Coding Implications
Revision log

CONCERT NON-GENETIC IMMUNOLOGY AND RHEUMATOLOGY TESTING

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

OVERVIEW

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

For additional information see the Rationale and References 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.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TEST (LABS)	SUPPORT
Celiac Disease		
HLA-DQ Genotyping Analysis	Celiac *HLA DQ* Association (LabCorp)	Rationale/ References
Periodic Fever Syndrome		

Periodic Fever Syndromes Multigene Panel	Periodic Fever Syndromes Panel (Invitae Corporation)	Rationale/ References
	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 (Scipher Medicine)	Rationale/ References
Emerging Evidence Rheumatoid Arthritis Algorithmic Tests	Vectra (LabCorp)	Rationale/ References
	Vectra with CV Risk (LabCorp)	
Antinuclear Antibody (ANA) Tests		
Antinuclear Antibody (ANA) Tests	Anti-Nuclear Antibodies (ANA), Serum (Mayo Clinic Laboratories)	Rationale/ References
	Anti-Nuclear Antibodies, Synovial Fluid (Mayo Clinic Laboratories)	
	ANA Multiplex, with Reflex to dsDNA (Quest Diagnostics)	
	Autoimmune Profile (LabCorp)	
Antinuclear Antibody (ANA) Subserology Tests	Antiextractable Nuclear Antigens (LabCorp)	Rationale/ References
	Extractable Nuclear Antigen Antibodies (Smith/RNP, Smith, SSA 52, SSA 60, and SSB) (ARUP Laboratories)	
	DNA (ds) Antibody, Crithidia IFA with Reflex to Titer (ARUP Laboratories)	

	DNA (ds) Antibody (Quest Diagnostics)	
	Smith (ENA) Antibody, IgG (ARUP Laboratories)	
Systemic Lupus Erythmatosus Algorithmic Tests		
Systemic Lupus Erythematosus Diagnostic and Prognostic Algorithmic Tests	Avise Lupus - 0312U (Exagen, Inc.)	Rationale/ References
	SLE-key Rule Out - 0062U (Veracis, Inc.)	
	aiSLE DX Disease Activity Index - 0446U (Progentec Diagnostics, Inc.)	
	aiSLE DX Flare Risk Index - 0447U (Progentec Diagnostics, Inc.)	
Rheumatoid Factor and/or Anti-Cyclic Citrullinated Peptide Antibody Tests		
Rheumatoid Factor and/or Anti-Cyclic Citrullinated Peptide Antibody Tests	Rheumatoid Factor (RF) (LabCorp)	Rationale/ References
	Anti-CCP (Cyclic Citrullinated Peptide) Antibodies, IgG and IgA, ELISA (LabCorp)	
	Rheumatoid Arthritis Diagnostic Panel 1 (Quest Diagnostics)	
Other Covered Immune, Autoimmune, and Rheumatoid Disorders		
Other Covered Immune, Autoimmune, and Rheumatoid Disorders	See list below	Additional References

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 the use of HLA-DQA1 and HLA-DQB1 genotyping analysis to rule out celiac disease 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 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. Current evidence does not support the use of 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 for all other indications.

view rationale
back to top

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** a maximum of one time for therapeutic selection 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**

         a) The member/enrollee is unresponsive/refractory or intolerant to a therapeutic dose.

II. Current evidence does not support the use of rheumatoid 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.

view rationale
back to top

Emerging Evidence Rheumatoid Arthritis Algorithmic Tests

I. Current evidence does not support the use of rheumatoid arthritis algorithmic tests (Vectra) with insufficient evidence of clinical validity for all indications.

view rationale
back to top

ANTINUCLEAR ANTIBODY (ANA) TESTS

Antinuclear Antibody (ANA) Tests

I. Antinuclear antibody (ANA) tests are considered **medically necessary** when:

   A. The member/enrollee has signs or symptoms of autoimmune/systemic rheumatic disease.

II. Current evidence does not support the use of antinuclear antibody (ANA) tests for all other indications, including but not limited to:

   A. Monitoring disease status

   B. Isolated fatigue

   C. Fibromyalgia

   D. Screening of asymptomatic individuals

view rationale
back to top

Antinuclear Antibody (ANA) Subserology Tests

I. Antinuclear Antibody (ANA) subserology tests[1] are considered **medically necessary** when:

   A. The member/enrollee has signs or symptoms of autoimmune/systemic rheumatic disease, **AND**

      1. The member/enrollee has a positive antinuclear (ANA) test[2], **OR**

   B. The member/enrollee has signs or symptoms of myositis, **OR**

   C. The member/enrollee is being monitored after diagnosis with an autoimmune/systemic rheumatic disease.

II. Current evidence does not support the use of Antinuclear Antibody (ANA) subserology tests for all other indications.

1. ANA subserologies include antibodies to dsDNA, histone, SS-A (Ro), SS-B (La), Smith, Smith/RNP, Scl-70, Jo-1, and centromeric proteins.
2. This includes but is not limited to ANA subserology testing performed as an automatic reflex from initial ANA testing; this approach is considered appropriate for initial workup of autoimmune/systemic rheumatic disease.

view rationale
back to top

SYSTEMIC LUPUS ERYTHEMATOSIS ALGORITHMIC TESTS

Systemic Lupus Erythematosus Diagnostic and Prognostic Algorithmic Tests

I. Current evidence does not support the use of systemic lupus erythematosus diagnostic and prognostic algorithmic tests for all indications.

view rationale
back to top

RHEUMATOID FACTOR AND/OR ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODY TESTS

Rheumatoid Factor and/or Anti-Cyclic Citrullinated Peptide Antibody Tests

I. Rheumatoid factor and/or anti-cyclic citrullinated peptide antibody tests are considered **medically necessary** when:

   A. The member/enrollee has synovitis of at least one joint, **AND**

   B. The member's/enrollee's synovitis is NOT better explained by another diagnosis (e.g., injury, overuse/strain, gout).

II. Current evidence does not support the use of rheumatoid factor and/or anti-cyclic citrullinated peptide antibody tests for all other indications, including but not limited to:

   A. Screening of asymptomatic individuals.

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 or targeted biomarker 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. Axial Spondyloarthritis

M. WHIM Syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) (*CXCR4)*

N. 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, UpToDate or other scholarly source.

back to top

RATIONALE AND REFERENCES

HLA-DQ Genotyping Analysis

American College of Gastroenterology (ACG)

The ACG guidelines addressing the diagnosis and management of celiac disease (CD) (2023) state 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).

Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. Am J Gastroenterol. 2023;118(1):59-76. doi:10.14309/ajg.0000000000002075. Erratum in: Am J Gastroenterol. 2024 Jul 1;119(7):1441. doi: 10.14309/ajg.0000000000002210.

American Gastroenterological Association (AGA)

The AGA 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).

Husby S, Murray JA, Katzka DA. AGA Clinical Practice Update on Diagnosis and Monitoring of Celiac Disease-Changing Utility of Serology and Histologic Measures: Expert Review. Gastroenterology. 2019;156(4):885-889. doi:10.1053/j.gastro.2018.12.010

U.S. Preventive Services Task Force (USPSTF)

In 2017, the USPSTF released guidelines on screening adults and children for celiac disease (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).

US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for Celiac Disease: US Preventive Services Task Force Recommendation Statement. JAMA. 2017;317(12):1252-1257. doi:10.1001/jama.2017.1462

back to top

Periodic Fever Syndromes Multigene Panel

Soon and Laxer

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 common causes of fevers are ruled out (infections, malignancy, adverse drug reactions, etc.), autoinflammatory diseases including periodic fever syndromes should be considered (p. 758).

Soon GS, Laxer RM. Approach to recurrent fever in childhood. PubMed. 2017;63(10):756-762. https://pubmed.ncbi.nlm.nih.gov/29025800

back to top

Evidence-Based Rheumatoid Arthritis Algorithmic Tests

Centers for Medicare and Medicaid Services (CMS)

The CMS local coverage determination (LCD) entitled "MolDX: Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis (L39424)" states that ALL of the following must be true regarding eligibility for targeted therapy selection in rheumatoid arthritis:

- Adults (18 or older)
- Confirmed diagnosis of moderately to severely active rheumatoid arthritis (RA)
- First-line therapy administered at adequate dosing either failed, was intolerated, or is contraindicated for RA treatment
- A biologic or targeted synthetic therapy (b/tDMARD) for RA has not been initiated
- A biologic or targeted synthetic therapy (b/tDMARD) for RA HAS been initiated and an alternate therapy is being considered due to initial treatment failure, contraindication, or intolerance, despite adequate dosing.

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). Effective Date 08/22/2024. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39424

back to top

Emerging Evidence Rheumatoid Arthritis Algorithmic Tests

American College of Rheumatology (ACR)

In 2021, the ACR released a guideline for the treatment of rheumatoid arthritis (RA) in which there is no mention of the Vectra test to aid in the diagnosis or treatment of RA, nor are there recommendations for this type of biomarker testing for RA.

Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2021;73(7):924-939. doi:10.1002/acr.24596

Concert Note

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g., MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

back to top

Antinuclear Antibody (ANA) Tests

American Academy of Family Physicians (AAFP)

In the publication "Systemic Lupus Erythematosus: Diagnosis and Treatment" (2023), the authors propose a diagnostic workup for individuals with suspected systemic lupus erythematosus (SLE) based on the presence of symptoms affecting multiple organ systems (Table 1, p. 384). The proposed workup should begin with antinuclear antibody (ANA) testing (p. 385).

Lam NV, Brown JA, Sharma R. Systemic lupus erythematosus: diagnosis and treatment. Am Fam Physician. 2023;107(4):383-395.

In the publication "Rheumatologic Tests: A Primer for Family Physicians" (2018), the authors summarize the screening tests that are indicated for various suspected connective tissue disorders. They caution that serologic testing should only be performed when there is a high suspicion (i.e., high pretest probability) for a connective tissue disorder. Antinuclear antibody (ANA) testing is indicated for workup of suspected mixed/undifferentiated connective tissue disorders, dermatomyositis/polymyositis, Sjögren syndrome, and systemic lupus erythematosus (SLE) (Table 1, p. 165). Additionally, the authors point out that repeating an ANA test in a patient with a previously positive result is rarely helpful since levels fluctuate and do not benefit evaluation of disease activity (p. 165). Finally, the presenting signs/symptoms of several rheumatic diseases defined above are summarized (p. 164-168).

Ali Y. Rheumatologic tests: a primer for family physicians. Am Fam Physician. 2018;98(3):164-170.

American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR)
The 2019 joint ACR/EULAR classification criteria for systemic lupus erythematosus (SLE) defines positive ANA at any time as a required entry criterion based on the use of ANA as a highly sensitive screening test (p. 8).

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71(9):1400-1412. doi:10.1002/art.40930

Yazdany, et al.

In the publication "Choosing Wisely: The American College of Rheumatology's Top 5 List of Things Physicians and Patients Should Question" (2013), the authors discuss several concerns around inappropriate use of serial ANA testing, stating that current evidence does not support repeat measurements of ANA for the purpose of assessing ongoing disease activity (p. 334).

Yazdany J, Schmajuk G, Robbins M, et al. Choosing wisely: the American College of Rheumatology's top 5 list of things physicians and patients should question. Arthritis Care Res (Hoboken). 2013;65(3):329-339. doi:10.1002/acr.21930

American Society for Clinical Laboratory Science (ASCLS) and American Society for Clinical Pathology (ASCP)

In collaboration with the Choosing Wisely campaign, the ASCP/ASCLS put out a recommendation against performing ANA testing in absence of a suspected connective tissue disease. ANA tests have a high likelihood of false positivity (stated as up to 20%) in healthy individuals and those with a nonrheumatic disease, so misuse in individuals with a low pre-test probability can lead to additional unnecessary testing.

American Society for Clinical Laboratory Science/American Society for Clinical Pathology. Choosing Wisely. Don't order antinuclear antibody and extractable nuclear antigen unless the patient is suspected to have a connective tissue disease. Accessed January 21, 2025. https://www.aafp.org/pubs/afp/collections/choosing-wisely/359.html

Qaseem, et al.

In the publication "Appropriate Use of Screening and Diagnostic Tests to Foster High-Value, Cost-Conscious Care" (2013), the American College of Physicians used a consensus-based process to produce a list of several clinical situations and tests that do not improve patient care (i.e., provide no benefit or may be harmful). Among these, is "36. Performing an antinuclear antibody test in patients with nonspecific symptoms, such as fatigue and myalgia, or in patients with fibromyalgia" (p. 148).

Qaseem A, Alguire P, Dallas P, et al. Appropriate use of screening and diagnostic tests to foster high-value, cost-conscious care. Ann Intern Med. 2012;156(2):147-149. doi:10.7326/0003-4819-156-2-201201170-00011

UpToDate

In the publication "Undifferentiated systemic rheumatic (connective tissue) disease and overlap syndromes" (2024), the authors discuss clinical situations in which it can be challenging to make a specific diagnosis of systemic rheumatic disease, including: early or nonclassic presentations of a specific condition, overlapping clinical presentation with symptoms of two or more recognized conditions (e.g., systemic lupus erythematosus [SLE] and rheumatoid arthritis [RA]), and limitations of available classification criteria in clinical use.

Undifferentiated systemic rheumatic disease (USRD) and/or overlap syndromes should be considered when clinical presentation is consistent with some features of a specific rheumatic disease, such as SLE, but does not meet established diagnostic criteria for a single condition. There are no consensus/evidence-based guidelines for evaluation of USRD; here, the authors present a workup including baseline CBC with differential, CMP, and urinalysis with microscopy, followed by additional testing, including antinuclear antibodies (ANA), based on clinical presentation.

Panush RS, Kramer N, Elliot DR, Wise LM. Undifferentiated systemic rheumatic (connective tissue) disease and overlap syndromes. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Updated April 22, 2024. https://www.uptodate.com/contents/undifferentiated-systemic-rheumatic-connective-tissue-disease-and-overlap-syndromes

back to top

Antinuclear Antibody (ANA) Subserology Tests

American Academy of Family Physicians (AAFP)

In the publication "Rheumatologic Tests: A Primer for Family Physicians" (2018) the author states that patients with a suspected connective tissue disorder and a positive antinuclear antibody titer should receive further testing, such as anti-doublestranded DNA antibodies, anti-Smith antibodies, and Sjögren antibodies, based on clinical findings that raise suspicion for specific disorders. The author also reiterates the recommendation from the Choosing Wisely Campaign that antinuclear antibody subserologies/autoantibody panels should not be performed in absence of a positive ANA test result and clinical suspicion of rheumatic/immune-mediated disease. (p. 165-166).

The author also reiterates the recommendation from the Choosing Wisely Campaign that antinuclear antibody subserologies/autoantibody panels should not be performed in absence of a positive ANA test result and clinical suspicion of rheumatic/immune-mediated disease.

Ali Y. Rheumatologic tests: a primer for family physicians. Am Fam Physician. 2018;98(3):164-170.

In the publication "Systemic Lupus Erythematosus: Diagnosis and Treatment" (2023), it is recommended to perform anti-dsDNA antibody analysis at least every one to three months in individuals with active disease (p. 392).

Lam NV, Brown JA, Sharma R. Systemic lupus erythematosus: diagnosis and treatment. Am Fam Physician. 2023;107(4):383-395.

UptoDate

In the publication "Overview of and approach to the idiopathic inflammatory myopathies" (2024), the authors include autoantibody testing as part of the workup for myositis due to overlap with other systemic diseases. An antinuclear antibody (ANA) test is not necessary before subtyping in the case of myositis, as it is only positive about 60 percent of the time in dermatomyositis and polymyositis.

Christopher-Stine L, Amato A, Vleugels RA. Overview of and approach to the idiopathic inflammatory myopathies. In: UpToDate. Updated May 14, 2025. https://www.uptodate.com/contents/overview-of-and-approach-to-the-idiopathic-inflammatory-myo

In the publication "Undifferentiated systemic rheumatic (connective tissue) disease and overlap syndromes" (2024), the authors state that follow-up evaluation, dependent on the clinical picture, can include analysis of original diagnostic workup including autoantibody analysis. Repeat of autoantibody analysis may be especially warranted when the individual is considering pregnancy.

Panush RS, Kramer N, Elliot DR, Wise LM. Undifferentiated systemic rheumatic (connective tissue) disease and overlap syndromes. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Updated April 22, 2024. https://www.uptodate.com/contents/undifferentiated-systemic-rheumatic-connective-tissue-disease-and-overlap-syndromes

back to top

Systemic Lupus Erythematosus Diagnostic and Prognostic Algorithmic Tests

Concert Evidence Review for Coverage Determination (Published 06/15/2025)

This review focused on a search for evidence-based guidelines and peer-reviewed, published evidence of the clinical utility of systemic lupus erythematosus diagnostic and prognostic algorithmic tests from 05/29/2015 - 05/29/2025. A total of 71 abstracts were identified and 14 references were reviewed, 4 of which met the inclusion criteria.

Multiple studies have been published on AVISE Lupus test and the clinical utility of these and similar diagnostic or prognostic tests for individuals with suspected systemic lupus erythematosus (SLE). Overall, these studies inadequately demonstrate the clinical utility of these tests for diagnosing SLE.

Three studies involved retrospective review of medical records (one systematic and longitudinal review, one observational cohort study, and one longitudinal, case-control review). The purpose of these studies was broadly to evaluate the ability of the AVISE Lupus test to aid in the diagnosis of SLE and thus impact medical management (Alexander, et al., O'Malley, et al., and Mossell et al., respectively). We also identified a randomised prospective trial aiming to demonstrate clinical utility for a multianalyte assay panel for the diagnosis of SLE (Wallace, et al.).

While these studies present promising findings regarding the ability of the AVISE Lupus test to guide medical decisions, the largely retrospective study designs as well as significant conflict of interest - stemming from the researchers' affiliation with and funding from the laboratory that manufactures the test - limits the reliability of the results for informing policy decisions.

There was no literature found that was specific to SLE-key® Rule Out, aiSLE DX® Flare Risk Index, or aiSLE DX® tests.

There is **INSUFFICIENT EVIDENCE** in published guidelines and peer-reviewed literature to definitively demonstrate improved health outcomes from the use of systemic lupus erythematosus (SLE) diagnostic and prognostic algorithmic tests, such as AVISE-Lupus, SLE-key® Rule Out, aiSLE DX® Flare Risk Index, or aiSLE DX®, as compared to the current standard of care. At this time, the available evidence does not support health plan coverage of these tests, in part due to significant conflicts of interest in all clinical utility studies performed.

Concert Evidence Review for Coverage Determination for Systemic Lupus Erythematosis (SLE) Algorithmic Tests. Published 06/15/2025.

back to top

Rheumatoid Factor and/or Anti-Cyclic Citrullinated Peptide Antibody Tests

American Academy of Family Physicians (AAFP)

In the publication "Rheumatoid Arthritis: Diagnosis and Management for the Family Physician" (2024), the authors propose a diagnostic workup for individuals with suspected rheumatoid arthritis (RA) based on the presence of synovitis (painful joint inflammation), with or without additional signs/symptoms such as fever or unexplained weight loss. The presentation of RA is highly variable (Table 3, p. 518), therefore, laboratory evaluation should include complete blood cell count (CBC), comprehensive metabolic panel

(CMP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibodies (p. 516).

Peterson E, Gallagher MK, Wilbur J. Rheumatoid arthritis: diagnosis and management for the family physician. Am Fam Physician. 2024;110(5):515-526.

American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR)

The 2010 ACR/EULAR classification criteria for defining RA incorporates clinical assessment of joint involvement, serological test results (RF, anti-CCP antibodies), acute phase reactants (CRP, ESR), and duration of symptoms. A score of 6 or more indicates definite RA, while a score of 5 or less indicates that RA is unlikely. Use of this criteria is appropriate only for patients with current clinical synovitis in at least one joint, and when another diagnosis (e.g., lupus, gout) does not better explain the symptoms (p. 1583-1584).

Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581. doi:10.1002/art.27584

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.
2. **Signs or symptoms of autoimmune/systemic rheumatic disease** may be caused by underlying conditions including systemic lupus erythematosus (SLE), systemic sclerosis, dermatomyositis/polymyositis, Sjögren syndrome, rheumatoid arthritis (RA), and mixed/undifferentiated connective tissue disorders. The signs/symptoms vary by condition(s) and are typically multisystemic; they include:
    - Musculoskeletal involvement, such as joint pain/swelling (synovitis/arthritis, particularly polyarthritis), morning joint stiffness, muscle weakness, swallowing dysfunction
    - Cardiovascular/pulmonary involvement, such as pericardial effusion or pericarditis, interstitial lung disease/interstitial pneumonia, Raynaud phenomenon, pulmonary hypertension, vasculitis
    - Hematologic abnormalities, including leukopenia, thrombocytopenia, hemolysis

- Dermatologic involvement, such as nonscarring hair loss, oral ulcers/mucositis, cutaneous or discoid lupus/malar or "butterfly" rash, tight skin/skin lesions
- Neuropsychiatric manifestations, such as delirium, psychosis, and seizures
- Kidney dysfunction (proteinuria, nephritis)

3. **Signs or symptoms of myositis** are broad and often overlap with autoimmune/systemic rheumatic disease. These signs and symptoms may include:

    - Muscle weakness
    - Elevated muscles enzymes (especially creatine kinase [CK])
    - Interstitial lung disease
    - Inflammatory arthritis
    - Pulmonary disease
    - Dermatologic involvement, such as cutaneous eruptions, calcinosis cutis, rashes and erythemas (midfacial, periungual), poikiloderma of sunexposed skin, psoriasiform scaling, and hyperkeratotic/fissured skin (also known as "mechanic's hands")
    - Nailfold capillary abnormalities
    - Reynaud phenomenon

4. **Synovitis** is inflammation of the synovial membrane (joint lining). Synovitis presents clinically as pain, stiffness, swelling, erythema (redness), and/or warmth of the joint(s).

back to top

ADDITIONAL REFERENCES

1. Immune Deficiency Foundation. "Specific PI Diagnoses". 2020. https://primaryimmune.org/specific-pi-diagnoses. Accessed April 15, 2025.
2. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
3. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
4. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.

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 2025, 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.

CPT® Codes	Description
0062U	Autoimmune (systemic lupus erythematosus), IgG and IgM analysis of 80 biomarkers, utilizing serum, algorithm reported with a risk score
0312U	Autoimmune diseases (eg, systemic lupus erythematosus [SLE]), analysis of 8 IgG autoantibodies and 2 cell-bound complement activation products using enzyme-linked immunosorbent immunoassay (ELISA), flow cytometry and indirect immunofluorescence, serum, or plasma and whole blood, individual components reported along with an algorithmic SLE-likelihood assessment
0446U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 10 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic risk score for current disease activity
0447U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 11 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic prognostic risk score for developing a clinical flare
81375	HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
81376	HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81377	HLA Class II typing, low resolution (eg, antigen equivalents); one antigen equivalent, each
81382	HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81479	Unlisted molecular pathology procedure
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score
81599	Unlisted multianalyte assay with algorithmic analysis
86038	Antinuclear antibodies (ANA);
86039	Antinuclear antibodies (ANA); titer
86160	Complement; antigen, each component
86200	Cyclic citrullinated peptide (CCP), antibody
86225	Deoxyribonucleic acid (DNA) antibody; native or double stranded
86235	Extractable nuclear antigen, antibody to, any method (eg, nRNP, SS-A, SS-B, Sm, RNP, Sc170, J01), each antibody
86256	Fluorescent noninfectious agent antibody; titer, each antibody
86431	Rheumatoid factor; quantitative

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	1/26	1/26

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 members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/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 members/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.