Medica Central Coverage Policy

Policy Name:	**Genetic Testing - Specialty Testing: Immunology & Rheumatology**
Effective Date:	**July 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central 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 this general information 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 these 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 may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

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

OVERVIEW

This policy addresses the use of tests for autoimmune conditions and inherited immunodeficiency disorders.

For additional information see the Rationale section.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage.

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.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TEST (LABS)	COMMON BILLING CODES	REF
Celiac Disease			
HLA-DQ Genotyping Analysis	Celiac *HLA DQ* Association (Labcorp)	81375, 81376, 81377, 81382, 81383, K90.0, R10.0-R10.13, R10.3-R10.829, R10.84-R10.9	1, 2, 3
HLA Typing for Axial Spondyloarthritis			
HLA Typing for Axial Spondyloarthritis	*HLA-B27* DNA Typing (Quest Diagnostics)	81374, M04.8, M04.9, M05, M06, M45	9, 10, 11
Periodic Fever Syndrome			
Periodic Fever Syndromes Multigene Panel	Periodic Fever Syndromes Panel (Invitae)	81404, 81479, M04.1, R50.9, A68.9	12
	Periodic Fever Syndromes Panel (PreventionGenetics, part of Exact Sciences)		
	Periodic Fever Syndromes Panel (7 genes) (GeneDx)		
Rheumatoid Arthritis			
Evidence-Based Rheumatoid Arthritis Algorithmic Tests	PrismRA - 0456U (Scipher Medicine)	0456U, M05, M06, M08	13
Emerging Evidence Rheumatoid Arthritis Algorithmic Tests	Vectra (LabCorp)	81490, M05.00-M06.9	4
	Vectra with CV Risk (LabCorp)		
Other Covered Immune, Autoimmune, and Rheumatoid Disorders			
Other Covered Immune, Autoimmune, and Rheumatoid Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	5, 6, 7, 8

RELATED POLICIES

This policy document provides coverage criteria for immunology and rheumatology testing. Please refer to:

- ***Specialty Testing: Multisystem Genetic Conditions*** for coverage criteria related to diagnostic tests for genetic disorders that affect multiple organ systems (e.g. whole exome and genome sequencing, chromosomal microarray, and multigene panels for broad phenotypes).
- ***General Approach to Laboratory Testing*** for coverage criteria related to immunology and rheumatology, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

CELIAC DISEASE

HLA-DQ Genotyping Analysis

I. *HLA-DQA1* and *HLA-DQB1* genotyping analysis to rule out celiac disease (CD) is considered **medically necessary** when:

   A. The member is being evaluated for celiac disease, **AND**

   B. The member meets at least one of the following:

      1. Had an inconclusive serology (antibody) result, **OR**
      2. Had an inconclusive histology (biopsy) result, **OR**
      3. Started a gluten-free diet before evaluation for celiac disease, **AND**

   C. *HLA-DQA1* and *HLA-DQB1* genotyping analysis has not been previously performed.

II. *HLA-DQA1* and *HLA-DQB1* genotyping analysis to rule out celiac disease is considered **investigational** for all other indications.

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HLA TYPING FOR AXIAL SPONDYLOARTHRITIS

HLA Typing for Axial Spondyloarthritis

I. HLA-B27 typing for evaluation of axial spondyloarthritis is considered **medically necessary** when:

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

II. HLA-B27 typing for evaluation of axial spondyloarthritis 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 a multigene panel 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 a multigene panel is considered **investigational** for all other indications.

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RHEUMATOID ARTHRITIS

Evidence-Based Rheumatoid Arthritis Algorithmic Tests

I. Rheumatoid arthritis algorithmic tests (PrismRA) with sufficient evidence of clinical validity and utility to determine appropriateness of TNFi treatment are considered **medically necessary** when:

   A. The member is age 18 or older, **AND**

   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**

    a) The member 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. Rheumatoid arthritis algorithmic tests (PrismRA) with sufficient evidence of clinical validity and utility to determine appropriateness of TNFi treatment are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

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Emerging Evidence Rheumatoid Arthritis Algorithmic Tests

I. Rheumatoid arthritis algorithmic tests (Vectra) with insufficient evidence of clinical validity are considered **investigational** for all indications.

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OTHER COVERED IMMUNE, AUTOIMMUNE, AND RHEUMATOID DISORDERS

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 (*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 the *General Approach to Laboratory 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.

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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.

RATIONALE

HLA-DQ Genotyping Analysis

American College of Gastroenterology (ACG)

The guidelines from the American College of Gastroenterology (2023) addressing the diagnosis and management of celiac disease (CD) stated that genetic testing for CD- compatible HLA haplotype is not required for diagnosis in all cases but may be helpful in selected situations such as in the context of serology-histology discrepancy. If negative, celiac disease is ruled out. HLA testing is also central to the approach to CD testing for individuals who have already started a GFD (gluten free diet) before evaluation; in the presence of a CD-compatible haplotype, a gluten challenge can be offered (p. 63-64).

American Gastroenterological Association

A clinical practice update on diagnosis and monitoring of celiac disease (2019) states that HLA testing has value in its negative predictive value to rule out CD in patients who are seronegative but have histologic changes or did not have serology at the time of diagnosis. HLA testing may be reserved for second line evaluation of patients with an equivocal diagnosis (inconclusive serology, histology or prior gluten free diet).

U.S. Preventive Services Task Force

The US Preventive Service Task Form (2017) released guidelines on screening adults and children for CD. These guidelines reviewed the use of tTG IgA testing followed by an intestinal biopsy to screen asymptomatic patients. Genotype testing was not discussed. The overall conclusion of this review was that the current balance of evidence was insufficient to assess benefits and harms resulting from screening for CD (p. 1252).

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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

HLA-B27 testing can be helpful when radiographs or MRI show findings that are consistent with axSpA; a positive result can increase the probability of having axSpa to 80-90%. Negative testing would 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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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).

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Evidence-Based Rheumatoid Arthritis Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled MolDX: 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."

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Emerging Evidence Rheumatoid Arthritis Algorithmic Tests

American College of Rheumatology (ACR)

The ACR updated guidelines in 2019 regarding their recommendation for Rheumatoid Arthritis (RA) disease activity measures. They identified 11 measures of disease activity that fulfilled the studies minimum standard for regular use in most clinical settings (listed in Table 4 on page 1552), and this list included the Multibiomarker Disease Activity Score (MBDA score, Vectra DA).

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.

Concert Note

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.

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DEFINITIONS

1. **Unexplained fever** is 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.

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

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Medica Central Coverage Policy

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