Medica Coverage Policy

Policy Name:	**Genetic Testing: Immune, Autoimmune, and Rheumatoid Disorders**
Medica Effective Date:	**July 01, 2024**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between policy requirements and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

OVERVIEW

Immunodeficiency disorders typically result from the use of a drug or from a chronic 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, and cancer cells. As a result, infections or cancers can develop. Individuals with immunodeficiency can also have an autoimmune disorder, such as rheumatoid arthritis.
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.

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this 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.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Periodic Fever Syndromes				
Periodic Fever Syndromes Multigene Panel	Periodic Fever Syndromes Panel (Invitae)	81404, 81479	M04.1, R50.9, A68.9	11
	Periodic Fever Syndromes Panel			

	(PreventionGenetics, part of Exact Sciences)			
	Periodic Fever Syndromes Panel (7 genes) (GeneDx)			
Rheumatoid Arthritis Biomarker Activity Panels				
Rheumatoid Arthritis Biomarker Activity Panels	Vectra (Labcorp)	81490	M05.00-M06.9	1, 2
	Vectra with CV Risk (Labcorp)			
Genetic Rheumatoid Arthritis Algorithmic Tests				
Genetic Rheumatoid Arthritis for Tumor Necrosis Factor inhibitor (TNFi) Treatment	PrismRA (Scipher Medicine)	81599, 81479	M05, M06, M08	10
HLA Typing for Axial Spondyloarthritis				
HLA Typing for Axial Spondyloarthritis	HLA-B27 DNA Typing (Quest Diagnostics)	81374	M04.8, M04.9, M05, M06, M45	7, 8, 9
Other Covered Immune, Autoimmune, and Rheumatoid Disorders				
Other Covered Immune Disorders	See below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408		3, 4, 5, 6

OTHER RELATED POLICIES

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

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

back to top

COVERAGE CRITERIA

PERIODIC FEVER SYNDROME

Periodic Fever Syndromes 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, tumor necrosis factor receptor-associated periodic fever [TRAPS]) via multigene panel (81404, 81479) is considered **investigational** for all other indications.

back to top

RHEUMATOID ARTHRITIS BIOMARKER ACTIVITY PANELS

Rheumatoid Arthritis Biomarker Activity Panels

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

back to top

GENETIC RHEUMATOID ARTHRITIS ALGORITHMIC TESTS

Tumor Necrosis Factor Inhibitor (TNFi) Treatment

I. The use of genetic rheumatoid arthritis algorithmic tests to determine appropriateness of TNFi treatment (ie, PrismRA) (81599, 81479) is considered **investigational**.

back to top

HLA TYPING FOR AXIAL SPONDYLOARTHRITIS

I. The use of HLA-B27 typing (81374) to confirm or establish the diagnosis of axial spondyloarthritis is considered **medically necessary** when:

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

B. HLA-B27 results are needed to establish a diagnosis of axial spondyloarthritis.

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

back to top

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* consistent with the disorder (the list is not meant to be comprehensive, see II below):

A. Agammaglobulinemia: X-Linked and Autosomal Recessive
B. Autoimmune Lymphoproliferative Syndrome (ALPS)
C. Chronic Granulomatous Disease (CGD)
D. Common Variable Immune Deficiency (CVID)
E. Complement Deficiencies
F. Congenital Neutropenia Syndromes (e.g., *ELANE*-Related Neutropenia)
G. Familial Hemophagocytic Lymphohistiocytosis (HLH)

H. Hyper IgE Syndrome (HIES)
I. Hyper IgM Syndromes
J. Leukocyte Adhesion Deficiency (LAD)
K. NEMO Deficiency Syndrome
L. Severe Combined Immune Deficiency (SCID) and Combined Immune Deficiency
M. WHIM Syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis)
N. Wiskott-Aldrich Syndrome

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).

*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.

back to top

PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

DEFINITIONS

1. **Multibiomarker disease activity (MBDA) tests:** Approach that uses serum biomarkers to 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.

back to top

BACKGROUND AND RATIONALE

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

In 2019, The American College of Rheumatology 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.

ter Haar, et. al 2015

An expert committee of pediatric and adult rheumatologists convened and created a set of recommendations for the management of autoinflammatory disease, using the European League Against Rheumatism standard operating procedure, that included the following regarding genetic evaluation:

- Management of patients with AID should ideally be guided by a multidisciplinary team in a tertiary centre with expertise in AID, with access to genetic counseling (Expert opinion, based on level 4 evidence). (p. 1637)

There is insufficient evidence to support the use of this test. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified

Genetic Rheumatoid Arthritis Algorithmic Tests - Genetic Rheumatoid Arthritis for Tumor Necrosis Factor Inhibitor (TNFi) Treatment

Concert Genetics Evidence Review for Coverage Determination

The 2021 statement for the treatment of rheumatoid arthritis by the American College of Rheumatology includes recommendations for genetic testing to determine the effectiveness of TNFi therapy. The peer-reviewed published clinical utility studies show there is the possibility of management changes and improved outcomes based on results of PrismRA. However, these studies have flaws, such as concern for investigator group bias and lack of randomization, as well as limited study population. Additional real-world evidence on larger and more diverse populations is needed.

At the present time, Genetic Algorithmic Rheumatoid Arthritis Tests for Anti-Tumor Necrosis Factor Inhibitor (TNFi) Treatment tests such as PrismRA have insufficient evidence in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

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, 2023

"HLA-B27 can be useful to increase the confidence of a diagnosis of axSpA [axial spondyloarthritis] in patients in whom plain radiographs or magnetic resonance imaging (MRI) also exhibit abnormalities consistent with axSpA. HLA-B27 can also be used as a screening tool in primary care in patients presenting with chronic back pain or IBP [inflammatory back pain] suspected by the primary clinician as having a significant probability for axSpA, depending upon the availability and the costs of local HLA-B27 testing. The probability of axSpA goes up from 5 to about 30 percent in chronic back pain patients and from 14 to about 60 percent in patients with IBP if HLA-B27 is positive Thus, these patients might warrant further evaluation, including imaging."

back to top

REFERENCES:

1. England BR, Tiong BK, Bergman MJ, et al. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken). 2019;71(12):1540-1555. doi:10.1002/acr.24042
2. ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis. 2015;74(9):1636-1644. doi:10.1136/annrheumdis-2015-207546
3. Immune Deficiency Foundation. "Specific PI Diagnoses". 2020. https://primaryimmune.org/specific-pi-diagnoses. Accessed February 22, 2021.
4. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
5. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
6. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
7. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. Jun 2009;68(6):777-83. doi:10.1136/ard.2009.108233
8. Akgul O, Ozgocmen S. Classification criteria for spondyloarthropathies. World J Orthop. 2011;2(12):107-115. doi:10.5312/wjo.v2.i12.07
9. Yu D, van Tubergen A. Diagnosis and differential diagnosis of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. In: Romain PL, ed. UpToDate. UpToDate; 2022. Accessed October 23, 2023. https://uptodate.com/contents/diagnosis-and-differential-diagnosis-of-axial-spondyloarthritis-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-in-adults
10. Concert Genetics. Evidence Review for Coverage Determination for Genetic Algorithmic Rheumatoid Arthritis Tests for TNFi treatment. Published 9/1/2023.
11. Soon GS, Laxer RM. Approach to recurrent fever in childhood. Can Fam Physician. 2017;63(10):756-762.

back to top

Note: Medica uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

Medica Original Effective Date: February 20, 2023
- Concert Genetics Effective Date: January 01, 2023 (V.1.2022)

Medica Re-Review Date(s):
- June 21, 2023

- Concert Genetics Effective Date: July 01, 2023 (V.2.2023)
- December 20, 2023
  - Concert Genetics Effective Date: January 01, 2024 (V.1.2024)
- June 19, 2024
  - Concert Genetics Effective Date: July 01, 2024 (V.2.2024)

© 2023-2024 Medica.