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
Known Familial Variant Analysis for Immune, Autoimmune, and Rheumatoid Disorders				
Known Familial Variant Analysis for Immune, Autoimmune, and Rheumatoid	Targeted Mutation Analysis for a Known Familial Variant	81403		12

Disorders				
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)			
	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 Algorithmic Rheumatoid Arthritis Tests				
Genetic Rheumatoid Arthritis for Tumor Necrosis Factor inhibitor (TNFi) Treatment	PrismRA (Scipher Medicine)	81599, 81479	M05, M06, M08	10
HLA Typing for Ankylosing Spondylitis, Rheumatoid Arthritis, and Autoimmune Disorders				
HLA Typing for Ankylosing Spondylitis, Rheumatoid Arthritis, and Autoimmune Disorders	HLA-B27 DNA Typing (Quest Diagnostics)	81374	M04.8, M04.9, M05, M06, M45	7, 8, 9
	HLA-B51 Behcet's Disease Association Test (Quest Diagnostics)			
	HLA DRB1 Typing, High Resolution (Quest Diagnostics)	81382		
Other Covered Immune, Autoimmune, and Rheumatoid Disorders				
Other Covered Immune Disorders	See below	81400-81408		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 Testing*** for coverage criteria related to immune disorders not specifically addressed in the policy reference table.

COVERAGE CRITERIA

KNOWN FAMILIAL VARIANT ANALYSIS FOR IMMUNE, AUTOIMMUNE, AND RHEUMATOID DISORDERS

I. Targeted mutation analysis for a known familial variant (81403) for an immune, autoimmune, and rheumatoid disorder is considered **medically necessary** when:

   A. The member has a close relative with a known pathogenic or likely pathogenic variant causing the condition.

II. Targeted mutation analysis for a known familial variant (81403) for an immune, autoimmune, and rheumatoid disorder is considered **investigational** for all other indications.

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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.

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RHEUMATOID ARTHRITIS BIOMARKER ACTIVITY PANELS

Rheumatoid Arthritis Biomarker Activity Panels

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

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GENETIC ALGORITHMIC RHEUMATOID ARTHRITIS TESTS

Tumor Necrosis Factor Inhibitor (TNFi) Treatment

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

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

I. The use of HLA-B27 typing (81374, 81382) 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 (81374, 81382) for ankylosing spondylitis, rheumatoid arthritis, and autoimmune disorders is considered **investigational** for all other indications.

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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.

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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 [FUO]) 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.

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BACKGROUND AND RATIONALE

Known Familial Variant Analysis for Immune, Autoimmune, and Rheumatoid Disorders

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

> Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

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." (page 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 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, which 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 counselling (Expert opinion, based on level 4 evidence). (p. 1637)

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

Neither the 2015 nor the 2021 recommendations for the treatment of rheumatoid arthritis by the American College of Rheumatology include 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, lack of blinding that could affect results, and only a single study that provides real world evidence showing changed management based on PrismRA results alone.

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 Ankylosing Spondylitis, Rheumatoid Arthritis, and Autoimmune Disorders

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, 2020

“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. Several diagnostic criteria sets include HLA-B27, including the Amor criteria, and ASAS [Assessment of SpondyloArthritis International Society] axial and peripheral spondyloarthritis criteria."

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