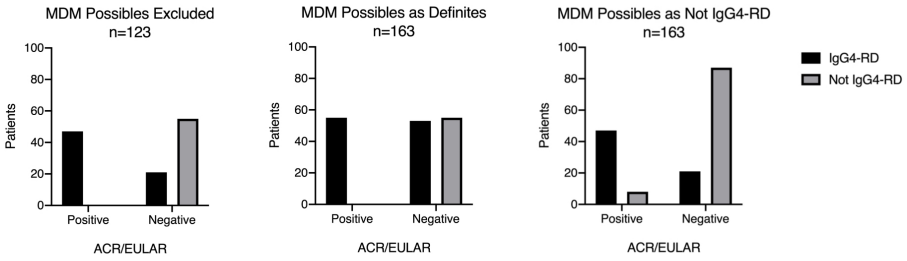
Correspondence on 'The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease'

IgG4-related disease (IgG4-RD) is a multisystem fibroinflammatory disorder diagnosed and managed across a broad spectrum of specialities. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IgG4-RD, recently published in this journal,[1] provide robust and validated measures for discrimination from disease mimics with excellent test performance. The classification criteria incorporates three domains: entry, exclusion and inclusion criteria, with numerically weighted inclusion criteria reaching a score of 20 points or more to support a diagnosis of IgG4-RD. We sought to evaluate these criteria in a real-world cohort of patients referred for discussion to our supraregional UK IgG4-RD multidisciplinary meeting (MDM) over a 3-year period from 2016 to 2019.[2]

We reviewed 165 patients discussed at our IgG4 MDM who had been classified as definite IgG4-RD, possible IgG4-RD or not IgG4-RD according to standard diagnostic criteria (HISORt for pancreas/biliary disease,[3] Japanese Consensus Diagnostic Criteria for systemic disease,[4] Consensus Statement on Pathology[5]) and MDM consensus opinion with prospective follow-up in a dedicated clinic. We applied the new ACR/EULAR classification criteria retrospectively to these cases to assess diagnostic accuracy. Of 165 patients, 2 had insufficient data available. Test performance of the ACR/EULAR classification criteria in our cohort are demonstrated in figure 1A.

Sixty-eight of 163 patients (42%) were considered to have definite IgG4-RD by the MDM. Of these, 47/68 (69%) met the ACR/EULAR classification criteria for IgG4-RD. Twenty-one

A



Sensitivity	69.1%	50.9%	69.1%
Specificity	100%	100%	91.6%
PPV	1.0	1.0	0.85
NPV	0.72	0.51	0.81

B

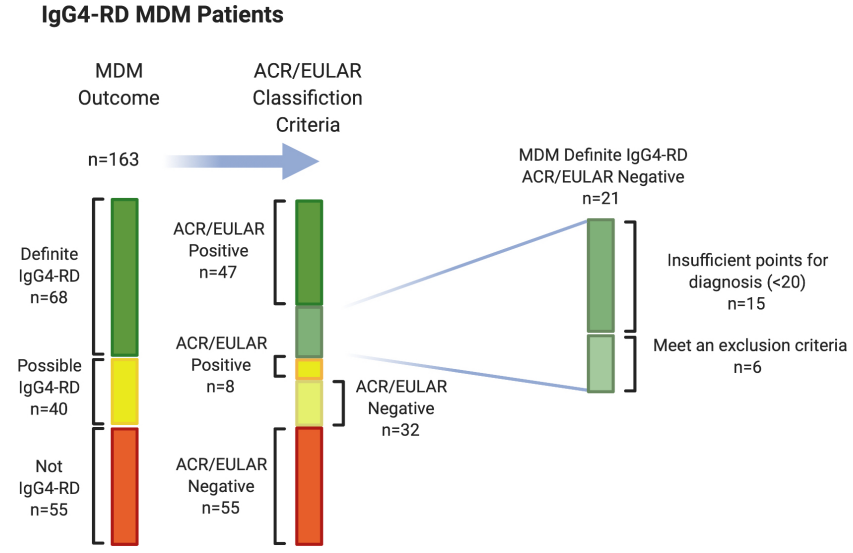


Figure 1 (A) Contingency table plots demonstrating ACR/EULAR criteria performance when patients considered possible IgG4-RD at MDM were either excluded, designated as definite IgG4-RD or designated as not IgG4-RD. Patients considered possible IgG4-RD at MDM are followed up and managed as IgG4-RD. (B) A total of 163 patients discussed in the joint Oxford-University College London Hospitals (UCLH) IgG4-RD MDM over 3 years were given a diagnosis of definite, possible or not IgG4-RD. ACR/EULAR classification criteria were retrospectively applied to this cohort, and reasons for disagreement are highlighted. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; IgG4-RD, IgG4-related disease; MDM, multidisciplinary meeting.

patients did not meet the criteria (figure 1B). Of the 21 patients, 15 (71%) scored less than 20 points (median 18) and 6 (29%) met one or more exclusion criteria (n=3 coexisting diagnosis of inflammatory bowel disease with both pancreas and biliary involvement, n=2 disease-specific autoantibody of low titre and not considered clinically relevant, n=2 histological exclusions (1 granuloma and 1 neutrophil)). During prospective follow-up (median 63 months), these patients continued to be managed as IgG4-RD with no alternative diagnosis made.

The greatest diagnostic disparity was in the pancreatobiliary IgG4 phenotype.[6] Fourteen of the 21 patients with IgG4-RD who did not meet the criteria had pancreatobiliary involvement. Of the 14 patients, 9 scored less than 20 points, and 5 met the exclusion criteria. Cases failed to score points within the numerically weighted imaging subdomain if presenting with biliary disease in isolation or in conjunction with pancreatic atrophy (lacking classical pancreatic swelling or pseudocapsule). In our experience, diffuse or focal pancreatic enlargement and rim enhancement are typical of early inflammatory autoimmune pancreatitis while atrophy occurs in the latter stages; the scoring does not account for this continuum.

Fifty-five of the 163 patients (34%) were considered not to have IgG4-RD by the MDM. In agreement, none met the ACR/EULAR classification criteria for IgG4-RD (figure 1B). Such high specificity gives these criteria excellent discriminatory value for the purpose of clinical therapeutic trials where excluding IgG4-RD mimics is critical to rigorous evaluation of treatment efficacy.

Application of the new ACR/EULAR classification criteria for IgG4-RD to our real-world IgG4 MDM has confirmed their high specificity in excluding those without the disease, but highlights lower sensitivity, especially in those with the pancreatobiliary IgG4 phenotype. Adjustments to the numerically weighted imaging criteria to include steroid-responsive cholangiopathy in isolation and pancreatic atrophy with biliary involvement, and modified exclusion criteria to include classical pancreatic disease with coexistent inflammatory colitis would increase sensitivity in our cohort. Furthermore, the aforementioned adjustments could also reduce the potential for selection bias in future clinical trials.

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Contributors RJRP was involved in study design, data collection, analysis and interpretation, in addition to drafting and critical appraisal of the manuscript. AV, EF, HB, MR-J, MC, EB and GW were involved in data collection and analysis, in addition to critical review of the manuscript. ELC was responsible for the original concept and was involved in study design, data collection, analysis and interpretation in addition to drafting and critical appraisal of the manuscript.

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Competing interests ELC consults for Viela Bio Pharma for IgG4-RD outside the submitted work. There are no commercial or financial conflicts of interest related to this article.

Patient and public involvement Regular patient engagement is conducted through the UK IgG4-related disease patient and public involvement group, and a lay summary of this work will appear on the patient pages of the authors' website (https://igg4-rd.ndm.ox.ac.uk).

Patient consent for publication Not required.

Ethics approval Ethical approval for this study was provided by Oxfordshire Research Ethics Council (10/H0604/51). The study was registered on the NIHR Portfolio UK Clinical Research Network.

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