Limited role of specificity of ANA for SLE classification. Response to: 'European League against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus: the laboratory immunologist's point of view' by Infantino *et al*

In their letter, Drs Infantino, Manfredi and Bizzaro express concerns regarding the low specificity of antinuclear antibodies (ANA) for systemic lupus erythematosus (SLE) classification.¹ In particular, they propose that the entry criterion definition of positive ANA in the new European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria as 'Antinuclear antibodies (ANA) at a titre of $\geq 1:80$ on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid phase ANA screening immunoassay with at least equivalent performance is highly recommended'^{2,3} could be associated with low specificity for SLE.

While specificity is important for classification criteria, as Dr Infantino and colleagues correctly stress,¹ it is important to take both the overall test characteristics of ANA and its position as an *entry criterion* into account. The systematic literature review and metaregression of published ANA data on patients with SLE performed as part of the EULAR/ACR SLE classification criteria project⁴ showed a relevant loss in *sensitivity* at a titre of 1:160 and above (table 1). At the titre of 1:80 selected for the EULAR/ACR 2019 classification criteria for SLE, specificity of the ANA test by itself is around 75% (table 1), far lower than the final specificity of 93.4% that the new set of EULAR/ACR criteria reached in the validation cohort.^{2,3} This is because an entry criterion on its own has limited influence on increasing specificity. It is just the first step before the application of many other criteria that ultimately improve the specificity of SLE classification.

ANA have an inherent inability to differentiate between SLE and other connective tissue diseases, so that high specificity is not realistic. Precisely therefore the position of this test was changed to that of an entry criterion.⁵ This was also more in line with the use of ANA as a highly sensitive screening parameter for connective tissue diseases. Given the role of the ANA test as an entry criterion, it was more important to provide a solution for centres without access to HEp-2 immunofluorescence than to try further improve specificity by more specific ANA tests. This said, we fully agree with Dr Infantino and colleagues that high quality ANA testing is extremely important and support efforts to standardise these tests.

For the EULAR/ACR criteria, issues concerning ANA test *sensitivity* using some HEp-2-cell substrates, raised by Pisetsky

and colleagues,⁶ are likely to have more impact on the EULAR/ACR criteria than ANA specificity issues considered by Infantino *et al*.¹ For diagnostic purposes, however, where a positive ANA result will often lead to several additional tests, ANA specificity plays an important role. We therefore agree that high quality ANA testing is crucial and that steps are necessary towards reaching this goal.

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Table 1 ANA sensitivity and specificity per ANA titre as per metaregression of published data on 13 080 patients with SLE⁴ 2017, American College of Rheumatology

Cut-off	Sensitivity		Specificity	
ANA titre	%	95% CI	%	95% CI
1:40	98.4	97.6 to 99.0	66.9	57.8 to 74.9
1:80	97.8	96.8 to 98.5	74.7	66.7 to 81.3
1:160	95.8	94.1 to 97.1	86.2	80.4 to 90.5
1:320	86.0	77.0 to 91.9	96.6	93.9 to 98.1

ANA, antinuclear antibodies; SLE, systemic lupus erythematosus.