Revision log
Coding Implications

CONCERT GENETIC TESTING: IMMUNE, AUTOIMMUNE, AND RHEUMATOID DISORDERS

See Important Reminder at the end of this policy for important regulatory and legal information.

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. 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.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are

included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Periodic Fever Syndrome				
Periodic Fever Syndromes Multigene Panel	Periodic Fever Syndromes Panel (Invitae)	81404, 81479	M04.1, R50.9, A68.9	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	1
	Vectra with CV Risk (LabCorp)			
Rheumatoid Arthritis TNFi Treatment Response Algorithmic Tests	PrismRA (Scipher Medicine)	0456U	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	6, 7, 8
Other Covered Immune, Autoimmune, and Rheumatoid Disorders				
Other Covered Immune,	See below	81400, 81401, 81402, 81403,		2, 3, 4, 5

Autoimmune, and Rheumatoid Disorders		81404, 81405, 81406, 81407, 81408		

OTHER RELATED POLICIES

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

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

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CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related 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/enrollee 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

Rheumatoid Arthritis Biomarker Activity Panels

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

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Rheumatoid Arthritis TNFi Treatment Response Algorithmic Tests

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

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

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

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

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

E. One of the following:

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

2. The member/enrollee 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/enrollee 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 appropriateness of TNFi treatment (PrismRA) (0456U) is considered **investigational** for all other indications.

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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/enrollee has clinical or radiographic features of axial spondyloarthritis**.**

II. The use of HLA-B27 typing (81374) for evaluation of axial spondyloarthritis 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/enrollee 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 *General Approach to Genetic and Molecular Testing* (see policy for 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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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.

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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 (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.

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.

Rheumatoid Arthritis TNFi Treatment Response 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."

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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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Policy Reference Table; under Other Covered Immune, Autoimmune, and Rheumatoid Disorders: added "81401, 81402, 81403, 81404, 81405, 81406, 81407,". For Other Related Policies: added "and Molecular". For Other Covered Immune, Autoimmune, and Rheumatoid Disorders: added "and Molecular". For Background and Rationale; under Known Familial Variant Analysis for Immune, Autoimmune, and Rheumatoid Disorders: replaced "inheritance patterns with "genetic testing"; under Rheumatoid Arthritis Biomarker Activity Panels: removed "its 2019 guidelines…" and added "2019".	10/23	10/23
Semi-annual review. Updated title to reflect V2.2024 version. In Known Familial Variant Analysis for Immune, Autoimmune, and Rheumatoid Disorders criteria, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate criteria for known familial variant tests. In HLA Typing for Axial Spondyloarthritis criteria, updated criteria to clarify name of the condition. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	04/24	04/24
Semi-annual review. Updated title to reflect V1.2025 version. Rheumatoid Arthritis Biomarker Activity Panels: Streamlined portions of Background and Rationale section for brevity; References updated in Policy Reference Table to better reflect the information supporting the criteria set. Rheumatoid Arthritis TNFi Treatment Response Algorithmic Tests: Coverage status changed from non-covered to covered based on LCD guidelines; Added PLA code	11/24	11/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date
0456U to Policy Reference Table; Streamlined portions of Background and Rationale section for brevity; Updated References. HLA Typing for Axial Spondyloarthritis: Removed criterion that required HLA-B27 results to establish a diagnosis of axial spondyloarthritis as this criterion is not applicable to the test type; Reworded criteria for improved clarity. Other Covered Immune, Autoimmune, and Rheumatoid Disorders: Removed "Common Variable Immune Deficiency (CVID)" from condition list for brevity given the number of genes associated with this condition; The condition list is not intended to be comprehensive; Added genes for each of the listed conditions for further clarity; Updated GeneReviews copyright dates in Reference list.		

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. Immune Deficiency Foundation. “Specific PI Diagnoses”. 2020. https://primaryimmune.org/specific-pi-diagnoses. Accessed April 19th, 2024.
3. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
4. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
5. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
6. 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
7. Akgul O, Ozgocmen S. Classification criteria for spondyloarthropathies. World J Orthop. 2011;2(12):107-115. doi:10.5312/wjo.v2.i12.07
8. Yu D, van Tubergen A. Diagnosis and differential diagnosis of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Accessed March 21, 2024. https://uptodate.com/contents/diagnosis-and-differential-diagnosis-of-axial-

spondyloarthritis-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-in-adults
9. Soon GS, Laxer RM. Approach to recurrent fever in childhood. Can Fam Physician. 2017;63(10):756-762.
10. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis (LCD L39424). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39424

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible

for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.

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