Response to: 'Development and initial validation of diagnostic gene signatures for systemic lupus erythematosus' by Wang *et al*

In their letter, Dr Wang and colleagues¹ correctly remark that no novel molecular biomarkers were included in the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2019 classification criteria for systemic lupus erythematosus (SLE), although a variety of such markers were considered in the process, including the type I interferon signature.^{2,3} As cited by Wang *et al*,¹ sufficient evidence and worldwide availability were of importance for inclusion into the list of classification criteria items.

Their approach presently is on the opposite side of the field, where early hypotheses are generated. Dr Wang and colleagues¹ used robust rank aggregation for analysing multiple transcriptome data sets. Essentially all hits in this approach were interferon-regulated genes. Accordingly, the authors worked at enriching for genes of other modules, and over several steps arrived at a five-gene score, which was superior to any single gene in distinguishing SLE from healthy individuals.

This approach is interesting, and may in the end lead to markers relevant for diagnosis, as discussed by Dr Wang *et al*,¹ but eventually also for classification. However, testing against various other autoimmune diseases, such as in the EULAR/ACR SLE classification project,^{2,3} has not yet been shown. This in our view is relevant given, for example, the presence of an interferon signature also in other autoimmune diseases.⁴⁻⁶ Once this is successfully done, it will be interesting to see whether the combination of established criteria and such novel markers further improve classification.

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