Concert Genetic Testing: ~~Immune, Autoimmune,~~Immunology and ~~Rheumatoid Disorders~~ Rheumatology

Reference Number: LA.CP.CG.10
Date of Last Revision ~~06/24~~03/26
Revision Log

Coding implications

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.~~

~~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.~~

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

For additional information see the Rationale section.

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~~2024, 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 and may not support medical necessity. 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, 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. Please see the Concert Platform for additional registered tests.

~~**NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.**~~

The tests and associated laboratories and CPT 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 Genetics Platform for a comprehensive list of registered tests.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

~~Criteria Sections~~	~~Example Tests (Labs)~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~Ref~~	
~~**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, part of Exact Sciences)~~				
	~~Periodic Fever Syndromes Panel (7 genes) (GeneDx)~~				
~~**Rheumatoid Arthritis Biomarker Activity Panels**~~					

~~Criteria Sections~~	~~Example Tests (Labs)~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~Ref~~	
~~Rheumatoid Arthritis Biomarker Activity Panels~~	~~Vectra (Labcorp)~~ ~~Vectra with CV Risk (Labcorp)~~		~~81490*~~	~~M05.00-M06.9~~	~~1,~~
~~**Genetic Rheumatoid Arthritis Algorithmic Tests**~~					
~~Genetic Rheumatoid Arthritis for Tumor Necrosis Factor inhibitor (TNFi) Treatment~~	~~PrismRA (Scipher Medicine)~~		~~81599*, 81479~~	~~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~~	~~7,~~
~~**Other Covered Immune, Autoimmune, and Rheumatoid Disorders**~~					
~~Other Covered Immune Disorders~~	~~See below~~	~~81400*, 81401*, 81402*, 81403*, 81404*, 81405*, 81406*, 81407*,~~		~~3, 4, 5, 6~~	

~~Criteria Sections~~	~~Example Tests (Labs)~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~Ref~~
		~~81408*~~		

~~OTHER~~

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 criteria for ~~Genetic Testing for Immune, Autoimmune, and Rheumatoid Disorders.~~immunology and rheumatology testing. Please refer to:

- ***~~Genetic~~Specialty* Testing: Multisystem *~~Inherited Disorders, Intellectual Disability, and Developmental Delay~~Genetic Conditions*** for 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).
- ***~~Genetic Testing:~~ General Approach to ~~Genetic and Molecular~~Laboratory Testing*** for criteria related to ~~immune disorders~~immunology and rheumatology, including known familial variant testing, that is not specifically ~~addressed~~discussed in ~~the~~this or another non-general policy ~~reference table~~.

~~back to top~~back to top

CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related 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/enrollee is being evaluated for celiac disease, **AND**

B. The member/enrollee 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. Current evidence does not support *HLA-DQA1* and *HLA-DQB1* genotyping analysis to rule out celiac disease for all other indications.

view rationale

back to top

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

II. Current evidence does not support HLA-B27 typing for evaluation of axial spondyloarthritis for all other indications.

view rationale

back to top

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 ~~(81404, 81479)~~ is considered **medically necessary** when:

A. The member/enrollee has three or more episodes of ~~unexplained fever~~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~~Current evidence does not support *g*enetic 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 ~~(81404, 81479) is considered **investigational**~~ for all other indications.

~~back to top~~

view rationale

back to top

RHEUMATOID ARTHRITIS ~~BIOMARKER ACTIVITY PANELS~~

Evidence-Based Rheumatoid Arthritis ~~Biomarker Activity Panels~~Algorithmic Tests

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

~~back to top~~

~~GENETIC RHEUMATOID ARTHRITIS ALGORITHMIC TESTS~~

~~Tumor Necrosis Factor Inhibitor (TNFi) Treatment~~

~~I.~~ ~~The use of genetic rheumatoid~~Rheumatoid arthritis algorithmic tests (PrismRA) with sufficient evidence of clinical validity and utility to determine appropriateness of TNFi treatment ~~(ie, PrismRA) (81599, 81479) is considered **investigational**.~~

~~back to top~~

are ~~HLA TYPING FOR AXIAL SPONDYLOARTHRITIS (ankylosing spondylitis and nonradiographic axial spondyloarthritis)~~

I. ~~The use of HLA-B27 typing (81374) to confirm or establish the diagnosis of axial spondyloarthritis is~~ considered **medically necessary** when:

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

~~A.~~ The member/enrollee has ~~clinical or radiographic features of axial spondyloarthritis, **AND**~~

~~A.~~B. ~~HLA-B27 results are needed to establish~~ a diagnosis of ~~axial spondyloarthritis.~~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 ~~use of HLA typing (81374~~member/enrollee has not yet initiated a biologic or targeted synthetic therapy (b/tDMARD) for ~~axial spondyloarthritis is considered **investigational**~~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**

a) The member/enrollee 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. Current evidence does not support *r*heumatoid arthritis algorithmic tests (PrismRA) with sufficient evidence of clinical validity and utility to determine appropriateness of TNFi treatment for all other indications where clinical validity and utility have not been demonstrated.

~~back to top~~

view rationale

back to top

Emerging Evidence Rheumatoid Arthritis Algorithmic Tests

I. Current evidence does not support rheumatoid arthritis algorithmic tests (Vectra).

view rationale

back to top

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/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*)

~~A.~~ Chronic Granulomatous Disease (CGD)

C. ~~Common Variable Immune Deficiency (CVID~~ *(CYBA, CYBC1, NCF1, NCF2,* and *NCF4, CYBB)*

D. Complement Deficiencies

E. Congenital Neutropenia Syndromes (e.g., *ELANE*-Related Neutropenia) *(ELANE, HAX1)*

~~B. Familial Hemophagocytic Lymphohistiocytosis (HLH)~~
F. Familial Hemophagocytic Lymphohistiocytosis (HLH) (*PRF1*, *STX11*, *STXBP2*, or *UNC13D*)

~~F.~~G. Hyper IgE Syndrome (HIES) *(STAT3)*

~~G.~~H. Hyper IgM Syndromes *(CD40LG)*

~~H.~~I. Leukocyte Adhesion Deficiency (LAD) *(CD18, Kindlin-3, ITGB2)*

~~I.~~J. NEMO Deficiency Syndrome *(NEMO*, aka *IKK gamma* or *IKKG)*

~~J.~~K. Severe Combined Immune Deficiency (SCID) and Combined Immune Deficiency *(IL2RG)*

~~K.~~L. WHIM Syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) *(CXCR4)*

~~L.~~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 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.

~~back to top~~

~~DEFINITIONS~~

~~1. **Multibiomarker disease activity (MBDA) tests:** Approach that uses serum biomarkers to measure rheumatoid arthritis disease activity.~~

~~2.~~1. **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.~~

~~BACKGROUND AND~~ back to top

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**~~

HLA-DQ Genotyping Analysis

American College of ~~Rheumatology~~Gastroenterology (ACG)

~~In 2019, 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, 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 counseling (Expert opinion, based on level 4 evidence). (p. 1637)~~

~~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.~~

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

~~*Concert Genetics Evidence Review for Coverage Determination*~~

~~The 2021 statement for the treatment of rheumatoid arthritis by the American College of Rheumatology includes 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 and lack of randomization, as well as limited study population. Additional real-world evidence on larger and more diverse populations is needed.~~

~~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.~~

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).

back to top

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, ~~2023~~2024

~~“HLA-B27 can be useful to increase the confidence of a diagnosis of axSpA [axial spondyloarthritis] in patients in whom plain~~HLA-B27 testing can be helpful when radiographs or

~~magnetic resonance imaging (~~MRI~~) also exhibit abnormalities~~ 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 ~~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~~ with a significant probability ~~for axSpA, depending upon the availability and the costs of local HLA-B27 testing. The probability of~~ of axSpA ~~goes up from 5 to about 30 percent in chronic back pain patients and from 14 to about 60 percent in patients with IBP if HLA-B27 is positive Thus, these patients might warrant further~~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.

back to top

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 ~~imaging."~~periodic fever syndromes–should be considered" (p. 758).

back to top

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:

"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."

back to top

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.

back to top

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.

~~back to top~~

back to top

Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Converted corporate to local policy.	09/23	11/27/23	
Semi-annual review. 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”. Fo 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”	12/23	2/27/24	
Semi-annual review. 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.	06/24	5/13/2025	6/13/2025

~~**References**~~

Annual review. Policy title changed from Concert Genetic Testing: Immune, Autoimmune, and Rheumatoid Disorders to Concert Genetic Testing: Immunology and Rheumatology. "Rheumatoid Arthritis Biomarker Activity Panels" criteria title changed to to "Emerging Evidence Rheumatoid Arthritis Algorithmic Tests." Minor rewording without clinical significance. HLA-DQ Genotyping Analysis criteria moved from Concert Genetic Testing: Gastroenterologic Disorders to this policy. “Investigational” policy statements changed to note that “current evidence does not support…”	03/26	

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~~back to top~~

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back to top

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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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 LHCC has no control or right of control. Providers are not agents or employees of LHCC.