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2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis With Polyangiitis

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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Objective. To develop and validate revised classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA).

Methods. Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in 5 phases: 1) identification of candidate criteria items using consensus methodology, 2) prospective collection of candidate items present at the time of diagnosis, 3) data-driven reduction of the number of candidate items, 4) expert panel review of cases to define the reference diagnosis, and 5) derivation of a points-based risk score for disease classification in a development set using least absolute shrinkage and selection operator logistic regression, with subsequent validation of performance characteristics in an independent set of cases and comparators.

Results. The development set for EGPA consisted of 107 cases of EGPA and 450 comparators. The validation set consisted of an additional 119 cases of EGPA and 437 comparators. From 91 candidate items, regression analysis identified 11 items for EPGA, 7 of which were retained. The final criteria and their weights were as follows: maximum eosinophil count ≥1 × 10^9/liter (+5), obstructive airway disease (+3), nasal polyps (+3), cytoplasmic antineutrophil cytoplasmic antibody (ANCA) or anti–proteinase 3 ANCA positivity (−3), extravascular eosinophilic predominant inflammation (+2), mononeuritis multiplex/motor neuropathy not due to radiculopathy (+1), and hematuria (−1). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as having EGPA if the cumulative score was ≥6 points. When these criteria were tested in the validation data set, the sensitivity was 85% (95% confidence interval [95% CI] 77–91%) and the specificity was 99% (95% CI 98–100%).

Conclusion. The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for EGPA demonstrate strong performance characteristics and are validated for use in research.

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The Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, of which the development of these classification criteria was a part, was funded by grants from the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), the Vasculitis Foundation, and the University of Pennsylvania Vasculitis Center.

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a form of vasculitis that is histologically defined by eosinophil-rich, necrotizing granulomatous inflammation primarily involving the respiratory tract, along with necrotizing vasculitis of small- to medium-sized arteries (1). EGPA is considered a form of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), along with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). ANCAs are detected in ~40–60% of patients with EGPA and are typically directed against myeloperoxidase (MPO) (2,3).

In 1990, the American College of Rheumatology (ACR) published classification criteria for EGPA (4). By current standards, these criteria have never been validated because they were developed using data from only 20 patients with EGPA without independent test and validation sets. Furthermore, the criteria were derived by comparing clinical data from patients with EGPA to data from 787 patients with other forms of vasculitis. Many of these comparators were patients with giant cell arteritis, a form of large-vessel vasculitis that is typically not difficult to readily distinguish from EGPA based on obvious clinical differences. Despite these methodologic weaknesses, the 1990 ACR criteria for EGPA have existed unchanged for several decades and have been useful to advance clinical research in these diseases. This article outlines the development and validation of the new ACR/European Alliance of Associations for Rheumatology (EULAR)–endorsed classification criteria for EGPA.

METHODS

A detailed and complete description of the methods involved in the development and validation of the classification criteria for EGPA is provided in Supplementary Appendix 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract. Briefly, an international Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians, and data managers was established to oversee the overall Diagnostic and Classification Criteria in Vasculitis (DCVAS) project (5). The Steering Committee established a 5-stage plan using data-driven and consensus methodology to develop the criteria for each of 6 forms of vasculitis.

Stage 1: generation of candidate classification items for the systemic vasculitides. Candidate classification items were generated by expert opinion and reviewed by a group of vasculitis experts across a range of specialties using a nominal group technique.

Stage 2: DCVAS prospective observational study. A prospective, international, multisite observational study was conducted (see Appendix A for study investigators and sites). Ethical approval was obtained from national and local ethics committees. Consecutive patients representing the full spectrum of disease were recruited from academic and community practices. Patients were included if they were 18 years or older and had a diagnosis of vasculitis or a condition that mimics vasculitis. Patients with AAV could only be enrolled within 2 years of diagnosis. Only data present at diagnosis were recorded.

Stage 3: refinement of candidate items specifically for AAV. The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases and comparators for AAV. Items were selected for exclusion if they had a prevalence of <5% within the data set and/or they were not clinically relevant for classification criteria (e.g., related to infection, malignancy, or demographic characteristics). Low-frequency items of clinical importance could be combined, when appropriate.

Stage 4: expert review to derive a gold standard–defined final set of cases of AAV. Experts in vasculitis from a wide range of geographic locations and specialties reviewed all submitted cases of vasculitis and a random subset of mimics of vasculitis. Each reviewer was asked to review ~50 submitted cases to confirm the diagnosis and to specify the certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty were retained for further analysis.

Stage 5: derivation and validation of the final classification criteria for EGPA. The DCVAS AAV data set was randomly split into development (50%) and validation (50%) sets. Comparisons were performed between cases of EGPA and a comparator group randomly selected from the DCVAS cohort in the following proportions: another type of AAV (including GPA and MPA), 60%; another form of small-vessel vasculitis (e.g., cryoglobulinemic vasculitis) or medium-vessel

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[Correction added on 20 June 2022, after first online publication: Appendices A and S1 have been replaced and Appendix S2 has been added online.]

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vasculitis (e.g., polyarteritis nodosa), 40%. Least absolute shrinkage and selection operator (lasso) logistic regression was used to identify items from the data set and create a parsimonious model including only the most important items. The final items in the model were formulated into a clinical risk-scoring tool with each factor assigned a weight based on its respective regression coefficient. A threshold that best balanced sensitivity and specificity was identified for classification.

In sensitivity analyses, the final classification criteria were applied to an unselected population of cases and comparators from the DCVAS data set based on the submitting physician diagnosis. Comparison was also made between the measurement properties of the new classification criteria for EGPA and the 1990 ACR classification criteria for EGPA using pooled data from the development and validation sets.

RESULTS

Generation of candidate classification items for the systemic vasculitides. The Steering Committee identified >1,000 candidate items for the DCVAS case report form (see Supplementary Appendix 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

DCVAS prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and participants is listed in Supplementary Appendices 3, 4, and 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract.

Refinement of candidate items specifically for AAV. Following a data-driven and expert consensus process, 91 items from the DCVAS case report form were retained for regression analysis, including 45 clinical (14 composite), 18 laboratory (2 composite), 12 imaging (all composite), and 16 biopsy (1 composite) items. Some clinical items were removed in favor of similar but more specific pathophysiologic descriptors. For example, "Hearing loss or reduction" was removed, and the composite item "Conductive hearing loss/sensorineural hearing loss" was retained. See Supplementary Appendix 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract, for the final candidate items used in the derivation of the classification criteria for GPA, MPA, and EGPA.

Expert review to derive a gold standard–defined final set of cases of AAV. Fifty-five independent experts reviewed vignettes derived from the case report forms for 2,871 cases submitted with a diagnosis of either small-vessel vasculitis (90% of case report forms) or another type of vasculitis or a mimic of vasculitis (10% of case report forms). The characteristics of the expert reviewers are shown in Supplementary Appendix 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract. A flow chart showing the results of the expert review process is shown in Supplementary Appendix 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract. A total of 2,072 cases (72%) passed the process and were designated as cases of vasculitis; these cases were used for the stage 5 analyses.

After expert panel review, 226 of 315 cases of EGPA were retained for subsequent analysis. Compared to patients who were retained, patients who were excluded from further analysis

Table 1. Demographic and disease features of cases of EGPA and comparators*

	EGPA (n = 226)	Comparators (n = 887)†	*P*
Age, mean ± SD years	52.9 ± 14.4	56.2 ± 17.6	0.009
Sex, no. (%) female	113 (50.0)	445 (50.2)	1.000
Maximum serum creatinine, mean ± SD			<0.001
μmoles/liter	85.0 ± 53.6	205.90 ± 237.0	
mg/dl	0.96 ± 0.6	2.33 ± 2.7	
cANCA positive, no. (%)	17 (7.5)	251 (28.3)	<0.001
pANCA positive, no. (%)	83 (36.7)	289 (32.6)	0.271
Anti–PR3-ANCA positive, no. (%)	7 (3.1)	264 (29.8)	<0.001
Anti–MPO-ANCA positive, no. (%)	98 (43.4)	323 (36.4)	0.065
Maximum eosinophil count ≥1 × 10^9/liter, no. (%)	208 (92.0)	53 (6.0)	<0.001

* cANCA = cytoplasmic antineutrophil cytoplasmic antibody; pANCA = perinuclear ANCA; anti–PR3-ANCA = anti–proteinase 3–ANCA; anti–MPO-ANCA = anti–myeloperoxidase-ANCA.
† Diagnoses of comparators for the classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA) included granulomatosis with polyangiitis (n = 300), microscopic polyangiitis (n = 291), polyarteritis nodosa (n = 51), non–ANCA-associated small-vessel vasculitis that could not be subtyped (n = 51), Behçet's disease (n = 50), IgA vasculitis (n = 50), cryoglobulinemic vasculitis (n = 34), ANCA-associated vasculitis that could not be subtyped (n = 25), primary central nervous system vasculitis (n = 19), and anti–glomerular basement membrane disease (n = 16).

had significantly higher serum creatinine levels (mean ± SD 102.8 ± 88.7 versus 85.0 ± 53.6 μmoles/liter; $P = 0.03$), lower rates of MPO-ANCA positivity (22% versus 43%; $P < 0.01$), and were less likely to have maximum eosinophil counts ≥1 × 10^9/liter (62% versus 92%; $P < 0.01$). There were 887 comparators randomly selected for analysis. Table 1 shows the demographic and disease features of the 1,113 cases included in this analysis (226 patients with EGPA and 887 comparators), of which 557 (50%;107 patients with EGPA and 450 comparators) were in the development set, and 556 (50%; 119 patients with EGPA and 437 comparators) were in the validation set.

Derivation and validation of the final classification criteria for EGPA. Lasso regression of the previously selected 91 items yielded 11 independent items for EGPA (Supplementary Appendix 9A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract). Each item was then adjudicated by the DCVAS Steering Committee for inclusion based on clinical relevance and specificity to EGPA, resulting in 7 final items. Weighting of an individual criterion was based on logistic regression fitted to the 7 selected items (see Supplementary Appendix 10A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

Model performance. Use of a cutoff of ≥6 for total risk score (see Supplementary Appendix 11A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract, for different cut points) yielded a sensitivity of 84.9% (95% confidence interval [95% CI] 77.2–90.8%) and a specificity of 99.1% (95% CI 98.3–99.8%) in the validation set. The area under the curve (AUC) for the model was 0.98 (95% CI 0.97–1.00) in the development set and 0.99 (95% CI 0.97–1.00) in the validation set for the final EGPA classification criteria (Supplementary Appendix 12A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

Blood eosinophil count ≥ 1 x10^9/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Sum the scores for 7 items, if present. A score of ≥ 6 is needed for classification of EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS.

Figure 1. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis.

The final classification criteria for EGPA are presented in Figure 1 (for the slide presentation version, see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

Sensitivity analyses. The classification criteria for EGPA were applied to 2,871 patients in the DCVAS database using the original physician-submitted diagnosis (n = 315 EGPA and 2,556 randomly selected comparators). Use of the same cut point of ≥6 points for the classification of EGPA yielded a similar specificity of 99% but a lower sensitivity of 75%. This upheld the a priori hypothesis that specificity would remain unchanged but sensitivity would be reduced in a population of patients that included fewer clearcut diagnoses of EGPA (i.e., cases that did not pass expert panel review).

When the 1990 ACR classification criteria for EGPA were applied to the DCVAS data set, the criteria performed poorly due to low sensitivity (44%) but retained excellent specificity (99%), with an AUC of 0.72 (95% CI 0.68–0.75).

DISCUSSION

Presented here are the final 2022 ACR/EULAR EGPA classification criteria. A 5-stage approach has been used, underpinned by data from the multinational prospective DCVAS study and informed by expert review and consensus at each stage. The comparator group for developing and validating the criteria were patients with other forms of AAV and other small- and medium-vessel vasculitides, which are the clinical entities where discrimination from EGPA is difficult, but important. The new criteria for EGPA have excellent sensitivity and specificity and incorporate ANCA testing. The criteria were designed to have face and content validity for use in clinical trials and other research studies.

These criteria are validated and intended for the purpose of *classification* of vasculitis and are not appropriate for use in establishing a *diagnosis* of vasculitis. The aim of the classification criteria is to differentiate cases of EGPA from similar types of vasculitis in research settings. Therefore, the criteria should only be applied when a diagnosis of small- or medium-vessel vasculitis has been made and all potential "vasculitis mimics" have been excluded. The exclusion of mimics is a key aspect of many classification criteria, including those for Sjögren's syndrome (6) and rheumatoid arthritis (7). The 1990 ACR classification criteria for vasculitis perform poorly when used for diagnosis (i.e., when used to differentiate between cases of vasculitis versus mimics without vasculitis) (8), and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria in people in whom alternative diagnoses, such as infection or other non-vasculitis inflammatory diseases, are still being considered. Specifically, the criteria were not developed to differentiate patients with EGPA from those with other related hypereosinophilic syndromes or eosinophilic malignancies (9).

The 2022 ACR/EULAR EGPA classification criteria reflect the collaborative effort of the international vasculitis community to delineate the salient clinical features that differentiate EGPA from other forms of vasculitis. The final criteria include 7 clinical items that are easily assessed during routine clinical evaluation of patients with EGPA. The criteria highlight the importance of blood eosinophilia, asthma, and eosinophilic inflammation to classify EGPA among other forms of vasculitis and specify additional features (e.g., nasal polyps, mononeuritis multiplex) that function as important disease classifiers. Classification criteria are intended to define a homogeneous group of patients with a particular disease for inclusion into clinical research studies. By maximizing specificity, the revised criteria for EGPA ensure that few cases will inappropriately meet the criteria threshold of ≥6 points; thus, these criteria will function to facilitate the conduct of future clinical trials and other studies in EGPA.

The negative items included in the final criteria underscore that these criteria are intended for use as classification, not diagnostic, criteria to differentiate EGPA from other forms of vasculitis in research settings. Both hematuria and anti–proteinase 3 ANCA (anti–PR3-ANCA) function as negative items in the new EGPA classification criteria, yet glomerulonephritis and ANCA are features of disease that, when present, can be useful to diagnose EGPA. When compared to other forms of AAV, however, biopsy-proven glomerulonephritis was significantly less common in the DCVAS cohort in patients with EGPA (4.9%) compared to those with GPA (27.8%) or MPA (48.5%). Similarly, anti–PR3-ANCAs have been reported in few patients with EGPA but are much more prevalent in GPA (10). For these reasons, hematuria and anti–PR3-ANCAs work against a patient with small-vessel vasculitis being classified as having EGPA. Although anti–MPO-ANCAs can be detected in 40–60% of patients with EGPA, anti–MPO-ANCA positivity was not included in the final criteria because these antibodies are significantly more prevalent in diseases like MPA and thus are not discriminant classifiers for EGPA (11).

There are some study limitations to consider. Although this was the largest international study ever conducted in vasculitis, most patients were recruited from Europe, Asia, and North America. The performance characteristics of the criteria should be further tested in African and South American populations, which may have different clinical presentations of vasculitis. These criteria were developed using data collected from adult patients with vasculitis. Although the clinical characteristics of EGPA and the other vasculitides which these criteria were tested against are not known to differ substantially between adults and children, these criteria should be applied to children with some caution. The scope of the criteria is intentionally narrow and applies only to patients who have been diagnosed as having vasculitis. Diagnostic criteria are not specified. The criteria are intended to identify homogeneous populations of disease and, therefore, may not be appropriate for studies focused on the full spectrum of clinical heterogeneity in these conditions. To maximize relevance and face

validity of the new criteria, study sites and expert reviewers were recruited from a broad range of countries and different medical specialties. Nonetheless, the majority of patients were recruited from academic rheumatology or nephrology units, which could have introduced referral bias.

There are several strengths to the new 2022 ACR/EULAR EGPA classification criteria. The criteria were developed within a large cohort reflecting international expertise in systemic vasculitis according to ACR guidance for classification criteria development (11). The criteria represent several important methodologic advancements compared to the original 1990 ACR classification criteria for EGPA. Expert review rather than submitting physician diagnosis was used as the diagnostic reference standard to minimize investigator bias. Second, while the 1990 ACR criteria were entirely derived in 20 patients with EGPA and not validated, the new criteria were developed in 107 patients with EGPA and validated in an independent test set that contained an additional 119 patients with EGPA. Third, unlike the 1990 ACR criteria, the new ACR/EULAR EGPA criteria are weighted to reflect the relative importance of specific items (e.g., eosinophil counts). Finally, when both criteria sets were tested within the DCVAS cohort, the performance characteristics of the 1990 ACR criteria were suboptimal when compared to the 2022 revised ACR/EULAR EGPA criteria.

The 2022 ACR/EULAR classification criteria for EGPA are the product of a rigorous methodologic process that utilized an extensive data set generated by the work of a remarkable international group of collaborators. These criteria have been endorsed by the ACR and EULAR and are now ready for use to differentiate one type of vasculitis from another to define populations in research studies.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Grayson, Ponte, Suppiah, Robson, Craven, Judge, Hutchings, Luqmani, Watts, Merkel.

Acquisition of data. Grayson, Ponte, Suppiah, Robson, Craven, Luqmani, Watts, Merkel.

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APPENDIX A: THE DCVAS INVESTIGATORS

The DCVAS study investigators are as follows: Paul Gatenby (ANU Medical Centre, Canberra, Australia); Catherine Hill (Central Adelaide Local Health Network: The Queen Elizabeth Hospital, Australia); Dwarakanathan Ranganathan (Royal Brisbane and Women's Hospital, Australia); Andreas Kronbichler (Medical University Innsbruck, Austria); Daniel Blockmans (University Hospitals Leuven, Belgium); Lillian Barra (Lawson Health Research Institute, London, Ontario, Canada); Simon Carette, Christian Pagnoux (Mount Sinai Hospital, Toronto, Canada); Navjot Dhindsa (University of Manitoba, Winnipeg, Canada); Aurore Fifi-Mah (University of Calgary, Alberta, Canada); Nader Khalidi (St Joseph's Healthcare, Hamilton, Ontario, Canada); Patrick Liang (Sherbrooke University Hospital Centre, Canada); Nataliya Milman (University of Ottawa, Canada); Christian Pineau (McGill University, Canada); Xinping Tian (Peking Union Medical College Hospital, Beijing, China); Guochun Wang (China-Japan Friendship Hospital, Beijing, China); Tian Wang (Anzhen Hospital, Capital Medical University, China); Ming-hui Zhao (Peking University First Hospital, China); Vladimir Tesar (General University Hospital, Prague, Czech Republic); Bo Baslund (University Hospital, Copenhagen [Rigshospitalet], Denmark); Nevin Hammam (Assiut University, Egypt); Amira Shahin (Cairo University, Egypt); Laura Pirila (Turku University Hospital, Finland); Jukka Putaala (Helsinki University Central Hospital, Finland); Bernhard Hellmich (Kreisklinken Esslingen, Germany); Jörg Henes (Universitätsklinikum Tübingen, Germany); Julia Holle (Klinikum Bad Bramstedt, Germany); Peter

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