BSC_CON_2.21	Genetic Testing: Immune, Autoimmune, and Rheumatoid Disorders		
Original Policy Date:	December 1, 2023	**Effective Date:**	July 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 13

Example Test Table

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

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Known Familial Variant Analysis for Immune, Autoimmune, and Rheumatoid Disorders		
Periodic Fever Syndromes		
Periodic Fever Syndromes Multigene Panel	Periodic Fever Syndromes Panel (Invitae)	81404, 81479
	Periodic Fever Syndromes Panel (PreventionGenetics, part of Exact Sciences)	
	Periodic Fever Syndromes Panel (7 genes) (GeneDx)	
Rheumatoid Arthritis Biomarker Activity Panels		
Rheumatoid Arthritis Biomarker Activity Panels	Vectra (Labcorp)	81490
	Vectra with CV Risk (Labcorp)	
Genetic Algorithmic Rheumatoid Arthritis Tests		
Genetic Rheumatoid Arthritis for Tumor Necrosis Factor inhibitor (TNFi) Treatment	PrismRA (Scipher Medicine)	81599, 81479
HLA Typing for Axial Spondyloarthritis		
HLA Typing for Axial Spondyloarthritis	HLA-B27 DNA Typing (Quest Diagnostics)	81374
Other Covered Immune, Autoimmune, and Rheumatoid Disorders		
Other Covered Immune Disorders	See below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408

Policy Statement

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) may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member 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. 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.

RHEUMATOID ARTHRITIS BIOMARKER ACTIVITY PANELS

Rheumatoid Arthritis Biomarker Activity Panels

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

Genetic Rheumatoid Arthritis Algorithmic Tests

IV. The use of genetic rheumatoid arthritis algorithmic tests to determine appropriateness of TNFi treatment (PrismRA) (0456U) may be considered **medically necessary** when **all** of the following are met
   A. The member is age 18 or older
   B. The member has a diagnosis of moderately to severely active rheumatoid arthritis (RA)
   C. The member previously received first-line therapy for treatment of rheumatoid arthritis conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)
   D. The member is unresponsive/refractory or intolerant to the therapy despite a therapeutic dose
   E. **One** of the following:
      1. The member has not yet initiated a biologic or targeted synthetic therapy (b/tDMARD) for RA (i.e., TNFi)
      2. The member 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
   F. The member has not had previous testing using molecular biomarkers for predictive therapy selection.

V. The use of genetic rheumatoid arthritis algorithmic tests to determine appropriateness of TNFi treatment (PrismRA) (0456U) is considered **investigational** for all other indications.

HLA Typing For Axial Spondyloarthritis

VI. The use of HLA-B27 typing (81374) to confirm or establish the diagnosis of axial spondyloarthritis may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member has clinical or radiographic features of axial spondyloarthritis
   B. HLA-B27 results are needed to establish a diagnosis of axial spondyloarthritis.

VII. The use of HLA typing (81374) for axial spondyloarthritis is considered **investigational** for all other indications.

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.

VIII. Genetic testing to establish or confirm one of the following immune, autoimmune, or rheumatoid disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):
   A. Agammaglobulinemia: X-Linked and Autosomal Recessive
   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

IX. 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 coverage 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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

DEFINITIONS

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

Coding

See the Codes table for details.

Description

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.

Related Policies

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

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to genetic disorders that affect multiple organ systems *(to be published)*
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to immune disorders not specifically addressed in the policy reference table.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

State:
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

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
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.

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

"HLA-B27 can be useful to increase the confidence of a diagnosis of axSpA [axial spondyloarthritis] in patients in whom plain radiographs or magnetic resonance imaging (MRI) also exhibit abnormalities consistent with axSpA. HLA-B27 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 a significant probability for axSpA, depending upon the availability and the costs of local HLA-B27 testing. The probability 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 evaluation, including imaging."

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."

References

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3. Immune Deficiency Foundation. "Specific PI Diagnoses". 2020. https://primaryimmune.org/specific-pi-diagnoses. Accessed February 22, 2021.
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9. 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; 2022. Accessed October 23, 2023. https://uptodate.com/contents/diagnosis-and-differential-diagnosis-of-axial-spondyloarthritis-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-in-adults

10. Concert Genetics. Evidence Review for Coverage Determination for Genetic Algorithmic Rheumatoid Arthritis Tests for TNFi treatment. Published 9/1/2023.
11. Soon GS, Laxer RM. Approach to recurrent fever in childhood. Can Fam Physician. 2017;63(10):756-762.
12. 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

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
	0456U	Autoimmune (rheumatoid arthritis), next-generation sequencing (NGS), gene expression testing of 19 genes, whole blood, with analysis of anti-cyclic citrullinated peptides (CCP) levels, combined with sex, patient global assessment, and body mass index (BMI), algorithm reported as a score that predicts nonresponse to tumor necrosis factor inhibitor (TNFi) therapy ***(Code effective 7/1/2024)***
CPT®	81374	HLA Class I typing, low resolution (e.g., antigen equivalents); one antigen equivalent (e.g., B*27), each

Type	Code	Description
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 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 (e.g., >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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2023	New policy.
07/01/2024	Annual review. Policy statement, guidelines and literature updated. Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Genetic Testing: Immune, Autoimmune, and Rheumatoid Disorders **BSC_CON_2.21** **Policy Statement:** KNOWN FAMILIAL VARIANT ANALYSIS FOR IMMUNE, AUTOIMMUNE, AND RHEUMATOID DISORDERS I. Targeted mutation analysis for a known familial variant (81403) for an immune, autoimmune, and rheumatoid disorder may be considered **medically necessary** when: A. The member has a close relative with a known pathogenic or likely pathogenic variant causing the condition. II. Targeted mutation analysis for a known familial variant (81403) for an immune, autoimmune, and rheumatoid disorder is considered **investigational** for all other indications. PERIODIC FEVER SYNDROME **Periodic Fever Syndromes Multigene Panel** III. 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) may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member 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. IV. 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.	**Genetic Testing: Immune, Autoimmune, And Rheumatoid Disorders** **BSC_CON_2.21** **Policy Statement:** **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) may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member 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. 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.

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
RHEUMATOID ARTHRITIS BIOMARKER ACTIVITY PANELS **Rheumatoid Arthritis Biomarker Activity Panels** V. The use of multibiomarker disease activity scores for rheumatoid arthritis (81490) is considered **investigational**.	**RHEUMATOID ARTHRITIS BIOMARKER ACTIVITY PANELS** **Rheumatoid Arthritis Biomarker Activity Panels** III. The use of multibiomarker disease activity (MBDA) scores for rheumatoid arthritis (81490) is considered **investigational**.
GENETIC ALGORITHMIC RHEUMATOID ARTHRITIS TESTS	**Genetic Rheumatoid Arthritis Algorithmic Tests** IV. The use of genetic rheumatoid arthritis algorithmic tests to determine appropriateness of TNFi treatment (PrismRA) (0456U) may be considered **medically necessary** when **all** of the following are met A. The member is age 18 or older B. The member has a diagnosis of moderately to severely active rheumatoid arthritis (RA) C. The member previously received first-line therapy for treatment of rheumatoid arthritis conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) D. The member is unresponsive/refractory or intolerant to the therapy despite a therapeutic dose E. **One** of the following: 1. The member has not yet initiated a biologic or targeted synthetic therapy (b/tDMARD) for RA (i.e., TNFi) 2. The member 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 F. The member has not had previous testing using molecular biomarkers for predictive therapy selection.
Tumor Necrosis Factor Inhibitor (TNFi) Treatment VI. The use of genetic algorithmic rheumatoid arthritis tests to determine appropriateness of TNFi treatment (i.e., PrismRA) (81599, 81479) is considered **investigational**.	V. The use of genetic rheumatoid arthritis algorithmic tests to determine appropriateness of TNFi treatment (PrismRA) (0456U) is considered **investigational** for all other indications.
HLA TYPING FOR ANKYLOSING SPONDYLITIS, RHEUMATOID ARTHRITIS, AND AUTOIMMUNE DISORDERS VII. The use of HLA-B27 typing (81374, 81382) to confirm or establish the diagnosis of ankylosing spondylitis, or another	**HLA Typing For Axial Spondyloarthritis** VI. The use of HLA-B27 typing (81374) to confirm or establish the diagnosis of axial spondyloarthritis may be considered **medically necessary** when **BOTH** of the following criteria are met:

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
spondyloarthropathies, may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member 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.	A. The member has clinical or radiographic features of axial spondyloarthritis B. HLA-B27 results are needed to establish a diagnosis of axial spondyloarthritis.
VIII. The use of HLA typing (81374, 81382) for ankylosing spondylitis, rheumatoid arthritis, and autoimmune disorders is considered **investigational** for all other indications.	VII. The use of HLA typing (81374) for axial spondyloarthritis is considered **investigational** for all other indications.
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.	**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.
IX. Genetic testing to establish or confirm one of the following immune, autoimmune, or rheumatoid disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see X 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	VIII. Genetic testing to establish or confirm one of the following immune, autoimmune, or rheumatoid disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below): A. Agammaglobulinemia: X-Linked and Autosomal Recessive 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

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
M. WHIM Syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) N. Wiskott-Aldrich Syndrome X. 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 coverage 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.	M. WHIM Syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) N. Wiskott-Aldrich Syndrome IX. 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 coverage 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.