GENETIC TESTING: IMMUNE, AUTOIMMUNE, AND RHEUMATOID DISORDERS

OVERVIEW

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, 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

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

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, Sequencing and Deletion/Duplication (ARUP Laboratories)	81402, 81404, 81479	M04.1, R50.9	4, 5

	Periodic Fever/Autoinflammatory Disorders NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) Invitae Periodic Fever Syndromes Panel (Invitae)			
Biochemical Rheumatoid Arthritis Tests				
Biochemical Rheumatoid Arthritis Tests	Vectra® DA (LabCorp) Vectra® (LabCorp)	81490	M05.00-M06.9	1, 2, 3, 6
HLA Typing for Ankylosing Spondylitis, Rheumatoid Arthritis, and Autoimmune Disorders				
HLA Typing for Ankylosing Spondylitis, Rheumatoid Arthritis, and Autoimmune Disorders	HLA-B*27 Antigen Typing HLA-B*51 Antigen Typing HLA-DRB1 Typing	81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383	M04.8, M04.9, M05, M06, M45	11, 12, 13, 14
Other Covered Immune, Autoimmune, and Rheumatoid Disorders				
Other Covered Immune Disorders	See below	81400-81408		7, 8, 9, 10

OTHER RELATED POLICIES

This policy document provides coverage criteria for Genetic Testing for Immune 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 Testing*** for coverage criteria related to immune disorders not specifically addressed in the policy reference table.

COVERAGE CRITERIA

PERIODIC FEVER SYNDROME

Periodic Fever Syndrome Multigene Panel

I. Genetic testing for periodic fever syndromes (e.g., Familial Mediterranean Fever, TRAPS) via multigene panel (81402, 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 (e.g., Familial Mediterranean Fever, TRAPS) via multigene panel (81402, 81404, 81479) is considered **investigational** for all other indications.

back to top

BIOCHEMICAL RHEUMATOID ARTHRITIS TESTS

Rheumatoid Arthritis Biomarker Tests

I. The use of multibiomarker disease activity scores for rheumatoid arthritis (eg, Vectra® DA) (81490) is considered **investigational**.

back to top

HLA TYPING FOR ANKYLOSING SPONDYLITIS, RHEUMATOID ARTHRITIS, AND AUTOIMMUNE DISORDERS

I. The use of HLA-B27 typing (81374, 81381) to confirm or establish the diagnosis of ankylosing spondylitis, or another spondyloarthropathies, is considered **medically necessary** when:

   A. The member has clinical or radiographic features of ankylosing spondylitis, or another spondyloarthropathy, **AND**

   B. HLA-B27 results are needed to establish a diagnosis of ankylosing spondylitis, or another spondyloarthropathy.

II. The use of HLA typing (81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383) for ankylosing spondylitis, rheumatoid arthritis, and autoimmune disorders 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 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

NOTES AND DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
    a. **First-degree relatives** are parents, siblings, and children
    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
    c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Multibiomarker disease activity (MBDA)** tests for rheumatoid arthritis are an approach that uses serum biomarkers to measure rheumatoid arthritis disease activity.
3. **Unexplained fever** (or fever of unknown origin) is defined as 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

American College of Rheumatology

In its 2019 guidelines on the treatment of rheumatoid arthritis, 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 and that includes the leptin-adjusted MBDA score (now called the "adjusted MBDA score") 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 counselling (Expert opinion, based on level 4 evidence).

Rudwaleit et al 2009

“Refinement of the candidate criteria resulted in new ASAS 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").”

Akgul and Ozgocmen, 2011

“HLA B-27 positivity is extremely relevant to the early diagnosis of SpA. Five to 10% of the population are HLA B-27 positive and in patients with AS and SpA the positivity of HLA B-27 changes to 70% to 95% and nearly 70%, respectively.”

Yu and van Tubergen, UpToDate, 2020

“HLA-B27 can be useful to increase the confidence of a diagnosis of axSpA 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 suspected by the primary clinician as having a significant probability for axSpA, depending upon the availability and the costs of local HLA-B27 testing. Several diagnostic criteria sets include HLA-B27, including the Amor criteria, and ASAS axial and peripheral spondyloarthritis criteria.”

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. Crescendo Biosciences, Inc. Vectra Technical Specifications. May 2019. https://vectrascore.com/clinicians/vectra-test-description/. Accessed November 2, 2020.
3. Curtis JR, Xie F, Yang S, Danila MI, Owensby JK, Chen L. Uptake and Clinical Utility of Multibiomarker Disease Activity Testing in the United States. J Rheumatol. 2019;46(3):237-244. doi:10.3899/jrheum.180071
4. Shohat M. Familial Mediterranean Fever. 2000 Aug 8 [Updated 2016 Dec 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1227/
5. 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
6. Fleischmann R. 2019 update of the American College of Rheumatology-recommended rheumatoid arthritis disease activity measures: comment on the article by England et al. Arthritis Care Res (Hoboken). 2020;72(5):736. doi:10.1002/acr.24153
7. Immune Deficiency Foundation. “Specific PI Diagnoses”. 2020. https://primaryimmune.org/specific-pi-diagnoses. Accessed February 22, 2021.
8. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
9. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
10. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
11. Hwang MC, Ridley L, Reveille JD. Ankylosing spondylitis risk factors: a systematic literature review [published online ahead of print, 2021 Mar 22]. Clin Rheumatol. 2021;10.1007/s10067-021-05679-7. doi:10.1007/s10067-021-05679-7
12. 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
13. Akgul O, Ozgocmen S. Classification criteria for spondyloarthropathies. *World J Orthop*. 2011;2(12):107-115. doi:10.5312/wjo.v2.i12.07

14. 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; 2021. Accessed December 15, 2021. https://uptodate.com/contents/diagnosis-and-differential-diagnosis-of-axial-spondyloarthritis-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-in-adults

back to top