European League against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus: the laboratory immunologist's point of view

We read with great interest the new European League against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE) by Aringer *et al*,¹ that recommend a positive antinuclear antibody (ANA) test as an entry criterion for SLE classification. According to these criteria, ANA testing has to be performed by a *highly sensitive* screening method before initiating the cascade work algorithm. This is a strategic move compared with the previous criteria by the Systemic Lupus International Collaborating Clinics (SLICC)² in which ANA was considered just one of the immunological items together with the more specific antibodies against Sm and dsDNA. With this new concept, ANA testing has been separated from its corresponding level tests, strengthening the idea that ANA is necessary to define the clinical lupus phenotype.

However, as laboratory immunologists we have some concerns about the ANA definition both in the previous and new criteria. The SLICC criteria which considered 'an ANA above laboratory reference range' as a criterion, left a great deal to arbitrariness about which method to use, and when the indirect immunofluorescence (IIF) method on HEp-2 cells is used, to the discriminating screening titer. Referring instead to the new classification criteria, we would like to note that the provision 'Testing by immunofluorescence on HEp-2 cells or a solid phase ANA screening immunoassay with at least equivalent performance' is somehow inaccurate, in that equivalence might be understood in this context in terms of sensitivity at the expense of specificity, which is a hallmark for classification purposes.³ While we acknowledge that specificity can be achieved by completing the classification algorithm and that the ACR/EULAR decision has been made in view of ongoing work on the standardisation of autoimmune diagnostics and its potential future advances, we maintain that this is a risky definition that might be misinterpreted, thereby encouraging the use of alternative methods, even when they lack (or provide suboptimal) clinical specificity.

Hopefully, the American College of Rheumatology Antinuclear Antibody Task Force will take a position towards the individual alternative methods.⁴⁻⁶ The great majority of studies performed in recent years⁷⁻⁹ have mainly analysed the performance of new solid-phase screening assay, the so-called connective tissue disease screen test, which is currently the main 'competitor' to the ANA-IIF, having shown itself to be the closest in terms of sensitivity and specificity.^{10 11} However, since a lot of different methods are available today to the clinical lab, they can be inappropriately used as an alternative to the ANA-IIF test, without a solid evidence of being really equivalent. Therefore, efforts in standardising diagnostic tests and their brisk evolution and perfection make it fundamental nowadays not only to suggest the test name among the criteria, but to define and take a strong position on the method to use, and better yet, on what method not to use.

Maria Infantino ¹, Mariangela Manfredi,² Nicola Bizzaro,² On behalf of the Study Group on Autoimmune Diseases of the Italian Society of Clinical Pathology and Laboratory Medicine

¹Laboratory of Immunology and Allergology, Ospedale San Giovanni di Dio, Firenze, Italy

²Laboratorio di Patologia Clinica, Azienda Sanitaria Universitaria Integrata, Udine, Italy

Correspondence to Dr Maria Infantino, Laboratory of Immunology and Allergology, Ospedale San Giovanni di Dio, 55100 Firenze, Italy; maria2.infantino@uslcentro.toscana.it

Contributors MI drafted the article. NB participated in the design of the letter and revised the manuscript. MM revised the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite Infantino M, Manfredi M, Bizzaro N, *et al*. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2019-216591

Received 5 November 2019

Accepted 13 November 2019

Ann Rheum Dis 2019;0:1. doi:10.1136/annrheumdis-2019-216591

ORCID iD

Maria Infantino <http://orcid.org/0000-0002-6200-4467>

REFERENCES

- 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;71:1400–12.
- Petri M, Orbai A-M, Alarcón GS, *et al*. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
- Aggarwal R, Ringold S, Khanna D, *et al*. Distinctions between diagnostic and classification criteria? *Arthritis Care Res* 2015;67:891–7.
- Meroni PL, Chan EK, Damoiseaux J, *et al*. Unending story of the indirect immunofluorescence assay on HEp-2 cells: old problems and new solutions? *Ann Rheum Dis* 2019;78:e46.
- Pisetsky DS, Bossuyt X, Meroni PL. Ana as an entry criterion for the classification of SLE. *Autoimmun Rev* 2019;102400.
- Willems P, De Langhe E, Westhovens R, *et al*. Antinuclear antibody as entry criterion for classification of systemic lupus erythematosus: pitfalls and opportunities. *Ann Rheum Dis* 2019;78:e76.
- Claessens J, Belmonto T, De Langhe E, *et al*. Solid phase assays versus automated indirect immunofluorescence for detection of antinuclear antibodies. *Autoimmun Rev* 2018;17:533–40.
- Bizzaro N, Brusca I, Previtali G, *et al*. The association of solid-phase assays to immunofluorescence increases the diagnostic accuracy for ANA screening in patients with autoimmune rheumatic diseases. *Autoimmun Rev* 2018;17:541–7.
- Bossuyt X, Claessens J, De Langhe E, *et al*. Antinuclear antibodies by indirect immunofluorescence and solid phase assays. *Ann Rheum Dis* 2019;annrheumdis-2019-215443.
- Orme ME, Andalucia C, Sjölander S, *et al*. A comparison of a fluorescence enzyme immunoassay versus indirect immunofluorescence for initial screening of connective tissue diseases: systematic literature review and meta-analysis of diagnostic test accuracy studies. *Best Pract Res Clin Rheumatol* 2018;32:521–34.
- Bizzaro N. Can solid-phase assays replace immunofluorescence for ANA screening? *Ann Rheum Dis* 2018;annrheumdis-2018-214805.