



If a conflict arises between a Clinical Payment and Coding Policy and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. "Plan documents" include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. Blue Cross and Blue Shield of Oklahoma may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSOK has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing Editor, American Medical Association, Current Procedural Terminology, CPT® Assistant, Healthcare Common Procedure Coding System, ICD-10 CM and PCS, National Drug Codes, Diagnosis Related Group guidelines, Centers for Medicare and Medicaid Services National Correct Coding Initiative Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

Biomarker Testing for Autoimmune Rheumatic Disease

Policy Number: CPCPLAB011

Version 1.0

Approval Date: November 19, 2024

Plan Effective Date: January 15, 2025

Description

BCBSOK has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

Reimbursement Information:

1. For individuals with a clinical suspicion or autoimmune disease, testing for antinuclear antibodies/ANA **may be reimbursable**:
 - a. Once per lifetime in individuals with stable symptoms.
 - b. Repeat testing only if a significant change in symptoms occurs.
2. For individuals with an abnormal, raised ANA titer or with abnormal immunological findings in the serum and a clinical correlation with the appropriate autoimmune disorder, extractable nuclear antigens/ENA panel testing of specific autoantibodies **may be reimbursable**.
3. For individuals with painful and swollen joints and a clinical suspicion of rheumatoid arthritis, testing for rheumatoid factor/RF and/or anti-cyclic citrullinated peptide/anti-CCP antibodies **may be reimbursable**:
 - a. Once per lifetime in individuals with stable symptoms.
 - b. Repeat testing only if a significant change in symptoms occurs.
4. For individuals with an initial positive ANA test and a diagnosis of systemic autoimmune rheumatic disease, testing of dsDNA up to four times per year **may be reimbursable**.
5. For individuals with a negative or low positive ANA test, the following condition specific antibody testing **may be reimbursable**:
 - a. Testing for anti-Jo-1 in a unique clinical subset of myositis.
 - b. Testing for anti-SSA in the setting of lupus or Sjögren's syndrome.
6. Monitoring of disease with ANA testing or ANA titers **is not reimbursable**.
7. For individuals without symptoms suggestive of an autoimmune disorder, ANA and/or ENA testing, **is not reimbursable**.
8. For all other situations not described above, testing of specific antibodies in the absence of a positive ANA test **is not reimbursable**.
9. For asymptomatic individuals, testing of ANA and/or ENA during a wellness visit or a general exam without abnormal findings **is not reimbursable**.
10. For the management of rheumatoid arthritis/RA serum biomarker panel testing (e.g., Vectra DA score, PrismRA) **is not reimbursable**.
11. For the diagnosis of systemic lupus erythematosus/SLE the use of cell-bound complement activation products (e.g., AVISE Lupus) **is not reimbursable**.
12. For the diagnosis, prognosis, or monitoring of SLE or connective tissue diseases, serum biomarker panel testing with proprietary algorithms and/or index scores (e.g., AVISE CTD, AVISE SLE Monitor, AVISE SLE prognostic) **is not reimbursable**.

Procedure Codes

The following is not an all-encompassing code list. The inclusion of a code does not guarantee it is a covered service or eligible for reimbursement.

Codes

References:

- AAFP. (2019). *Autoimmune Rheumatic Diseases*.
https://www.aafp.org/dam/AAFP/images/about-us/content/Quest_SH8265_SoH_Autoimmune%20Rheumatic%20Diseases_HealthcareProviders_April_FINAL-2.pdf
- ACR. (1997). *1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus*. Retrieved 09/02/2020 from
<https://assets.contentstack.io/v3/assets/bltee37abb6b278ab2c/bltf92eb727fa57db8f/systemic-lupus-erythematosus-classification-criteria-revised-update-1997.pdf>
- ACR. (2015). Position Statement on Methodology of Testing for Antinuclear Antibodies.
<https://primexlab.com/wp-content/uploads/2016/10/Methodology-of-Testing-Antinuclear-Antibodies-Position-Statement.pdf>
- ACR. (2024). *Policy & Position Statements*. Retrieved 11/12/20 from
<https://rheumatology.org/policy-position-statements>
- Aggarwal, A. (2014). Role of autoantibody testing. *Best Pract Res Clin Rheumatol*, 28(6), 907-920. <https://doi.org/10.1016/j.berh.2015.04.010>
- Alexander, R. V., Rey, D. S., Conklin, J., Domingues, V., Ahmed, M., Qureshi, J., & Weinstein, A. (2021). A multianalyte assay panel with cell-bound complement activation products demonstrates clinical utility in systemic lupus erythematosus. *Lupus Sci Med*, 8(1).
<https://doi.org/10.1136/lupus-2021-000528>
- Alsaed, O. S., Alamliah, L. I., Al-Radideh, O., Chandra, P., Alemadi, S., & Al-Allaf, A. W. (2021). Clinical utility of ANA-ELISA vs ANA-immunofluorescence in connective tissue diseases. *Sci Rep*, 11(1), 8229. <https://doi.org/10.1038/s41598-021-87366-w>
- Aringer, M., Costenbader, K., Daikh, D., Brinks, R., Mosca, M., Ramsey-Goldman, R., Smolen, J. S., Wofsy, D., Boumpas, D. T., Kamen, D. L., Jayne, D., Cervera, R., Costedoat-Chalumeau, N., Diamond, B., Gladman, D. D., Hahn, B., Hiepe, F., Jacobsen, S., Khanna, D., . . . Johnson, S. R. (2019). 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis*, 78(9), 1151-1159. <https://doi.org/10.1136/annrheumdis-2018-214819>
- AVISE. (2024). AVISE Testing Exclusively from Exagen Inc. . <https://avisetest.com/provider/>
- Baker, J. F. (2023). Diagnosis and differential diagnosis of rheumatoid arthritis.
<https://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-rheumatoid-arthritis#H1530529584>
- Bakker, M. F., Cavet, G., Jacobs, J. W., Bijlsma, J. W., Haney, D. J., Shen, Y., Hesterberg, L. K., Smith, D. R., Centola, M., van Roon, J. A., Lafeber, F. P., & Welsing, P. M. (2012). Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. *Ann Rheum Dis*, 71(10), 1692-1697.
<https://doi.org/10.1136/annrheumdis-2011-200963>

- Bergman, M. J., Kivitz, A. J., Pappas, D. A., Kremer, J. M., Zhang, L., Jeter, A., & Withers, J. B. (2020). Clinical Utility and Cost Savings in Predicting Inadequate Response to Anti-TNF Therapies in Rheumatoid Arthritis. *Rheumatol Ther*, 7(4), 775-792. <https://doi.org/10.1007/s40744-020-00226-3>
- Bhana, S. (2023). *Antinuclear Antibodies (ANA)*. <https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Antinuclear-Antibodies-ANA>
- Bloch, D. (2022, March 30, 2022). *Antibodies to double-stranded (ds)DNA, Sm, and U1 RNP*. <https://www.uptodate.com/contents/antibodies-to-double-stranded-ds-dna-sm-and-u1-rnp>
- Bloch, D. (2023, December 4, 2023). *Measurement and clinical significance of antinuclear antibodies - UpToDate*. <https://www.uptodate.com/contents/measurement-and-clinical-significance-of-antinuclear-antibodies>
- Brahe, C. H., Ostergaard, M., Johansen, J. S., Defranoux, N., Wang, X., Bolce, R., Sasso, E. H., Ornbjerg, L. M., Horslev-Petersen, K., Stengaard-Pedersen, K., Junker, P., Ellingsen, T., Ahlquist, P., Lindegaard, H., Linauskas, A., Schlemmer, A., Dam, M. Y., Hansen, I., Lottenburger, T., . . . Hetland, M. L. (2019). Predictive value of a multi-biomarker disease activity score for clinical remission and radiographic progression in patients with early rheumatoid arthritis: a post-hoc study of the OPERA trial. *Scand J Rheumatol*, 48(1), 9-16. <https://doi.org/10.1080/03009742.2018.1464206>
- British Columbia Rheumatoid Arthritis. (2012). *Diagnosis, Management and Monitoring Guideline*. <https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/rheumatoid-arthritis>
- Castro, C. T. d., Queiroz, M. J. d., Albuquerque, F. C., Brandão, C. C., Gerlack, L. F., Pereira, D. C. R., Barros, S. C., Andrade, W. W., Bastos, E. d. A., Azevedo, J. d. N. B., Carreiro, R., Barreto, M. L., & Santos, D. B. d. (2022). Real-world effectiveness of biological therapy in patients with rheumatoid arthritis: Systematic review and meta-analysis [Systematic Review]. *Frontiers in Pharmacology*, 13. <https://doi.org/10.3389/fphar.2022.927179>
- CDC. (2022, 07/05/2022). *Systemic Lupus Erythematosus (SLE)*. Centers for Control and Prevention. Retrieved 09/02/2020 from <https://www.cdc.gov/lupus/facts/detailed.html#diagnose>
- Centola, M., Cavet, G., Shen, Y., Ramanujan, S., Knowlton, N., Swan, K. A., Turner, M., Sutton, C., Smith, D. R., Haney, D. J., Chernoff, D., Hesterberg, L. K., Carulli, J. P., Taylor, P. C., Shadick, N. A., Weinblatt, M. E., & Curtis, J. R. (2013). Development of a Multi-Biomarker Disease Activity Test for Rheumatoid Arthritis. *PLoS One*, 8(4). <https://doi.org/10.1371/journal.pone.0060635>
- Chan, E. K., Damoiseaux, J., Carballo, O. G., Conrad, K., de Melo Cruvinel, W., Francescantonio, P. L., Fritzler, M. J., Garcia-De La Torre, I., Herold, M., Mimori, T., Satoh, M., von Muhlen, C. A., & Andrade, L. E. (2015). Report of the First International Consensus on Standardized Nomenclature of Antinuclear Antibody HEp-2 Cell Patterns 2014-2015. *Front Immunol*, 6, 412. <https://doi.org/10.3389/fimmu.2015.00412>

- Chan, E. K., Damoiseaux, J., de Melo Cruvinel, W., Carballo, O. G., Conrad, K., Francescantonio, P. L., Fritzler, M. J., Garcia-De La Torre, I., Herold, M., Mimori, T., Satoh, M., von Muhlen, C. A., & Andrade, L. E. (2016). Report on the second International Consensus on ANA Pattern (ICAP) workshop in Dresden 2015. *Lupus*, 25(8), 797-804. <https://doi.org/10.1177/0961203316640920>
- Clarke, A. E., Weinstein, A., Piscitello, A., Heer, A., Chandra, T., Doshi, S., Wegener, J., Goss, T. F., & Powell, T. (2020). Evaluation of the Economic Benefit of Earlier Systemic Lupus Erythematosus (SLE) Diagnosis Using a Multivariate Assay Panel (MAP). *ACR Open Rheumatology*, n/a(n/a). <https://doi.org/10.1002/acr2.11177>
- Cohen, S., Wells, A. F., Curtis, J. R., Dhar, R., Mellors, T., Zhang, L., Withers, J. B., Jones, A., Ghiassian, S. D., Wang, M., Connolly-Strong, E., Rapisardo, S., Gatalica, Z., Pappas, D. A., Kremer, J. M., Saleh, A., & Akmaev, V. R. (2021). A Molecular Signature Response Classifier to Predict Inadequate Response to Tumor Necrosis Factor- α Inhibitors: The NETWORK-004 Prospective Observational Study. *Rheumatol Ther*, 8(3), 1159-1176. <https://doi.org/10.1007/s40744-021-00330-y>
- Curtis, J. R., Flake, D. D., Weinblatt, M. E., Shadick, N. A., Ostergaard, M., Hetland, M. L., Brahe, C. H., Hwang, Y. G., Furst, D. E., Strand, V., Etzel, C. J., Pappas, D. A., Wang, X., Hwang, C. C., Sasso, E. H., Gutin, A., Hitraya, E., & Lanchbury, J. S. (2019). Adjustment of the multi-biomarker disease activity score to account for age, sex and adiposity in patients with rheumatoid arthritis. *Rheumatology (Oxford)*, 58(5), 874-883. <https://doi.org/10.1093/rheumatology/key367>
- Curtis, J. R., Greenberg, J. D., Harrold, L. R., Kremer, J. M., & Palmer, J. L. (2018). Influence of obesity, age, and comorbidities on the multi-biomarker disease activity test in rheumatoid arthritis. *Semin Arthritis Rheum*, 47(4), 472-477. <https://doi.org/10.1016/j.semarthrit.2017.07.010>
- Curtis, J. R., Schabert, V. F., Harrison, D. J., Yeaw, J., Korn, J. R., Quach, C., Yun, H., Joseph, G. J., & Collier, D. H. (2014). Estimating effectiveness and cost of biologics for rheumatoid arthritis: application of a validated algorithm to commercial insurance claims. *Clin Ther*, 36(7), 996-1004. <https://doi.org/10.1016/j.clinthera.2014.05.062>
- Curtis, J. R., van der Helm-van Mil, A. H., Knevel, R., Huizinga, T. W., Haney, D. J., Shen, Y., Ramanujan, S., Cavet, G., Centola, M., Hesterberg, L. K., Chernoff, D., Ford, K., Shadick, N. A., Hamburger, M., Fleischmann, R., Keystone, E., & Weinblatt, M. E. (2012). Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken)*, 64(12), 1794-1803. <https://doi.org/10.1002/acr.21767>
- Curtis, J. R., Weinblatt, M. E., Shadick, N. A., Brahe, C. H., Østergaard, M., Hetland, M. L., Saevarsdottir, S., Horton, M., Mabey, B., Flake, D. D., Ben-Shachar, R., Sasso, E. H., & Huizinga, T. W. (2021). Validation of the adjusted multi-biomarker disease activity score as a prognostic test for radiographic progression in rheumatoid arthritis: a combined analysis of multiple studies. *Arthritis Research & Therapy*, 23(1), 1. <https://doi.org/10.1186/s13075-020-02389-4>
- Damoiseaux, J., Andrade, L. E., Fritzler, M. J., & Shoenfeld, Y. (2015). Autoantibodies 2015: From diagnostic biomarkers toward prediction, prognosis and prevention. *Autoimmun Rev*, 14(6), 555-563. <https://doi.org/10.1016/j.autrev.2015.01.017>

- Deighton, C., O'Mahony, R., Tosh, J., Turner, C., & Rudolf, M. (2009). Management of rheumatoid arthritis: summary of NICE guidance. *Bmj*, 338, b702. <https://doi.org/10.1136/bmj.b702>
- Deng, X., Peters, B., Ettore, M. W., Ashworth, J., Brunelle, L. A., Crowson, C. S., Moder, K. G., & Snyder, M. R. (2016). Utility of Antinuclear Antibody Screening by Various Methods in a Clinical Laboratory Patient Cohort. *J Appl Lab Med*, 1(1), 36-46. <https://doi.org/10.1373/jalm.2016.020172>
- Dervieux, T., Conklin, J., Ligayon, J. A., Wolover, L., O'Malley, T., Alexander, R. V., Weinstein, A., & Ibarra, C. A. (2017). Validation of a multi-analyte panel with cell-bound complement activation products for systemic lupus erythematosus. *J Immunol Methods*, 446, 54-59. <https://doi.org/10.1016/j.jim.2017.04.001>
- Durcan, L., O'Dwyer, T., & Petri, M. (2019). Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet*, 393(10188), 2332-2343. [https://doi.org/10.1016/s0140-6736\(19\)30237-5](https://doi.org/10.1016/s0140-6736(19)30237-5)
- Exagen. (2024). *AVISE Lupus*. <https://exagen.com/tests/lupus/>
- Fava, A., & Petri, M. (2019). Systemic lupus erythematosus: Diagnosis and clinical management. *J Autoimmun*, 96, 1-13. <https://doi.org/10.1016/j.jaut.2018.11.001>
- Finzel, S., Schaffer, S., Rizzi, M., & Voll, R. E. (2018). [Pathogenesis of systemic lupus erythematosus]. *Z Rheumatol*, 77(9), 789-798. <https://doi.org/10.1007/s00393-018-0541-3> (Pathogenese des systemischen Lupus erythematosus.)
- Fleischmann, R., Liu, J., Zhu, J., Segurado, O. G., & Furst, D. E. (2022). Discrepancy Between Multibiomarker Disease Activity and Clinical Disease Activity Scores in Patients With Persistently Active Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)*, 74(9), 1477-1483. <https://doi.org/10.1002/acr.24583>
- Fraenkel, L., Bathon, J. M., England, B. R., St Clair, E. W., Arayssi, T., Carandang, K., Deane, K. D., Genovese, M., Huston, K. K., Kerr, G., Kremer, J., Nakamura, M. C., Russell, L. A., Singh, J. A., Smith, B. J., Sparks, J. A., Venkatachalam, S., Weinblatt, M. E., Al-Gibbawi, M., . . . Akl, E. A. (2021). 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)*, 73(7), 924-939. <https://doi.org/10.1002/acr.24596>
- Global Autoimmune Institute. (2022). *Autoimmunity on the Rise*. <https://www.autoimmuneinstitute.org/articles/about-autoimmune/autoimmunity-on-the-rise/#:~:text=The%20best%20guess%20that%20current,2%2C3%2C4%5D>.
- Guthridge, J. M., Wagner, C. A., & James, J. A. (2022). The promise of precision medicine in rheumatology. *Nat Med*, 28(7), 1363-1371. <https://doi.org/10.1038/s41591-022-01880-6>
- Hargraves, M. M., Richmond, H., & Morton, R. (1948). Presentation of two bone marrow elements; the tart cell and the L.E. cell. *Proc Staff Meet Mayo Clin*, 23(2), 25-28.
- Hirata, S., Dirven, L., Shen, Y., Centola, M., Cavet, G., Lems, W. F., Tanaka, Y., Huizinga, T. W., & Allaart, C. F. (2013). A multi-biomarker score measures rheumatoid arthritis disease

activity in the BeSt study. *Rheumatology (Oxford)*, 52(7), 1202-1207.
<https://doi.org/10.1093/rheumatology/kes362>

Hochberg, M. C. (1997). Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*, 40(9), 1725.
<https://doi.org/10.1002/art.1780400928>

Johnson, K. J., Sanchez, H. N., & Schoenbrunner, N. (2019). Defining response to TNF-inhibitors in rheumatoid arthritis: the negative impact of anti-TNF cycling and the need for a personalized medicine approach to identify primary non-responders. *Clin Rheumatol*, 38(11), 2967-2976. <https://doi.org/10.1007/s10067-019-04684-1>

Josef, S. S., Robert, B. M. L., Sytske Anne, B., Andreas, K., Alexandre, S., Daniel, A., Roberto, C., Christopher John, E., Kimme, L. H., Janet, E. P., Savia de, S., Tanja, A. S., Tsutomu, T., Patrick, V., Kevin, L. W., Alejandro, B., Joan, M. B., Maya, H. B., Gerd, R. B., . . . Désirée van der, H. (2023). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Annals of the Rheumatic Diseases*, 82(1), 3. <https://doi.org/10.1136/ard-2022-223356>

Kim, J., Lee, W., Kim, G. T., Kim, H. S., Ock, S., Kim, I. S., & Jeong, S. (2019). Diagnostic utility of automated indirect immunofluorescence compared to manual indirect immunofluorescence for anti-nuclear antibodies in patients with systemic rheumatic diseases: A systematic review and meta-analysis. *Semin Arthritis Rheum*, 48(4), 728-735.
<https://doi.org/10.1016/j.semarthrit.2018.03.015>

LFA. (2021, 05/01/2019). *Lupus Foundation of America Survey: More than Half of Americans Lack Awareness, Understanding of Lupus*. Retrieved 08/31/2020 from
<https://www.lupus.org/resources/lupus-facts-and-statistics#:~:text=The%20Lupus%20Foundation%20of%20America%20estimates%20that%201.5,%2890%25%29%20of%20people%20living%20with%20lupus%20are%20women.>

Li, W., Sasso, E. H., Emerling, D., Cavet, G., & Ford, K. (2013). Impact of a multi-biomarker disease activity test on rheumatoid arthritis treatment decisions and therapy use. *Curr Med Res Opin*, 29(1), 85-92. <https://doi.org/10.1185/03007995.2012.753042>

Li, W., Sasso, E. H., van der Helm-van Mil, A. H., & Huizinga, T. W. (2016). Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis. *Rheumatology (Oxford)*, 55(2), 357-366. <https://doi.org/10.1093/rheumatology/kev341>

Liang, E., Taylor, M., & McMahon, M. (2020). Utility of the AVISE Connective Tissue Disease test in predicting lupus diagnosis and progression. *Lupus Science & Medicine*, 7(1), e000345. <https://doi.org/10.1136/lupus-2019-000345>

Luan, H., Gu, W., Li, H., Wang, Z., Lu, L., Ke, M., Lu, J., Chen, W., Lan, Z., Xiao, Y., Xu, J., Zhang, Y., Cai, Z., Liu, S., & Zhang, W. (2021). Serum metabolomic and lipidomic profiling identifies diagnostic biomarkers for seropositive and seronegative rheumatoid arthritis patients. *J Transl Med*, 19(1), 500. <https://doi.org/10.1186/s12967-021-03169-7>

Ma, M. H. Y., Defranoux, N., Li, W., Sasso, E. H., Ibrahim, F., Scott, D. L., & Cope, A. P. (2020). A multi-biomarker disease activity score can predict sustained remission in rheumatoid

arthritis. *Arthritis Research & Therapy*, 22(1), 158. <https://doi.org/10.1186/s13075-020-02240-w>

McArdle, A., Flatley, B., Pennington, S. R., & FitzGerald, O. (2015). Early biomarkers of joint damage in rheumatoid and psoriatic arthritis. *Arthritis Res Ther*, 17(1), 141. <https://doi.org/10.1186/s13075-015-0652-z>

Mellors, T., Withers, J. B., Ameli, A., Jones, A., Wang, M., Zhang, L., Sanchez, H. N., Santolini, M., Valle, I. D., Sebek, M., Cheng, F., Pappas, D. A., Kremer, J. M., Curtis, J. R., Johnson, K. J., Saleh, A., Ghiassian, S. D., & Akmaev, V. R. (2020). Clinical Validation of a Blood-Based Predictive Test for Stratification of Response to Tumor Necrosis Factor Inhibitor Therapies in Rheumatoid Arthritis Patients. *Network and Systems Medicine*, 3(1), 91-104. <https://doi.org/http://doi.org/10.1089/nsm.2020.0007>

Mosca, M., Costenbader, K. H., Johnson, S. R., Lorenzoni, V., Sebastiani, G. D., Hoyer, B. F., Navarra, S., Bonfa, E., Ramsey-Goldman, R., Medina-Rosas, J., Piga, M., Tani, C., Tedeschi, S. K., Dörner, T., Aringer, M., & Touma, Z. (2019). Brief Report: How Do Patients With Newly Diagnosed Systemic Lupus Erythematosus Present? A Multicenter Cohort of Early Systemic Lupus Erythematosus to Inform the Development of New Classification Criteria. *Arthritis Rheumatol*, 71(1), 91-98. <https://doi.org/10.1002/art.40674>

Mossell, J., Goldman, J. A., Barken, D., & Alexander, R. V. (2016). The Avise Lupus Test and Cell-bound Complement Activation Products Aid the Diagnosis of Systemic Lupus Erythematosus. *Open Rheumatol J*, 10, 71-80. <https://doi.org/10.2174/1874312901610010071>

Oglesby, A., Korves, C., Laliberté, F., Dennis, G., Rao, S., Suthoff, E. D., Wei, R., & Duh, M. S. (2014). Impact of early versus late systemic lupus erythematosus diagnosis on clinical and economic outcomes. *Appl Health Econ Health Policy*, 12(2), 179-190. <https://doi.org/10.1007/s40258-014-0085-x>

Pappas, D. A., St John, G., Etzel, C. J., Fiore, S., Blachley, T., Kimura, T., Punekar, R., Emeanuru, K., Choi, J., Boklage, S., & Kremer, J. M. (2021). Comparative effectiveness of first-line tumour necrosis factor inhibitor versus non-tumour necrosis factor inhibitor biologics and targeted synthetic agents in patients with rheumatoid arthritis: results from a large US registry study. *Ann Rheum Dis*, 80(1), 96-102. <https://doi.org/10.1136/annrheumdis-2020-217209>

Petri, M., Orbai, A. M., Alarcón, G. S., Gordon, C., Merrill, J. T., Fortin, P. R., Bruce, I. N., Isenberg, D., Wallace, D. J., Nived, O., Sturfelt, G., Ramsey-Goldman, R., Bae, S. C., Hanly, J. G., Sánchez-Guerrero, J., Clarke, A., Aranow, C., Manzi, S., Urowitz, M., . . . Magder, L. S. (2012). Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*, 64(8), 2677-2686. <https://doi.org/10.1002/art.34473>

Putterman, C., Furie, R., Ramsey-Goldman, R., Askanase, A., Buyon, J., Kalunian, K., Chatham, W. W., Massarotti, E., Kirou, K., Jordan, N., Blanco, I., Weinstein, A., Chitkara, P., Manzi, S., Ahearn, J., O'Malley, T., Conklin, J., Ibarra, C., Barken, D., & Dervieux, T. (2014). Cell-bound complement activation products in systemic lupus erythematosus: comparison with anti-double-stranded DNA and standard complement measurements. *Lupus Sci Med*, 1(1), e000056. <https://doi.org/10.1136/lupus-2014-000056>

- RACGP. (2009). *Recommendations for the diagnosis and management of early rheumatoid arthritis*.
<https://www.racgp.org.au/FSDEDEV/media/documents/Clinical%20Resources/Guidelines/Joint%20replacement/Rheumatoid-arthritis-recommendations.pdf>
- Ramsey-Goldman, R., Alexander, R. V., Massarotti, E. M., Wallace, D. J., Narain, S., Arriens, C., Collins, C. E., Saxena, A., Putterman, C., Kalunian, K. C., O'Malley, T., Dervieux, T., & Weinstein, A. (2020). Complement Activation in Patients With Probable Systemic Lupus Erythematosus and Ability to Predict Progression to American College of Rheumatology-Classified Systemic Lupus Erythematosus. *Arthritis Rheumatol*, 72(1), 78-88.
<https://doi.org/10.1002/art.41093>
- Rees, F., Doherty, M., Grainge, M. J., Lanyon, P., & Zhang, W. (2017). The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology (Oxford)*, 56(11), 1945-1961.
<https://doi.org/10.1093/rheumatology/kex260>
- Rouster-Stevens, K. A., Ardoin, S. P., Cooper, A. M., Becker, M. L., Dragone, L. L., Huttenlocher, A., Jones, K. B., Kolba, K. S., Moorthy, L. N., Nigrovic, P. A., Stinson, J. N., & Ferguson, P. J. (2014). Choosing Wisely: the American College of Rheumatology's Top 5 for pediatric rheumatology. *Arthritis Care Res (Hoboken)*, 66(5), 649-657.
<https://doi.org/10.1002/acr.22238>
- Satoh, M., Chan, E. K., Sobel, E. S., Kimpel, D. L., Yamasaki, Y., Narain, S., Mansoor, R., & Reeves, W. H. (2014). Clinical implication of autoantibodies in patients with systemic rheumatic diseases. *Expert Rev Clin Immunol*, 3(5), 721-738.
<https://doi.org/10.1586/1744666x.3.5.721>
- Scherer, H. U., Häupl, T., & Burmester, G. R. (2020). The etiology of rheumatoid arthritis. *J Autoimmun*, 110, 102400. <https://doi.org/10.1016/j.jaut.2019.102400>
- Selmi, C., Ceribelli, A., Generali, E., Scire, C. A., Alborghetti, F., Colloredo, G., Porrati, L., Achenza, M. I., De Santis, M., Cavaciocchi, F., Massarotti, M., Isailovic, N., Paleari, V., Invernizzi, P., Matthias, T., Zucchi, A., & Meroni, P. L. (2016). Serum antinuclear and extractable nuclear antigen antibody prevalence and associated morbidity and mortality in the general population over 15 years. *Autoimmun Rev*, 15(2), 162-166.
<https://doi.org/10.1016/j.autrev.2015.10.007>
- Shapiro, S. C. (2021). Biomarkers in Rheumatoid Arthritis. *Cureus*, 13(5), e15063.
<https://doi.org/10.7759/cureus.15063>
- Shmerling, R. (2023, July 19, 2023). *Rheumatoid factor: Biology and utility of measurement*.
<https://www.uptodate.com/contents/rheumatoid-factor-biology-and-utility-of-measurement>
- Simon, T. A., Kawabata, H., Ray, N., Baheti, A., Suissa, S., & Esdaile, J. M. (2017). Prevalence of Co-existing Autoimmune Disease in Rheumatoid Arthritis: A Cross-Sectional Study. *Adv Ther*, 34(11), 2481-2490. <https://doi.org/10.1007/s12325-017-0627-3>
- Suurmond, J., & Diamond, B. (2015). Autoantibodies in systemic autoimmune diseases: specificity and pathogenicity. *J Clin Invest*, 125(6), 2194-2202.
<https://doi.org/10.1172/jci78084>

- Tan, E. M. (1989). Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. *Adv Immunol*, 44, 93-151.
- Taylor, P., & Maini, R. (2022, 04/22/2022). *Investigational biologic markers in the diagnosis and assessment of rheumatoid arthritis*. <https://www.uptodate.com/contents/investigational-biologic-markers-in-the-diagnosis-and-assessment-of-rheumatoid-arthritis>
- Tebo, A. E. (2017). Recent Approaches To Optimize Laboratory Assessment of Antinuclear Antibodies. *Clin Vaccine Immunol*, 24(12). <https://doi.org/10.1128/cvi.00270-17>
- Thong, B., & Olsen, N. J. (2017). Systemic lupus erythematosus diagnosis and management. *Rheumatology (Oxford)*, 56(suppl_1), i3-i13. <https://doi.org/10.1093/rheumatology/kew401>
- Tipu, H. N., & Bashir, M. M. (2018). Determination of Specificity and Pattern of Antinuclear Antibodies (ANA) in Systemic Rheumatic Disease Patients Positive for ANA Testing. *J Coll Physicians Surg Pak*, 28(1), 40-43. <https://pubmed.ncbi.nlm.nih.gov/29290190/>
- Tonutti, E., Bizzaro, N., Morozzi, G., Radice, A., Cinquanta, L., Villalta, D., Tozzoli, R., Tampoa, M., Porcelli, B., Fabris, M., Brusca, I., Alessio, M. G., Barberio, G., Sorrentino, M. C., Antico, A., Bassetti, D., Fontana, D. E., Imbastaro, T., Visentini, D., . . . Bagnasco, M. (2016). The ANA-reflex test as a model for improving clinical appropriateness in autoimmune diagnostics. *Auto Immun Highlights*, 7(1). <https://doi.org/10.1007/s13317-016-0080-3>
- van der Helm-van Mil, A. H. M., Knevel, R., Cavet, G., Huizinga, T. W. J., & Haney, D. J. (2013). An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. In *Rheumatology (Oxford)* (Vol. 52, pp. 839-846). <https://doi.org/10.1093/rheumatology/kes378>
- van der Pol, P., Bakker-Jonges, L. E., Kuijpers, J., & Schreurs, M. W. J. (2018). Analytical and clinical comparison of two fully automated immunoassay systems for the detection of autoantibodies to extractable nuclear antigens. *Clin Chim Acta*, 476, 154-159. <https://doi.org/10.1016/j.cca.2017.11.014>
- Wallace, D. J., Alexander, R. V., O'Malley, T., Khosroshahi, A., Hojjati, M., Loupasakis, K., Alper, J., Sherrer, Y., Fondal, M., Kataria, R., Powell, T., Ibarra, C., Narain, S., Massarotti, E., Weinstein, A., & Dervieux, T. (2019). Randomised prospective trial to assess the clinical utility of multianalyte assay panel with complement activation products for the diagnosis of SLE. *Lupus Science & Medicine*, 6(1), e000349. <https://doi.org/10.1136/lupus-2019-000349>
- Wallace, D. J., & Gladman, D. (2023, June 16, 2023). *Clinical manifestations and diagnosis of systemic lupus erythematosus in adults*. <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-systemic-lupus-erythematosus-in-adults>
- Yazdany, J., Schmajuk, G., Robbins, M., Daikh, D., Beall, A., Yelin, E., Barton, J., Carlson, A., Margaretten, M., Zell, J., Gensler, L. S., Kelly, V., Saag, K., King, C., & The American College of Rheumatology Core Membership, G. (2013). Choosing wisely: The American College of Rheumatology's top 5 list of things physicians and patients should question. *Arthritis Care & Research*, 65(3), 329-339. <https://doi.org/10.1002/acr.21930>

- Yeo, A. L., Le, S., Ong, J., Connelly, K., Ojaimi, S., Nim, H., Morand, E. F., & Leech, M. (2020). Utility of repeated antinuclear antibody tests: a retrospective database study. *The Lancet Rheumatology*, 2(7), e412-e417. [https://doi.org/10.1016/S2665-9913\(20\)30084-9](https://doi.org/10.1016/S2665-9913(20)30084-9)
- Yoo, I. Y., Oh, J. W., Cha, H. S., Koh, E. M., & Kang, E. S. (2017). Performance of an Automated Fluorescence Antinuclear Antibody Image Analyzer. *Ann Lab Med*, 37(3), 240-247. <https://doi.org/10.3343/alm.2017.37.3.240>
- Zucchi, D., Elefante, E., Calabresi, E., Signorini, V., Bortoluzzi, A., & Tani, C. (2019). One year in review 2019: systemic lupus erythematosus. *Clin Exp Rheumatol*, 37(5), 715-722. <https://pubmed.ncbi.nlm.nih.gov/31376267/>

Policy Update History:

Approval Date	Effective Date; Summary of Revisions
11/19/2024	01/01/2025: Added new CPT code 0521U effective 01/01/2025.
04/29/2024	01/15/2025: Document updated with literature review. Reimbursement information revised. Statement 1 edited for clarity. Added new #3: "For individuals with painful and swollen joints and a clinical suspicion of rheumatoid arthritis, testing for rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies may be reimbursable: a) Once per lifetime in individuals with stable symptoms; b) Repeat testing only if a significant change in symptoms occurs." Added codes 86200, 86340, 86341. References revised.
11/01/2023	11/01/2023: Document updated with literature review. Reimbursement information revised; Added "Once per lifetime in individuals with stable symptoms" to #1a; and "Repeat testing only if a significant change in symptoms occurs" to #1b. #9 "For the management of rheumatoid arthritis (RA< serum biomarker panel testing (e.g., Vectra DA score, PrismRA) is not reimbursable" was previously addressed on CPCPLAB039 Vectra DA Blood Test for Rheumatoid Arthritis. Title changed from ANA/ENA Testing.
11/1/2022	11/01/2022: New Policy