Clinical Policy: Genetic Testing Immune, Autoimmune, and Rheumatoid Disorders

Reference Number: CP.MP.226
Date of Last Revision: 02/22

Coding Implications
Revision Log

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

Description

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.

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

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81402,81404, 81479	Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication (ARUP Laboratories) Periodic Fever/Autoinflammatory Disorders NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) Invitae Periodic Fever Syndromes Panel (Invitae	Periodic Fever Syndromes Multigene Panel	M04.1, R50.9
81490	Vectra® DA (Crescendo Bioscience) Vectra® (Crescendo Bioscience)	Biochemical Rheumatoid Arthritis Tests	M05.00-M06.9

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383	HLA-B*27 Antigen Typing HLA-B*51 Antigen Typing HLA-DRB1 Typing	HLA Typing for Ankylosing Spondylitis, Rheumatoid Arthritis, and Autoimmune Disorders	M04.8, M04.9, M05, M06, M45
81400-81408	See below	Other Immune Disorders	N/A

This policy document provides criteria for Genetic Testing for Immune Disorders. Please refer to:

- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to genetic disorders that affect multiple organ systems
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to immune disorders not specifically addressed in the policy reference table.

Policy/Criteria

Periodic Fever Syndrome

I. It is the policy of health plans affiliated with Centene Corporation® that genetic testing for periodic fever syndromes (e.g., Familial Mediterranean Fever, TRAPS) via multigene panel (81402, 81404, 81479) is considered **medically necessary** when meeting both of the following:

   A. The member/enrollee has three or more episodes of unexplained fever in a six-month period, occurring at least seven days apart,

   B. Common causes of fever have been ruled out, including viral or bacterial infection.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support genetic testing for periodic fever syndromes (e.g., Familial Mediterranean Fever, TRAPS) via multigene panel (81402, 81404, 81479) for all other indications.

Biochemical Rheumatoid Arthritis Tests

Rheumatoid Arthritis Biomarker Tests

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of multibiomarker disease activity scores for rheumatoid arthritis (eg, Vectra® DA) (81490).

HLA Typing for Ankylosing Spondylitis, Rheumatoid Arthritis, and Autoimmune Disorders

I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting both of the following:

   A. The member/enrollee has clinical or radiographic features of ankylosing spondylitis, or another spondyloarthropathy,

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support 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 for all other indications.

Other Immune, Autoimmune and Rheumatoid Disorders

The following is a list of conditions that have a known genetic association. Due to their relative rareness, these genetic tests may be appropriate to establish or confirm a diagnosis.

I. It is the policy of health plans affiliated with Centene Corporation® that 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
   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. It is the policy of health plans affiliated with Centene Corporation® that 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 *CP.MP.222 General Approach to Genetic Testing* (see policy for 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.

Notes and Definitions

1. Close relatives include first, second, and third degree blood relatives:
    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.

Background

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.

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).

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 2021, 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.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

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

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, 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.