

University of Groningen

## 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis

DCVAS Study Group; Ponte, Cristina; Grayson, Peter C.; Robson, Joanna C.; Suppiah, Ravi; Gribbons, Katherine Bates; Judge, Andrew; Craven, Anthea; Khalid, Sara; Hutchings, Andrew

*Published in:*  
 Arthritis and Rheumatology

*DOI:*  
[10.1002/art.42325](https://doi.org/10.1002/art.42325)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
 Publisher's PDF, also known as Version of record

*Publication date:*  
 2022

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

DCVAS Study Group, Ponte, C., Grayson, P. C., Robson, J. C., Suppiah, R., Gribbons, K. B., Judge, A., Craven, A., Khalid, S., Hutchings, A., Watts, R. A., Merkel, P. A., & Luqmani, R. A. (2022). 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis. *Arthritis and Rheumatology*, 74(12), 1881-1889. <https://doi.org/10.1002/art.42325>

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

# 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis

Cristina Ponte,<sup>1</sup> Peter C. Grayson,<sup>2</sup> Joanna C. Robson,<sup>3</sup> Ravi Suppiah,<sup>4</sup> Katherine Bates Gribbons,<sup>2</sup> Andrew Judge,<sup>5</sup> Anthea Craven,<sup>6</sup> Sara Khalid,<sup>6</sup> Andrew Hutchings,<sup>7</sup> Richard A. Watts,<sup>8</sup> Peter A. Merkel,<sup>9</sup> and Raashid A. Luqmani,<sup>6</sup> for the DCVAS Study Group

*This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the 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.*

*The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.*

**Objective.** To develop and validate updated classification criteria for giant cell arteritis (GCA).

**Methods.** Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in 6 phases: 1) identification of candidate items, 2) prospective collection of candidate items present at the time of diagnosis, 3) expert panel review of cases, 4) data-driven reduction of candidate items, 5) derivation of a points-based risk classification score in a development data set, and 6) validation in an independent data set.

**Results.** The development data set consisted of 518 cases of GCA and 536 comparators. The validation data set consisted of 238 cases of GCA and 213 comparators. Age  $\geq 50$  years at diagnosis was an absolute requirement for classification. The final criteria items and weights were as follows: positive temporal artery biopsy or temporal artery halo sign on ultrasound (+5); erythrocyte sedimentation rate  $\geq 50$  mm/hour or C-reactive protein  $\geq 10$  mg/liter (+3); sudden visual loss (+3); morning stiffness in shoulders or neck, jaw or tongue claudication, new temporal headache, scalp tenderness, temporal artery abnormality on vascular examination, bilateral axillary involvement on imaging, and fluorodeoxyglucose–positron emission tomography activity throughout the aorta (+2 each). A patient could be classified as having GCA with a cumulative score of  $\geq 6$  points. When these criteria were tested in the validation data set, the model area under the curve was 0.91 (95% confidence interval [95% CI] 0.88–0.94) with a sensitivity of 87.0% (95% CI 82.0–91.0%) and specificity of 94.8% (95% CI 91.0–97.4%).

**Conclusion.** The 2022 American College of Rheumatology/EULAR GCA classification criteria are now validated for use in clinical research.

This article is published simultaneously in *Annals of the Rheumatic Diseases*.

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, which included the development of this classification criteria, was funded by grants from the American College of Rheumatology (ACR), EULAR, the Vasculitis Foundation, and the University of Pennsylvania Vasculitis Center. This study was also supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH.

<sup>1</sup>Cristina Ponte, MD, PhD: Department of Rheumatology, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa, Lisbon, Portugal, and Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisbon, Portugal; <sup>2</sup>Peter C. Grayson, MD, MSc, Katherine Bates Gribbons, BS: Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, Maryland; <sup>3</sup>Joanna C. Robson, MBBS, PhD:

Centre for Health and Clinical Research, University of the West of England, and Rheumatology Department, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK; <sup>4</sup>Ravi Suppiah, MBChB, MD, FRACP: Te Whatu Ora - Health New Zealand, Auckland, New Zealand; <sup>5</sup>Andrew Judge, PhD: Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, UK, Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK, and National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and University of Bristol, Bristol, UK; <sup>6</sup>Anthea Craven, BSc, Sara Khalid, DPhil, Raashid A. Luqmani, DM, FRCP: Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, UK; <sup>7</sup>Andrew Hutchings, MSc: Department of Health Services Research and Policy, London School

## INTRODUCTION

Giant cell arteritis (GCA), formerly known as temporal arteritis, is the most common form of systemic vasculitis in patients aged  $\geq 50$  years (1). GCA is defined by granulomatous arteritis that affects large- and medium-sized blood vessels with a predisposition to affect the cranial arteries (2). Common presenting features of the disease include headache, constitutional symptoms, jaw claudication, scalp tenderness, visual disturbances, and elevated inflammatory markers (3).

In 1990, the American College of Rheumatology (ACR) endorsed classification criteria for GCA (4). These criteria were established before the widespread use of noninvasive and advanced vascular imaging modalities, which have become increasingly incorporated in the clinical assessment of GCA. Vascular ultrasound can be used to diagnose GCA, and depending on the clinical setting, a noncompressible “halo” sign of a temporal  $\pm$  axillary artery may replace the need for temporal artery biopsy (TAB) (5–8). Moreover, vascular imaging has demonstrated that arterial involvement in GCA is not exclusively confined to the cranial arteries (9,10) and can commonly affect the aorta and primary branches in a pattern similar to Takayasu arteritis (TAK) (11,12).

The limitations of the ACR 1990 criteria for GCA have become more apparent in the conduct of recent clinical trials and other research studies, in which investigators typically modify the 1990 ACR criteria to reflect modern practice (6,13,14). Notably, the 1990 ACR criteria focus mostly on cranial features of GCA and do not perform well in classifying patients with disease predominantly affecting the larger arteries. The 1990 ACR criteria were derived using comparator populations which included many patients with small-vessel vasculitis, a form of vasculitis that is not typically difficult to differentiate from GCA. In addition, the 1990 ACR criteria for GCA followed the “number of criteria” rule, which considered each criterion to have equal weight as a classifier for the disease. Since then, methodologic advances in classification criteria have allowed movement toward weighted criteria with threshold scores that improve performance characteristics (15,16).

This article outlines the development and validation of the revised ACR/EULAR–endorsed classification criteria for GCA.

## METHODS

An international Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians, and data

managers was assembled to oversee the overall development of classification criteria for primary vasculitis (17). A detailed and complete description of the methods involved in the development and validation of the classification criteria for GCA is located in the Supplementary Appendix 1 (<http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). Briefly, the Steering Committee implemented a 6-stage plan using data-driven and consensus methodology to develop the following criteria.

**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 nominal group technique.

**Stage 2: Diagnostic and Classification Criteria for Vasculitis (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 local ethics committees. Consecutive patients representing the full spectrum of vasculitides 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 (e.g., infection, malignancy, atherosclerosis). Patients with GCA could only be enrolled within 2 years of diagnosis. Only data present at diagnosis were used to develop the classification criteria.

**Stage 3: expert review to derive a gold standard–defined set of cases of large-vessel vasculitis (LVV).** Experts in vasculitis from a wide range of geographic locations and specialties (see Appendix A) reviewed all submitted cases of vasculitis and a random selection of vasculitis mimics. Each reviewer was asked to review  $\sim 50$  submitted cases to confirm the diagnosis and to specify the degree of certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty by 2 reviewers were retained for further analysis.

**Stage 4: refinement of candidate items specifically for LVV.** The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases and comparators for LVV. Density plots were assessed to study age distribution at diagnosis and symptom onset for GCA

of Hygiene and Tropical Medicine, UK; <sup>8</sup>Richard A. Watts, MD: Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Oxford NIHR Biomedical Research Centre, University of Oxford, UK, and Norwich Medical School, University of East Anglia, Norwich, UK; <sup>9</sup>Peter A. Merkel, MD, MPH: Division of Rheumatology, Department of Medicine, and Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia.

Author disclosures are available at <https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42325&file=art42325-sup-0001-Disclosureform.pdf>.

Address correspondence via email to Peter A. Merkel, MD, MPH, at [pmerkel@upenn.edu](mailto:pmerkel@upenn.edu).

Submitted for publication February 14, 2022; accepted in revised form July 30, 2022.

and TAK. Absolute age requirements versus incorporation of age as a candidate criteria item was considered. Items related to the vascular physical examination, vascular imaging, arterial biopsy, and laboratory values were combined or eliminated based on consensus review. 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 demography). Low-frequency items of clinical importance could be combined, when appropriate. Patterns of vascular imaging findings detected by vascular ultrasound, angiography, or positron emission tomography (PET) were defined by K-means clustering (18).

**Stage 5: derivation of the final classification criteria for GCA.** The DCVAS data set was split into development (70%) and validation (30%) sets. Comparisons were performed between cases of GCA and a randomly selected comparator group in the following proportions: TAK, 33.5%; other vasculitides that mimic GCA and TAK (isolated aortitis, primary central nervous system vasculitis, polyarteritis nodosa, Behçet's disease, and other LVV), 33.4%; and other diagnoses that mimic LVV (e.g., atherosclerosis, unspecified headache), 33.1%. Least absolute shrinkage and selection operator (lasso) logistic regression was used to identify predictors from the data set and create a parsimonious model including only the most important predictors (19). 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.

**Stage 6: validation of the final classification criteria for GCA.** Performance of the new criteria was validated in an independent set of cases and comparators. Performance of the final classification criteria was examined in specific subsets of patients with GCA using data from the combined development and validation sets to maximize sample sizes for the subgroups. Patients were studied according to different disease subtypes (biopsy-proven GCA and large-vessel GCA) and regions of the world (North America, Europe) where clinical strategies to assess GCA are known to differ (20). Biopsy-proven GCA was defined as definite vasculitis on TAB reported by the submitting physician, and large-vessel GCA was defined as vasculitic involvement of the aorta or its branch arteries on either angiography (computed tomography, magnetic resonance imaging, or catheter-based angiography), ultrasound, or PET, without vasculitis on TAB. Comparison was made between the measurement properties of the new classification criteria for GCA and the 1990 ACR classification criteria in the validation data set. Performance characteristics of the criteria were also tested in patients with TAK and compared to those with GCA diagnosed between the ages of 50 and 60 years.

## 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, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>).

**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 study participants is listed in Supplementary Appendices 3, 4, and 5 (<http://onlinelibrary.wiley.com/doi/10.1002/art.42325>).

**Expert review methodology to derive a gold standard-defined final set of cases of LVV.** The LVV expert panel review process included 56 experts who reviewed vignettes derived from the Case Report Forms for 2,131 cases submitted with a diagnosis of LVV (1,608 [75.5% of Case Report Forms]), another type of vasculitis (118 [5.5% of Case Report Forms]), or a mimic of vasculitis (405 [19.0% of Case Report Forms]). Characteristics and the list of expert reviewers are shown in Supplementary Appendices 6 and 7 (<http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). A sample vignette and the LVV expert panel review flow chart are shown in Supplementary Appendices 8 and 9 (<http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). A total of 1,695 cases (80%) passed the main LVV process. An additional 373 cases of LVV and comparators, confirmed during a previous review process to derive the classification criteria for antineutrophil cytoplasmic antibody-associated vasculitis, were also included. In total, after both review processes, 2,068 cases were available for the stages 4 and 5 analyses.

The submitting physician diagnosis of GCA was confirmed in 913 of 1,137 cases (80.3%) after both expert panel reviews. The reasons for exclusion were diagnosis of GCA categorized as "uncertain" or "very uncertain" during panel review ( $n = 187$ ) or change in diagnosis during panel review to another type of vasculitis (isolated aortitis, TAK, other vasculitides) ( $n = 11$ ) or to a comparator disease ( $n = 26$ ). An additional 29 patients who were not initially diagnosed as having GCA by the submitting physician were diagnosed as having GCA after panel review and DCVAS Steering Committee member adjudication. In total, 942 cases of confirmed GCA were available for analysis. To balance the number of cases of GCA with the number of available comparators, 756 cases of GCA were randomly selected for subsequent analysis.

### Refinement of candidate items specifically for GCA.

Only 7 of 942 patients with GCA (<1%) were diagnosed at age <50 years (see Supplementary Appendix 10 for the distribution of "age at diagnosis" in patients with LVV, and the similar

distribution of “age at symptom onset,” <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). Therefore, an age of  $\geq 50$  years at diagnosis was considered an absolute requirement to classify GCA. Cluster analyses of vascular imaging data identified bilateral axillary involvement and diffuse fluorodeoxyglucose uptake throughout the aorta on PET as specific imaging patterns for GCA (see Supplementary Appendices 11 and 12, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). These imaging patterns were tested as potential classifiers.

Following a data-driven and expert consensus process, 72 items of the DCVAS Case Report Form were retained for regression analysis, including 32 demographic and clinical items, 14 laboratory items (including values of C-reactive protein [CRP] level and erythrocyte sedimentation rate [ESR], each divided into 5 categories), 14 imaging items (13 composite), 11 vascular examination items (5 composite, and upper extremity blood pressure divided into 6 categories), and 1 biopsy item (Supplementary Appendix 13, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>).

**Derivation of the final classification criteria for GCA.** A total of 1,505 patients were selected for analysis (756 GCA and 749 comparators), of which 1,054 (70%) were in the development data set (518 GCA and 536 comparators) and 451 (30%) in the validation data set (238 GCA and 213 comparators). Table 1 describes the demographic and clinical features of the patients with GCA and the comparators. The patients with GCA were recruited from Europe ( $n = 796$ ), North America ( $n = 112$ ), Oceania ( $n = 18$ ),

and Asia ( $n = 16$ ). Clinical diagnoses assigned to patients in the comparator group are detailed in Supplementary Appendix 14 (<http://onlinelibrary.wiley.com/doi/10.1002/art.42325>).

Lasso regression of the previously selected 72 items yielded 27 independent predictor variables for GCA (Supplementary Appendix 15A, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). Each predictor variable was then reviewed for inclusion by the DCVAS Steering Committee, based on their odds ratios and specificity to GCA, to ensure face validity. The variables “definitive vasculitis on TAB” and “halo sign on temporal artery ultrasound” were found to dominate the model as quite strong predictors of GCA (see Supplementary Appendix 16A for cluster plots showing almost a perfect overlap between the diagnosis of GCA and positive TAB or halo sign on temporal artery ultrasound, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). Therefore, for the remaining variables to have discriminatory value, both of these items were removed from the model, combined into one composite item “vasculitis on TAB or halo sign on temporal artery ultrasound” and given a risk score of one point below the final threshold set to classify GCA to maintain face validity. The variables “jaw claudication” and “tongue claudication” were combined into 1 item, as were the variables “maximum ESR ( $>50$  mm/hour)” and “maximum CRP ( $>10$  mg/liter).” Although the variable “new persistent headache, occipital or cervical” showed important statistical significance, it decreased the overall specificity of the model when testing their final performance characteristics (patients versus comparators) and was, therefore, also removed. Weighting of the individual criterion

**Table 1.** Demographic and disease features of the patients with giant cell arteritis and the comparators\*

	GCA ( $n = 756$ )	Comparators ( $n = 749$ )†	<i>P</i>
Age, mean $\pm$ SD years	72.2 $\pm$ 8.5	44.6 $\pm$ 18.0	<0.001
Female sex	511 (67.6)	447 (59.7)	0.001
Clinical features			
Morning stiffness, neck/torso	88 (11.6)	15 (2.0)	<0.001
Morning stiffness, shoulders/arms	174 (23.0)	23 (3.1)	<0.001
Sudden visual loss	102 (13.5)	29 (3.9)	<0.001
Jaw claudication	356 (47.1)	19 (2.5)	<0.001
Tongue claudication	21 (2.8)	1 (0.1)	<0.001
New persistent temporal headache	475 (62.8)	90 (12.0)	<0.001
Scalp tenderness	260 (34.4)	25 (3.3)	<0.001
Temporal artery abnormality on vascular examination‡	354 (46.8)	35 (4.7)	<0.001
Investigations			
Maximum ESR $\geq 50$ mm/hour	558 (73.8)	291 (38.9)	<0.001
Maximum CRP $\geq 10$ mg/liter	683 (90.3)	445 (59.4)	<0.001
Definitive vasculitis on temporal artery biopsy	335 (44.3)	1 (0.1)	<0.001
Halo sign on temporal artery ultrasound	211 (27.9)	1 (0.1)	<0.001
Bilateral axillary involvement on imaging§	57 (7.5)	12 (1.6)	<0.001
FDG-PET activity throughout aorta¶	52 (6.9)	9 (1.2)	<0.001

\* Except where indicated otherwise, values are the number (%). ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; FDG-PET =  $^{18}$ F-fluorodeoxyglucose-positron emission tomography.

† Diagnoses of comparators for the classification criteria for giant cell arteritis (GCA) included Takayasu arteritis ( $n = 251$ ), Behçet’s disease ( $n = 133$ ), polyarteritis nodosa ( $n = 74$ ), isolated aortitis ( $n = 16$ ), primary central nervous system vasculitis ( $n = 16$ ), large-vessel vasculitis (LVV) that could not be subtyped ( $n = 9$ ), other diseases that mimic LVV ( $n = 250$ ).

‡ Absent or diminished pulse, tenderness, or hard ‘cord like’ appearance.

§ Defined as damage (i.e., stenosis, occlusion, or aneurysm) on angiography (computed tomography, magnetic resonance, or catheter-based) or ultrasound, halo sign on ultrasound, or abnormal FDG uptake on PET.

¶ Descending thoracic and abdominal aorta.

included in the model was based on logistic regression fitted to the remaining 9 selected predictors (Supplementary Appendix 17A, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>).

### Validation of the final classification criteria for GCA.

Using a cutoff of  $\geq 6$  in total risk score in the validation data set (see Supplementary Appendix 18A at <https://onlinelibrary.wiley.com/doi/10.1002/art.42325> for different cutoff points), the sensitivity

was 87.0% (95% confidence interval [95% CI] 82.0–91.0%) and specificity was 94.8% (95% CI 91.0–97.4%). The area under the curve for the model was 0.91 (95% CI 0.88–0.94) (Supplementary Appendix 19A, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>). The final 2022 ACR/EULAR classification criteria for GCA are presented in Figure 1 (for the slide presentation versions, see Supplementary Figure 1, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>).

## 2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EULAR CLASSIFICATION CRITERIA FOR GIANT CELL ARTERITIS

### CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

### ABSOLUTE REQUIREMENT

Age  $\geq 50$  years at time of diagnosis

### ADDITIONAL CLINICAL CRITERIA

Morning stiffness in shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery <sup>1</sup>	+2

### LABORATORY, IMAGING, AND BIOPSY CRITERIA

Maximum ESR $\geq 50$ mm/hour or maximum CRP $\geq 10$ mg/liter <sup>2</sup>	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound <sup>3</sup>	+5
Bilateral axillary involvement <sup>4</sup>	+2
FDG-PET activity throughout aorta <sup>5</sup>	+2

**Sum the scores for 10 items, if present. A score of  $\geq 6$  points is needed for the classification of GIANT CELL ARTERITIS.**

1. Examination of the temporal artery showing absent or diminished pulse, tenderness, or hard 'cord-like' appearance.
2. Maximum erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) values prior to initiation of treatment for vasculitis.
3. Presence of either definitive vasculitis on temporal artery biopsy or halo sign on temporal artery ultrasound. There are no specific histopathologic criteria to define definitive vasculitis on temporal artery biopsy. Presence of giant cells, mononuclear leukocyte infiltration, and fragmentation of the internal elastic lamina were independently associated with histopathologic interpretation of definite vasculitis in the DCVAS cohort<sup>[24]</sup>. Halo sign is defined by the presence of an homogenous, hypoechoic wall thickening on ultrasound<sup>[25]</sup>.
4. Bilateral axillary involvement is defined as luminal damage (stenosis, occlusion, or aneurysm) on angiography (computed tomography, magnetic resonance, or catheter-based) or ultrasound, halo sign on ultrasound, or fluorodeoxyglucose uptake on positron emission tomography.
5. Abnormal fluorodeoxyglucose (FDG) uptake in the arterial wall (e.g., greater than liver uptake by visual inspection) throughout the descending thoracic and abdominal aorta on positron emission tomography (PET).

**Figure 1.** The final 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis.

**Table 2.** Performance characteristics of the 2022 ACR/EULAR classification criteria for giant cell arteritis\*

Patient subset	Total no. patients (no. GCA patients)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Development data set	1,054 (518)	84.8 (81.4–87.7)	95.0 (92.8–96.7)	0.90 (0.88–0.92)
Validation data set	451 (238)	87.0 (82.0–91.0)	94.8 (91.0–97.4)	0.91 (0.88–0.94)
Biopsy-proven GCA†	1,104 (355)	100.0 (99.0–100.0)	94.9 (93.1–96.4)	0.97 (0.97–0.98)
Large-vessel GCA‡	873 (124)	55.7 (46.5–64.6)	94.9 (93.1–96.4)	0.75 (0.71–0.80)

\* Performance characteristics were tested in the subsets using the combined development and validation data sets to maximize sample size. ACR = American College of Rheumatology; GCA = giant cell arteritis; 95% CI = 95% confidence interval; AUC = area under the curve.

† Definite vasculitis on temporal artery biopsy (TAB).

‡ Involvement of the aorta or its branch arteries on imaging, without vasculitis on TAB.

The performance characteristics of the criteria in different subsets of patients with GCA are shown in Table 2 and Supplementary Appendix 20A (<https://onlinelibrary.wiley.com/doi/10.1002/art.42325>). Biopsy-proven GCA showed a sensitivity of 100% (95% CI 99.0–100.0%) and a specificity of 94.9% (95% CI 93.1–96.4%), and large-vessel GCA showed a sensitivity of 55.7% (95% CI 46.5–64.6%) and a specificity of 94.9% (93.1–96.4%). Sensitivity of the criteria in North America was 77.8% (95% CI 67.8–85.9%) and in Europe was 87.2% (95% CI 84.4–89.7%). Specificity in North America was 95.6% (95% CI 90.6–98.4%) and in Europe was 88.8% (95% CI 84.9–92.0%).

When the 1990 ACR classification criteria for GCA were applied to the DCVAS validation data set, the criteria performed poorly due to low sensitivity (80.3% [95% CI 74.6–85.1%]) but retained good specificity (92.5% [95% CI 88.1–95.7%]). In particular, the 1990 ACR criteria had poor sensitivity for patients with large-vessel GCA (37.1% [95% CI 28.6–46.2%]).

Age restrictions are absolute requirements for the 2022 ACR/EULAR classification criteria for GCA ( $\geq 50$  years at diagnosis) and TAK ( $\leq 60$  years at diagnosis). However, of the 70 patients with GCA diagnosed between the ages of 50 and 60 years, 44 (62.9%) met the new GCA classification criteria, 9 (12.9%) met the new TAK classification criteria, and only 2 (2.9%) met both the new GCA and TAK classification criteria (Supplementary Appendix 21, <http://onlinelibrary.wiley.com/doi/10.1002/art.42325>).

## DISCUSSION

Presented here are the final 2022 ACR/EULAR GCA classification criteria. A 6-stage approach was 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 other vasculitides and conditions that mimic GCA, where discrimination from GCA is difficult but important. In the validation set, the new criteria had a sensitivity of 87.0% (95% CI 82.0–91.0%) and a specificity of 94.8% (95% CI 91.0–97.4%). These are the official final values that should be quoted when referring to the criteria. The sensitivity and specificity values calculated in the development set were very similar, providing reassurance that the

statistical methods avoided overfitting of models. The new criteria incorporate modern imaging techniques and have excellent specificity and sensitivity within a large, international cohort of patients with GCA. 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 to establish a *diagnosis* of vasculitis. The aim of the classification criteria is to differentiate cases of GCA from similar types of vasculitis in research settings (21). *Therefore, the criteria should only be applied when a diagnosis of large- 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 (22) and rheumatoid arthritis (16). 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) (23), and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria in people for whom alternative diagnoses, such as infection or other non-vasculitis inflammatory diseases, are still being considered.

The 2022 ACR/EULAR GCA classification criteria are the result of an incredibly large worldwide effort, in which an extensive set of data was collected from >1,000 patients with the submitted diagnosis of GCA. These criteria reflect current clinical practice, integrating different investigative methods (e.g., TAB, ultrasound, angiography, PET) from various countries and medical specialties. Real cases of GCA and comparators were reviewed by a wide range of experts in vasculitis to establish an unbiased diagnostic reference to derive the criteria. Advanced statistical methods including lasso logistic regression and cluster analyses were applied, which facilitated testing for different covariates of interest, namely specific patterns of vasculitic involvement in imaging. Modern classification techniques with weighted criterion with threshold scores were used, allowing for more discriminatory items to factor more heavily in disease classification.

When compared to the original 1990 ACR classification criteria for GCA, the 2022 ACR/EULAR GCA classification criteria

demonstrated greater sensitivity while maintaining similar specificity to the 1990 criteria. In particular, the new criteria were able to correctly classify more patients with the large-vessel GCA subtype, in whom the sensitivity of the 1990 ACR criteria was only 37.1%. Unlike the 1990 ACR criteria, an age of  $\geq 50$  years at diagnosis is a mandatory requirement to classify GCA in the 2022 ACR/EULAR criteria. This age threshold included >99% of patients with the reference diagnosis of GCA. The new criteria maintain good discriminative ability for patients diagnosed between the ages of 50 and 60 years, the interval where the absolute age requirements for the 2022 ACR/EULAR criteria for GCA and for TAK can overlap.

A potential limitation of these criteria was the nonstandardized acquisition of clinical and imaging data among patients with LVV and comparators (e.g., not all patients underwent vascular examination of the temporal arteries, PET was not available in many centers treating patients with LVV, and TAB and/or ultrasound was not performed in all patients with suspected GCA, etc.). However, this reflects existing differences in clinical practice, and the 11 items included in the criteria allow for a feasible evaluation of patients in any clinical setting. These criteria also provide flexibility for classifying a patient, regardless of the diagnostic assessment strategy employed by physicians. Definite vasculitis on TAB was defined by the submitting physician and did not undergo central review; ~20% of cases did not have specific histopathologic findings but were reported as “definitive vasculitis on TAB” alone. Most patients were recruited from Europe and North America, with fewer patients from Asia and Oceania. The performance characteristics of the criteria should be further tested in other populations that were underrepresented in the DCVAS cohort and may have different clinical presentations of GCA.

The 2022 ACR/EULAR classification criteria for GCA 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 in clinical research.

## ACKNOWLEDGMENTS

We acknowledge the patients and clinicians who provided data to the DCVAS project.

## 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.** Ponte, Grayson, Robson, Suppiah, Judge, Craven, Hutchings, Watts, Merkel, Luqmani.

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

**Analysis and interpretation of data.** Ponte, Grayson, Robson, Suppiah, Gribbons, Judge, Craven, Khalid, Hutchings, Watts, Merkel, Luqmani.

## REFERENCES

1. Watts RA, Robson J. Introduction, epidemiology and classification of vasculitis [review]. *Best Pract Res Clin Rheumatol* 2018; 32:3–20.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum* 2013;65:1–11.
3. Ponte C, Águeda AF, Luqmani RA. Clinical features and structured clinical evaluation of vasculitis. *Best Pract Res Clin Rheumatol* 2018; 32:31–51.
4. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;33:1122–8.
5. Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77:636–43.
6. Luqmani R, Lee E, Singh S, et al. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. *Health Technol Assess* 2016;20:1–238.
7. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020;79:19–30.
8. Mackie SL, Dejaco C, Appenzeller S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. *Rheumatology (Oxford)* 2020;59:e1–23.
9. Blockmans D, de Ceuninck L, Vanderschueren S, et al. Repetitive  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum* 2006;55:131–7.
10. Prieto-González S, Arguis P, García-Martínez A, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis* 2012;71:1170–6.
11. Grayson PC, Maksimowicz-McKinnon K, Clark TM, et al. Distribution of arterial lesions in Takayasu’s arteritis and giant cell arteritis. *Ann Rheum Dis* 2012;71:1329–34.
12. Furuta S, Cousins C, Chaudhry A, et al. Clinical features and radiological findings in large vessel vasculitis: are Takayasu arteritis and giant cell arteritis 2 different diseases or a single entity? *J Rheumatol* 2015;42:300–8.
13. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017;377:317–28.
14. Langford CA, Cuthbertson D, Ytterberg SR, et al. A randomized, double-blind trial of abatacept (CTLA-4lg) for the treatment of takayasu arteritis. *Arthritis Rheumatol* 2017;69:846–53.
15. Sanchez ML, Alarcón GS, McGwin G, et al. Can the weighted criteria improve our ability to capture a larger number of lupus patients into observational and interventional studies? A comparison with the American College of Rheumatology criteria. *Lupus* 2003;12:468–70.
16. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
17. Craven A, Robson J, Ponte C, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). *Clin Exp Nephrol* 2013;17:619–21.

18. Gribbons KB, Ponte C, Carette S, et al. Patterns of arterial disease in Takayasu's arteritis and giant cell arteritis. *Arthritis Care Res (Hoboken)* 2020;72:1615–24.
19. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model when there are few events. *BMJ* 2015;351:h3868.
20. Gribbons KB, Ponte C, Craven A, et al. Diagnostic assessment strategies and disease subsets in giant cell arteritis: data from an international observational cohort. *Arthritis Rheumatol* 2020;72:667–76.
21. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? [review] *Arthritis Care Res (Hoboken)* 2015;67:891–7.
22. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017;69:35–45.
23. Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. *Ann Intern Med* 1998;129:345–52.
24. Putman MS, Gribbons KB, Ponte C, et al. Clinicopathologic associations in a large international cohort of patients with giant cell arteritis. *Arthritis Care Res (Hoboken)* 2020;74:1013–8.
25. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. *RMD Open* 2018;4:e000598.

## 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); Dwarkanathan 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); Xiping 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 Pirla (Turku University Hospital, Finland); Jukka Putaala (Helsinki University Central Hospital, Finland); Bernhard Hellmich (Kreiskliniken Esslingen, Germany); Jörg Henes (Universitätsklinikum Tübingen, Germany); Julia Holle, Frank Moosig (Klinikum Bad Bramstedt, Germany); Peter Lamprecht (University of Lübeck, Germany); Thomas Neumann (Universitätsklinikum Jena, Germany); Wolfgang Schmidt (Immanuel Krankenhaus Berlin, Germany); Cord Sunderkoetter (Universitätsklinikum Münster, Germany); Zoltan Szekanez (University of Debrecen Medical and Health Science Center, Hungary); Debashish Danda (Christian Medical College & Hospital, Vellore, India); Siddharth Das (Chatrapathi Shahuji Maharaj Medical Center, Lucknow [IP], India); Rajiva Gupta (Medanta, Delhi, India); Liza Rajasekhar (NIMS, Hyderabad, India); Aman Sharma (Postgraduate Institute of Medical Education and Research, Chandigarh, India); Shrikant Wagh (Jehangir Clinical Development Centre, Pune [IP],

India); Michael Clarkson (Cork University Hospital, Ireland); Eamonn Molloy (St. Vincent's University Hospital, Dublin, Ireland); Carlo Salvarani (Santa Maria Nuova Hospital, Reggio Emilia, Italy); Franco Schiavon (L'Azienda Ospedaliera of University of Padua, Italy); Enrico Tombetti (Università Vita-Salute San Raffaele Milano, Italy); Augusto Vaglio (University of Parma, Italy); Koichi Amano (Saitama Medical University, Japan); Yoshihiro Arimura (Kyorin University Hospital, Japan); Hiroaki Dobashi (Kagawa University Hospital, Japan); Shouichi Fujimoto (Miyazaki University Hospital [HUB], Japan); Masayoshi Harigai, Fumio Hirano (Tokyo Medical and Dental University Hospital, Japan); Junichi Hirahashi (University Tokyo Hospital, Japan); Sakae Honma (Toho University Hospital, Japan); Tamihiro Kawakami (St. Marianna University Hospital Dermatology, Japan); Shigeto Kobayashi (Juntendo University Koshigaya Hospital, Japan); Hajime Kono (Teikyo University, Japan); Hirofumi Makino (Okayama University Hospital, Japan); Kazuo Matsui (Kameda Medical Centre, Kamogawa, Japan); Eri Muso (Kitano Hospital, Japan); Kazuo Suzuki, Kei Ikeda (Chiba University Hospital, Japan); Tsutomu Takeuchi (Keio University Hospital, Japan); Tatsuo Tsukamoto (Kyoto University Hospital, Japan); Shunya Uchida (Teikyo University Hospital, Japan); Takashi Wada (Kanazawa University Hospital, Japan); Hidehiro Yamada (St. Marianna University Hospital Internal Medicine, Japan); Kunihiko Yamagata (Tsukuba University Hospital, Japan); Wako Yumura (IUHW Hospital [Jichi Medical University Hospital], Japan); Kan Sow Lai (Penang General Hospital, Malaysia); Luis Felipe Flores-Suarez (Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico); Andrea Hinojosa-Azaola (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico); Bram Rutgers (University Hospital Groningen, Netherlands); Paul-Peter Tak (Academic Medical Centre, University of Amsterdam, Netherlands); Rebecca Grainger (Wellington, Otago, New Zealand); Vicki Quincey (Waikato District Health Board, New Zealand); Lisa Stapp (University of Otago, Christchurch, New Zealand); Ravi Suppiah (Auckland District Health Board, New Zealand); Emilio Besada (Tromsø, Northern Norway, Norway); Andreas Diamantopoulos (Hospital of Southern Norway, Kristiansand, Norway); Jan Sznajd (University of Jagiellonian, Poland); Elsa Azevedo (Centro Hospitalar de São João, Porto, Portugal); Ruth Gerales (Hospital de Santa Maria, Lisbon, Portugal); Miguel Rodrigues (Hospital Garcia de Orta, Almada, Portugal); Ernestina Santos (Hospital Santo Antonio, Porto, Portugal); Yeong-Wook Song (Seoul National University Hospital, Republic of Korea); Sergey Moiseev (First Moscow State Medical University, Russia); Alojzija Hočevar (University Medical Centre Ljubljana, Slovenia); Maria Cinta Cid (Hospital Clinic de Barcelona, Spain); Xavier Solanich Moreno (Hospital de Bellvitge-Idibell, Spain); Inoshi Atukorala (University of Colombo, Sri Lanka); Ewa Berglin (Umeå University Hospital, Sweden); Aladdin Mohammed (Lund-Malmö University, Sweden); Mårten Segelmark (Linköping University, Sweden); Thomas Däikeler (University Hospital Basel, Switzerland); Haner Direskeneli (Marmara University Medical School, Turkey); Gulen Hatemi (Istanbul University, Cerrahpasa Medical School, Turkey); Sevil Kamali (Istanbul University, Istanbul Medical School, Turkey); Ömer Karadağ (Hacettepe University, Turkey); Seval Pehlevan (Fatih University Medical Faculty, Turkey); Matthew Adler (Frimley Health NHS Foundation Trust, Wexham Park Hospital, UK); Neil Basu (NHS Grampian, Aberdeen Royal Infirmary, UK); Iain Bruce (Manchester University Hospitals NHS Foundation Trust, UK); Kuntal Chakravarty (Barking, Havering and Redbridge University Hospitals NHS Trust, UK); Bhaskar Dasgupta (Southend University Hospital NHS Foundation Trust, UK); Oliver Flossmann (Royal Berkshire NHS Foundation Trust, UK); Nagui Gendi (Basildon and Thurrock University Hospitals NHS Foundation Trust, UK); Alaa Hassan (North Cumbria University Hospitals, UK); Rachel Hoyles (Oxford University Hospitals NHS Foundation Trust, UK); David Jayne (Cambridge University Hospitals NHS Foundation Trust, UK); Colin Jones (York Teaching Hospitals NHS Foundation Trust, UK); Rainer Klocke (The Dudley Group NHS Foundation Trust, UK); Peter Lanyon (Nottingham University Hospitals NHS Trust, UK); Cathy Laversuch (Taunton & Somerset NHS Foundation Trust, Musgrove Park Hospital, UK); Raashid Luqmani, Joanna Robson (Nuffield Orthopaedic Centre, Oxford, UK); Malgorzata Magliano (Buckinghamshire Healthcare NHS Trust, UK); Justin Mason (Imperial College Healthcare NHS Trust, UK); Win Win Maw (Mid Essex Hospital Services NHS Trust, UK); Iain McInnes (NHS Greater Glasgow &

Clyde, Gartnavel Hospital & GRI, UK); John McLaren (NHS Fife, Whyteman's Brae Hospital, UK); Matthew Morgan (University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, UK); Ann Morgan (Leeds Teaching Hospitals NHS Trust, UK); Chetan Mukhtyar (Norfolk and Norwich University Hospitals NHS Foundation Trust, UK); Edmond O'Riordan (Salford Royal NHS Foundation Trust, UK); Sanjeev Patel (Epsom and St Helier University Hospitals NHS Trust, UK); Adrian Peall (Wye Valley NHS Trust, Hereford County Hospital, UK); Joanna Robson (University Hospitals Bristol NHS Foundation Trust, UK); Srinivasan Venkatachalam (The Royal Wolverhampton NHS Trust, UK); Erin Vermaak, Ajit Menon (Staffordshire & Stoke on Trent Partnership NHS Trust, Haywood Hospital, UK); Richard Watts (East Suffolk and North

Essex NHS Foundation Trust, UK); Chee-Seng Yee (Doncaster and Bassetlaw Hospitals NHS Foundation Trust, UK); Daniel Albert (Dartmouth-Hitchcock Medical Center, US); Leonard Calabrese (Cleveland Clinic Foundation, US); Sharon Chung (University of California, San Francisco, US); Lindsay Forbess (Cedars-Sinai Medical Center, US); Angelo Gaffo (University of Alabama at Birmingham, US); Ora Gewurz-Singer (University of Michigan, US); Peter Grayson (Boston University School of Medicine, US); Kimberly Liang (University of Pittsburgh, US); Eric Matteson (Mayo Clinic, US); Peter A. Merkel, Rennie Rhee (University of Pennsylvania, US); Jason Springer (University of Kansas Medical Center Research Institute, US); and Antoine Sreih (Rush University Medical Center, US).