (GeneDx)			
Rheumatoid Arthritis				
Rheumatoid Arthritis Biomarker Activity Panels	Vectra (LabCorp)	81490	M05.00-M06.9	
	Vectra with CV Risk (LabCorp)			
Rheumatoid Arthritis TNFi Treatment Response Algorithmic Tests	PrismRA (Scipher Medicine)	0456U	M05, M06, M08	
HLA Typing for Axial Spondyloarthritis				
HLA Typing for Axial Spondyloarthritis	HLA-B27 DNA Typing (Quest Diagnostics)	81374	M04.8, M04.9, M05, M06, M45	
Other Covered Immune, Autoimmune, and Rheumatoid Disorders				
Other Covered Immune, Autoimmune, and Rheumatoid Disorders	See below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408		



This policy document provides coverage criteria for Genetic Testing for Immune Disorders. Please refer to:

- **V.62 - Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for coverage criteria related to genetic disorders that affect multiple organ systems.
- **V.74 - Genetic Testing: General Approach to Genetic and Molecular Testing** for coverage criteria related to immune disorders not specifically addressed in the policy reference table, including known familial variant testing.

POLICY

PERIODIC FEVER SYNDROME

Periodic Fever Syndrome Multigene Panel

I. Genetic testing for periodic fever syndromes, also called hereditary recurrent fever syndromes, (e.g., Familial Mediterranean Fever, tumor necrosis factor receptor-associated periodic fever [TRAPS]) via multigene panel (81404, 81479) is considered **medically necessary** when:

A. The member has three or more episodes of unexplained fever in a six-month period, occurring at least seven days apart, **AND**

B. Common causes of fever have been ruled out, including viral or bacterial infection.

II. Genetic testing for periodic fever syndromes, also called hereditary recurrent fever syndromes (e.g., Familial Mediterranean Fever [TRAPS]) via multigene panel (81404, 81479) is considered **investigational** when the above criteria are not met and for all other indications.

RHEUMATOID ARTHRITIS

Rheumatoid Arthritis Biomarker Activity Panels

I. The use of multibiomarker disease activity (MBDA) scores for rheumatoid arthritis (81490) is considered **investigational**.

Rheumatoid Arthritis TNFi Treatment Response Algorithmic Test

I. The use of genetic rheumatoid arthritis algorithmic tests to determine appropriateness of TNFi treatment (PrismRA) (0456U) is considered



B. The member has a diagnosis of moderately to severely active rheumatoid arthritis (RA), **AND**

C. The member previously received first-line therapy for treatment of rheumatoid arthritis conventional synthetic disease-modifying anti-rheumatic drug (csDMARD), **AND**

D. The member is unresponsive/refractory or intolerant to the therapy despite a therapeutic dose, **AND**

E. One of the following:

1. The member has not yet initiated a biologic or targeted synthetic therapy (b/tDMARD) for RA (i.e., TNFi), **OR**

2. The member has initiated a biologic or targeted synthetic therapy (b/tDMARD) for RA (i.e., TNFi) and is unresponsive/refractory or intolerant to a therapeutic dose, **AND**

F. The member has not had previous testing using molecular biomarkers for predictive therapy selection for rheumatoid arthritis.

II. The use of genetic rheumatoid arthritis algorithmic tests to determine appropriate of TNFi treatment (PrismRA) (0456U) is considered **investigational** for all other indications.

HLA TYPING FOR AXIAL SPONDYLOARTHRITIS

I. The use of HLA-B27 typing (81374) for evaluation of axial spondyloarthritis is considered **medically necessary** when:

A. The member has clinical or radiographic features of axial spondyloarthritis.

II. The use of HLA typing (81374) for evaluation of axial spondyloarthritis is considered **investigational** for all other indications.

OTHER COVERED IMMUNE, AUTOIMMUNE, AND RHEUMATOID DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following immune, autoimmune, or rheumatoid disorders to guide management is considered **medically necessary** when the member demonstrates clinical features*



- A. [X-linked and Autosomal Recessive Agammaglobulinemia \(X-Linked and Autosomal Recessive \(BTK\)\)](#)
- B. [Autoimmune Lymphoproliferative Syndrome \(ALPS\) \(FAS\)](#)
- C. [Chronic Granulomatous Disease \(CGD\) \(CYBA, CYBC1, NCF1, NCF2, and NCF4, CYBB\)](#)
- D. Complement Deficiencies
- E. Congenital Neutropenia Syndromes (e.g., *ELANE*-Related Neutropenia) (*ELANE, HAX1*)
- F. [Familial Hemophagocytic Lymphohistiocytosis \(HLH\) \(PRF1, STX11, STXBP2, or UNC13D\)](#)
- G. [Hyper IgE Syndrome \(HIES\) \(STAT3\)](#)
- H. [Hyper IgM Syndromes \(CD40LG\)](#)
- I. Leukocyte Adhesion Deficiency (LAD) (*CD18, Kindlin-3, ITGB2*)
- J. NEMO Deficiency Syndrome (*NEMO*, aka *IKK gamma* or *IKKG*)
- K. [Severe Combined Immune Deficiency \(SCID\) and Combined Immune Deficiency \(IL2RG\)](#)
- L. WHIM Syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) (*CXCR4*)
- M. [Wiskott-Aldrich Syndrome \(WAS\)](#)

II. Genetic testing to establish or confirm the diagnosis of all other immune, autoimmune, or rheumatoid disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy for coverage criteria).

NOTE: Clinical features for a specific disorder may be outlined in resources such as [GeneReviews](#), [OMIM](#), [National Library of Medicine](#), [Genetics Home Reference](#), or other scholarly source.

DEFINITIONS

1. **Multibiomarker disease activity (MBDA) tests:** A validated approach that uses serum biomarkers to objectively measure rheumatoid arthritis disease activity.
2. **Unexplained fever:** A fever of unknown origin (FUO). A temperature higher than 38.3 C (100.9 F) that lasts for more than three weeks with no obvious source despite appropriate investigation. The four categories of potential etiology of FUO are classic, nosocomial, immune deficient, and human immunodeficiency virus-related. The four subgroups of the differential diagnosis of FUO are infections, malignancies, autoimmune conditions, and miscellaneous.



BACKGROUND

Periodic Fever Syndromes Multigene Panel

Soon and Laxer (2017)

A 2017 clinical review by Soon and Laxer addressing recurrent fever in childhood stated the following: "Recurrent or periodic fever syndromes are defined by 3 or more episodes of unexplained fever in a 6-month period, occurring at least 7 days apart." (p. 756) The authors recommend that: "Once infections, immunodeficiency, malignancy, inflammatory bowel disease, and adverse drug reactions have been ruled out, autoinflammatory diseases—including periodic fever syndromes—should be considered." (p. 758)

Rheumatoid Arthritis Biomarker Activity Panels

American College of Rheumatology (ACR)

The ACR updated guidelines on the treatment of rheumatoid arthritis (2019). In this update, the following 11 measures of disease activity were identified as fulfilling a minimum standard for regular use in most clinical settings:

- Disease Activity Score (DAS)
- Routine Assessment of Patient Index Data 3 (RAPID3)
- Routine Assessment of Patient Index Data 5 (RAPID5)
- Clinical Disease Activity Index (CDAI)
- Disease Activity Score with 28 joints (DAS28-ESR/CRP)
- Patient Derived DAS28, Hospital Universitario La Princesa Index (HUPI)
- Multibiomarker Disease Activity Score (MBDA score, Vectra DA)
- Rheumatoid Arthritis Disease Activity Index (RADAI)
- Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5)
- Simplified Disease Activity Index (SDAI)

Although the original Vectra DA test is included in this list, the current commercially available version of the test that is now called Vectra, includes the leptin-adjusted MBDA score (now called the "adjusted MBDA score") that was not addressed in the 2019 ACR guideline. This is because evidence on Vectra with the adjusted MBDA score was published subsequent to the ACR review end date.

A Rheumatoid Arthritis (RA) Measures toolkit was created by the ACR in 2021 (<https://ratoolkit.kotobee.com/#/reader>). There is no mention of Vectra testing to aid in the treatment of RA, nor are there recommendations for this type of biomarker testing for RA.



Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled MoIDX: Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis (L39424) states the following regarding guidance for targeted therapy selection in rheumatoid arthritis:

“Coverage criteria:

1. The patient is an adult with a confirmed diagnosis of moderately to severely active RA.
2. The patient has a history of failure, contraindication, or intolerance to at least one first-line therapy for the treatment of RA (i.e., conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)) despite adequate dosing.
3. The patient has not initiated a biologic or targeted synthetic therapy (b/tDMARD) for RA (i.e., Tumor Necrosis Factor-?? inhibitor [TNFi], Janus Kinase [JAK] inhibitor, etc.) 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.”

HLA Typing for Axial Spondyloarthritis

Rudwaleit et al 2009

“Refinement of the candidate criteria resulted in new ASAS [Assessment of SpondyloArthritis International Society] classification criteria that are defined as: the presence of sacroiliitis by radiography or by magnetic resonance imaging (MRI) plus at least one SpA feature ("imaging arm") or the presence of HLA-B27 plus at least two SpA features ("clinical arm")." (p. 777)

Akgul and Ozgocmen, 2011

“HLA B-27 positivity is extremely relevant to the early diagnosis of SpA [spondyloarthropathies]. Five to 10% of the population are HLA B-27 positive and in patients with AS [ankylosing spondylitis] and SpA the positivity of HLA B-27 changes to 70% to 95% and nearly 70%, respectively.” (p. 109)

Yu and van Tubergen, UpToDate, 2024



significantly reduce the likelihood of diagnosis. HLA-B27 testing can also be used in patients presenting with chronic back pain with a significant probability of axSpA after clinical evaluation. The results of this testing alone are not diagnostic nor do they exclude the diagnosis but should be interpreted with other clinical findings.

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REFERENCES



Targeted Therapy Selection in Rheumatoid Arthritis (LCD L39424). Available at: <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39424>

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REVISIONS



01-01-2024

Updated background and references. No policy changes.

09-29-2023

Removed "medically necessary" and replaced with "scientifically validated" and also added "investigational when the above criteria is not met and for all other indications"

07-01-2023

Added Known familial variant analysis for immune, autoimmune, and rheumatoid disorders, updated codes, background and references.

01-01-2023

Updated table and added 81599. Added algorithmic rheumatoid arthritis test for TNFi treatment as investigational.

07-01-2022

Updated table and added HLA typing criteria

01-01-2022

Minor updates made to Practice Guidelines sand Position Statements and updated references

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