AMERICAN COLLEGE OF RHEUMATOLOGY
POSITION STATEMENT

SUBJECT:	Clinical Laboratory Access & Optimization
PRESENTED BY:	Committee on Rheumatologic Care
FOR DISTRIBUTION TO:	Members of the American College of Rheumatology Medical Societies Members of Congress Health Care Organizations/Third Party Carriers Managed Care Entities U.S. Food & Drug Administration Clinical Laboratory Professional Organizations

POSITIONS:

1. The American College of Rheumatology (ACR) supports access to reliable and patient-centered laboratory testing to optimize the diagnosis and monitoring of patients with conditions diagnosed and treated by rheumatologists.

2. The ACR supports minimizing barriers to genetic test access for rheumatologic diseases.

3. The ACR supports the efforts of other clinical and laboratory professionals to provide access to advanced biomarkers while supporting laboratory stewardship, balancing the need to manage costs while optimizing laboratory assessment of individual patients.

4. The ACR encourages efforts to standardize and harmonize laboratory tests used in the diagnosis and management of patients with rheumatic disease.

BACKGROUND:

Access

Laboratory testing plays a central role in the practice of rheumatology. Formal diagnostic criteria and classification criteria as well as clinical practice rely on routine laboratory tests (such as complete blood counts and chemistry panels) and on specialized tests (such as autoantibody tests and genetic tests for autoinflammatory conditions). Laboratory tests are also used as prognostic markers (such as the use of C-reactive protein to indicate a need for rheumatoid arthritis treatment); to monitor response to treatment (such as following uric acid levels in patients treated for gout with urate-lowering therapies); as adjuncts to assess disease activity (such as C-reactive protein as a measure of rheumatoid arthritis); to predict risk of toxicity of treatments (such as HLA-5801 testing to assess the risk of allopurinol hypersensitivity(1)); and to monitor toxicity of medications (such as monitoring blood counts and tests of hepatotoxicity in patients taking

methotrexate). In some instances, measurement of drug levels or anti-drug antibodies may help to adjust the choice or dose of a medication.

The rheumatology practitioner caring for the individual patient is responsible for deciding if a given test is needed and the frequency with which a given test should be ordered, and the judgment of the provider should be assumed to be appropriate in most situations. For example, when doses of medications or the renal or liver function of an individual patient are changing, more frequent monitoring may be required. In some cases, autoantibody tests that are not available as FDA-approved reagents are critical for evaluating patients. For example, tests for antibodies to RNA synthetases and other myositis-specific autoantibodies contribute to complete clinical and antibody classification of patients with myositis (2–4), and some assays are available only as unapproved 'laboratory-developed tests'.

The ACR endorses the promotion of a scientific, regulatory, and financial infrastructure that promotes the development of novel assays and assays that are clinically useful but may serve only a limited group of patients with autoimmune rheumatic conditions (5). Access to laboratory-developed tests as well as FDA-approved assays should remain an option for rheumatologists to order when indicated to best assess and care for their patients.

Prior Authorization for Genetic Testing

Progress in understanding the genetic basis of disease has been remarkable. Efforts should be made to minimize barriers to access to genetic testing for autoinflammatory and rheumatic disease. For some conditions, the only way to make a certain diagnosis requires testing of patient DNA. Although clinical patterns can provide important clues to the diagnosis of some of those conditions, often the only path to a definite diagnosis involves a molecular diagnosis (6,7). Recent understanding of the molecular bases of disease often clarifies understanding and focuses care of patients with confusing clinical presentations, such as in advances in the condition known as VEXAS with its diverse inflammatory manifestations (8). Rapidly making a certain diagnosis often points to specific types of treatments, avoids unnecessary and often unrewarding and potentially misleading diagnostic testing, and avoids exposing patients to treatments that may be less effective than the specifically and appropriately targeted treatment.

Laboratory Stewardship

The ACR endorses efforts to support appropriate laboratory testing and avoid unnecessary testing, in accord with other professionals to support laboratory stewardship (9). The ACR recognizes that unnecessary testing raises costs. In addition, if tests are ordered on patients with a low pre-test probability, there is a high likelihood that a positive test result will be false-positive, with the potential to lead to an incorrect diagnosis and ineffective and even harmful therapies.

Rheumatology professionals are trained in and accustomed to challenges in diagnosing complex conditions. In some situations, and for some patients, particularly those with multiple medical diagnoses and clinical or psychosocial comorbidities, standard clinical evaluations and routine clinical tests are not sufficient to assess the rheumatologic condition being evaluated or treated. For those patients, non-standardized tests and/or test panels with a calculated probabilistic

summary result may be valuable. The ACR believes that laboratory tests included in published clinical practice guidelines are usually sufficient in most clinical situations, but tests that are not in guidelines may be indicated in some situations.

Standardization and Harmonization of Laboratory Tests

The ACR supports the efforts of regulatory agencies, clinical laboratory professionals, and international societies such as the World Health Organization to standardize laboratory testing, including specialized autoantibody tests used in diagnosis of autoimmune rheumatic diseases. However, standardization of routine ANA and autoantibody tests remains challenging, with both random and systematic differences between methods observed in clinical practice (10,11). As a consequence of lack of consistency between laboratories, clinicians often perform repeat testing, leading to unnecessary expense if results are reproducible, and to patient and provider confusion when results are not confirmed. We recognize the complexity of autoantigens and differences in autoantibody responses that depend on genetics of patients, environmental exposures, and other unknown factors. However, some approaches are achievable. For example, the ACR's 2009 position statement on the method of antinuclear antibody (ANA) testing (12) led the College of American Pathologists to require clinical laboratories to report their method of testing on each ANA lab report form. Use of automated multiplex panel testing has become even more widespread, and rheumatologists are increasingly understanding the strengths and limitations of such testing (13). Approaches for standardization and harmonization should be explored and implemented, if possible, by clinical laboratory professionals working with rheumatologists (14,15).

REFERENCES

1. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Rheumatol Hoboken NJ. 2020 Jun;72(6):879–95.
2. Halilu F, Christopher-Stine L. Myositis-specific Antibodies: Overview and Clinical Utilization. Rheumatol Immunol Res. 2022 Mar;3(1):1–10.
3. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EKL. A Comprehensive Overview on Myositis-Specific Antibodies: New and Old Biomarkers in Idiopathic Inflammatory Myopathy. Clin Rev Allergy Immunol. 2017 Feb;52(1):1–19.
4. Zanframundo G, Faghihi-Kashani S, Scirè CA, Bonella F, Corte TJ, Doyle TJ, et al. Defining anti-synthetase syndrome: a systematic literature review. Clin Exp Rheumatol. 2022 Feb;40(2):309–19.
5. Fritzler MJ, Choi MY, Satoh M, Mahler M. Autoantibody Discovery, Assay Development and Adoption: Death Valley, the Sea of Survival and Beyond. Front Immunol. 2021;12:679613.
6. Cetin Gedik K, Lamot L, Romano M, Demirkaya E, Piskin D, Torreggiani S, et al. The 2021 European Alliance of Associations for Rheumatology/American College of Rheumatology Points to Consider for Diagnosis and Management of Autoinflammatory Type I Interferonopathies: CANDLE/PRAAS, SAVI, and AGS. Arthritis Rheumatol.

2022;74(5):735–51.

7. Romano M, Arici ZS, Piskin D, Alehashemi S, Aletaha D, Barron K, et al. The 2021 EULAR/American College of Rheumatology Points to Consider for Diagnosis, Management and Monitoring of the Interleukin-1 Mediated Autoinflammatory Diseases: Cryopyrin-Associated Periodic Syndromes, Tumour Necrosis Factor Receptor-Associated Periodic Syndrome, Mevalonate Kinase Deficiency, and Deficiency of the Interleukin-1 Receptor Antagonist. Arthritis Rheumatol. 2022;74(7):1102–21.
8. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. N Engl J Med. 2020 Dec 31;383(27):2628–38.
9. Dickerson JA, Fletcher AH, Procop G, Keren DF, Singh IR, Garcia JJ, et al. Transforming Laboratory Utilization Review into Laboratory Stewardship: Guidelines by the PLUGS National Committee for Laboratory Stewardship. J Appl Lab Med. 2017 Sep 1;2(2):259–68.
10. Pisetsky DS, Spencer DM, Lipsky PE, Rovin BH. Assay variation in the detection of antinuclear antibodies in the sera of patients with established SLE. Ann Rheum Dis. 2018 Jun;77(6):911–3.
11. Wener MH, Fink S, Bashleben C, Sindelar S, Linden MA. Long-Term Variability in Immunofluorescence Titer of Antibodies to Nuclear Antigens Observed in Clinical Laboratory Proficiency Testing Surveys. Arch Pathol Lab Med. 2020 Dec 29;
12. Meroni PL, Schur PH. ANA screening: an old test with new recommendations. Ann Rheum Dis. 2010 Aug;69(8):1420–2.
13. Bossuyt X, De Langhe E, Borghi MO, Meroni PL. Understanding and interpreting antinuclear antibody tests in systemic rheumatic diseases. Nat Rev Rheumatol. 2020 Dec;16(12):715–26.
14. Meroni PL, Borghi MO. Diagnostic laboratory tests for systemic autoimmune rheumatic diseases: unmet needs towards harmonization. Clin Chem Lab Med. 2018 Sep 25;56(10):1743–8.
15. Damoiseaux J. The perspective on standardisation and harmonisation: the viewpoint of the EASI president. Auto- Immun Highlights. 2020 Feb 6;11(1):4.

Approved by the Board of Directors: 11/2023