ORIGINAL ARTICLE

Classification Criteria for Sarcoidosis-Associated Uveitis

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP[1,2,3,4,5,*]

• PURPOSE: **The purpose of this study was to determine classification criteria for sarcoidosis-associated uveitis.**

• DESIGN: **Machine learning of cases with sarcoid uveitis and 15 other uveitides.**

• METHODS: **Cases of anterior, intermediate, and panuveitides were collected in an informatics-designed preliminary database, and a final database was constructed including cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were analyzed by anatomic class, and each class was split into a training set and a validation set. Machine learning using multinomial logistic regression was used in the training sets to determine a parsimonious set of criteria that minimized the misclassification rate among the intermediate uveitides. The resulting criteria were evaluated in the validation sets.**

• RESULTS: **A total of 1,083 cases of anterior uveitides, 589 cases of intermediate uveitides, and 1,012 cases of panuveitides, including 278 cases of sarcoidosis-associated uveitis, were evaluated by machine learning. Key criteria for sarcoidosis-associated uveitis included a compatible uveitic syndrome of any anatomic class and evidence of sarcoidosis, either 1) tissue biopsy results demonstrating non-caseating granulomata or 2) bilateral hilar adenopathy on chest imaging. The overall accuracy of the diagnosis of sarcoidosis-associated uveitis in the validation set was 99.7% (95% confidence interval: 98.8-99.9). The misclassification rates for sarcoidosis-associated uveitis in the training sets were 3.2% in anterior uveitis, 2.6% in intermediate uveitis, and 1.2% in panuveitis; in the validation sets, the misclassification rates were 0% in anterior uveitis, 0% in intermediate uveitis, and 0% in panuveitis.**

• CONCLUSIONS: **The criteria for sarcoidosis-associated uveitis had a low misclassification rate and appeared to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 220–230. © 2021 Elsevier Inc. All rights reserved.)**

AJO.com Supplemental Material available at AJO.com.
Accepted for publication March 31, 2021.

[1] Members of the SUN Working Group are listed online at AJO.com.

[2] **Writing Committee:** Douglas A. Jabs, Nisha R. Acharya, Alastair K. Denniston, Susan L. Lightman, Peter McCluskey, Neal Oden, Annabelle A. Okada, Alan G. Palestine, Jennifer E. Thorne, Brett E. Trusko, and Albert Vitale.

[3] **Writing Committee Affiliations:** Department of Epidemiology (D.A.J., J.E.T.), Johns Hopkins University Bloomberg School of Public Health, and Department of Ophthalmology (D.A.J., J.E.T.), Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Francis I. Proctor Foundation (N.R.A.), University of California San Francisco, San Francisco, California, USA; Academic Unit of Ophthalmology (A.K.D.), University of Birmingham, Birmingham, UK; Moorfields Eye Hospital (S.L.L.), London, UK; Institute of Ophthalmology (S.L.L.), University College London, London, UK; Department of Ophthalmology (P.M.), Save Sight Institute, University of Sydney School of Medicine, Sydney, New South Wales, Australia; Emmes Co, LLC (N.O.), Rockville, Maryland, USA; Department of Ophthalmology (A.A.O.), Kyorin University School of Medicine, Tokyo, Japan; Department of Ophthalmology (A.G.P.), University of Colorado School of Medicine, Aurora, Colorado, USA; Department of Medicine (B.E.T.), Texas A&M University, College Station, Texas, USA; and the Department of Ophthalmology (A.V.), University of Utah School of Medicine, Salt Lake City, Utah, USA.

[4] Conflict of Interest: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

[5] Financial Disclosures: Douglas A. Jabs: none. Nisha A. Acharya: none. Alastair K. Denniston; none. Susan L. Lightman: none. Peter McCluskey: none. Neal Oden: none. Annabelle A. Okada: consultant for AbbVie Japan, Astellas Pharma Japan, Bayer AG, Daiichi Sankyo; and receives lecture fees from Alcon Pharma Japan, Mitsubishi Tanabe Pharma, Novartis Pharma Japan, Santen Pharmaceutical Corporation, and Senju Pharmaceutical Corporation; and receives grant support from Alcon Pharma Japan, Bayer Yakuhin, and Mitsubishi Tanabe Pharma. Alan G. Palestine: none. Jennifer E. Thorne: Dr. Thorne engaged in a part of this research as a consultant and was compensated for the consulting service. Brett E. Trusko: none. Albert Vitale: none.

* Inquiries to: Douglas A. Jabs, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, 615 N Wolfe St, Baltimore, Maryland 20215, USA. Phone: (212) 241-6752. E-mail: djabs@jhmi.edu.

THE AMERICAN THORACIC SOCIETY, THE EUROPEAN Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Diseases have defined sarcoidosis as a multisystem disease of unknown causes characterized by granuloma formation and with a predilection for pulmonary involvement. They further note that "the presence of non-caseating granulomata in a single organ…does not establish the diagnosis of sarcoidosis," and that the diagnosis of sarcoidosis requires a compatible clinical syndrome.[1] Sarcoidosis is present worldwide. In the United States, the incidence has been estimated at 5.9/100,000 population/year for men and 6.3/100,000 pop-

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2021.03.047

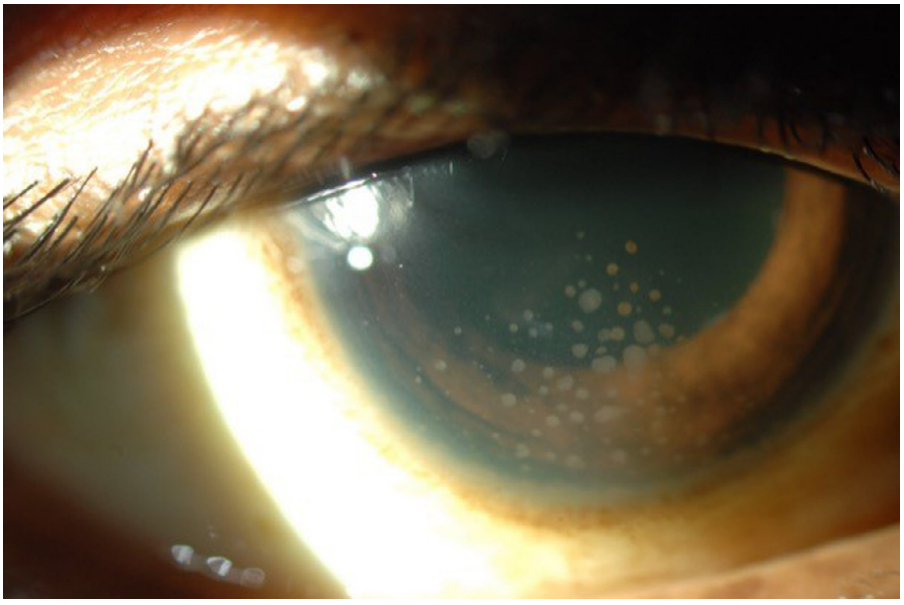

FIGURE 1. Sarcoidosis-associated anterior uveitis with mutton-fat keratic precipitates.

ulation/year for women. In the United States, sarcoidosis is more common among African Americans than whites. The cumulative lifetime risk has been estimated at 0.85% for whites and 2.4% for blacks, and the prevalence as 10.9/100,000 population for whites and 35.5/100,000 population for blacks.[1] Pulmonary disease is the most common abnormality, with bilateral hilar adenopathy the most characteristic feature on chest imaging (either chest radiography or computed tomography [CT]) and parenchymal lung disease having the most negative effect on pulmonary function. In multidisciplinary clinical settings, pulmonary involvement is seen in ~85%-95% of patients. Involvement of the liver, spleen, or lymph nodes is reported in 25%-35% of patients and in 12%-25% of the skin. The presence of erythema nodosum is reported in 4%-30% of cases but is not specific for a diagnosis of sarcoidosis, as it occurs with other diseases. Neurologic involvement is present in only ~5%. It is likely that some of that variation represents regional and racial and ethnic variation and that some of the variation represents referral bias. Ocular disease typically is reported as present in ~12%-25% of patients with documented sarcoidosis, with variable frequencies reported depending on the extent of examination (eg, whether aqueous tear deficiency is evaluated).[2,3] Uveitis typically is the most common ocular manifestation of ocular sarcoidosis. In a population-based study in Olmstead County, Minnesota, USA, 7% of patients with sarcoidosis had ocular involvement, uveitis was the most common form of ocular sarcoid (61%), and anterior uveitis (71% of uveitis) was the most common anatomic class of uveitis.[4] Conversely, sarcoidosis-associated uveitis accounts for ~5%-10% of uveitis presenting to tertiary care eye centers in the United States.[2,5,6]

Although anterior uveitis is the most common anatomic class of uveitis seen with sarcoidosis-associated uveitis in the United States, any anatomic class of uveitis may be seen with sarcoidosis, including intermediate, a mixed anterior and intermediate type, posterior, and panuveitis,[2,6-11] and in some parts of the world, intermediate uveitis and panuveitis may be more common.[9,11] Vitreous inflammatory manifestations include "snowballs" and "string of pearls" inflammatory debris. Posterior segment clinical findings include choroidal nodules, optic nerve nodules, multifocal choroiditis, and perivascular sheathing (eg, "candle wax drippings"), occasionally with vascular occlusion.[2,6-11] Among patients with sarcoidosis-associated uveitis, the reported frequencies of ocular manifestations typically are 65%-70% anterior uveitis; 11%-16% iris nodules; 3%-25% vitritis; 10%-17% periphlebitis; 4%-5% paucifocal, typically elevated, choroidal nodules (sometimes inappropriately termed "sarcoid granulomas"); and ~11% multifocal choroiditis.[2] Among patients with sarcoidosis-associated anterior uveitis, both acute anterior uveitis and chronic anterior uveitis have been reported.[2]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which has developed classification criteria for the leading 25 uveitides using a formal approach to development and classification.[12-17] Among the uveitides studied was sarcoidosis-associated uveitis. Figs 1–5

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in 4 phases as previously de-

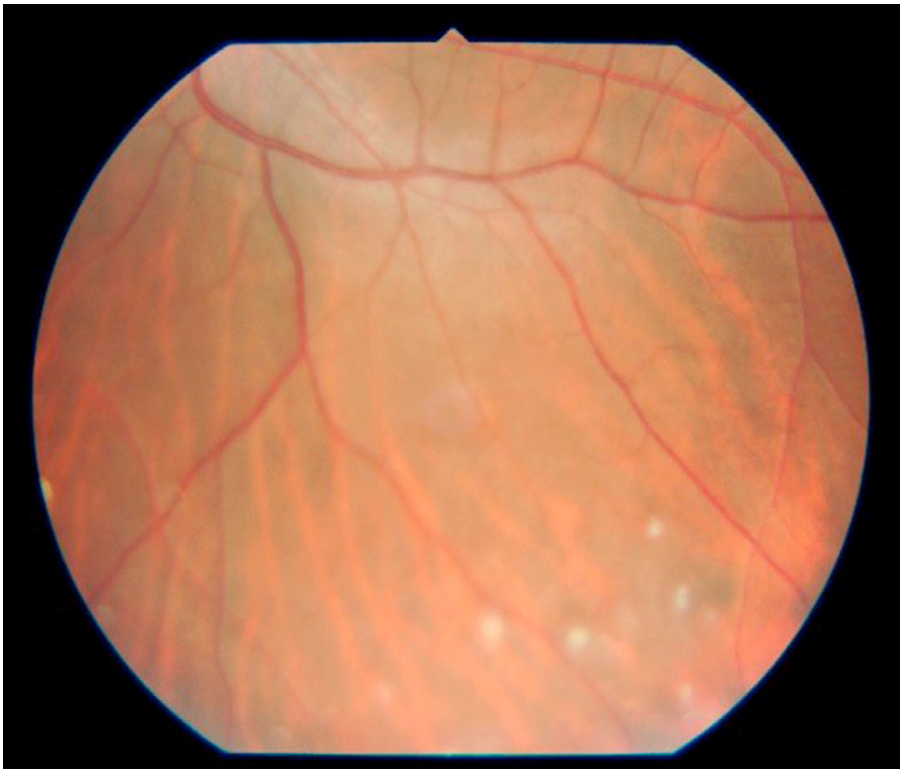

FIGURE 2. Sarcoidosis-associated uveitis with vitritis.

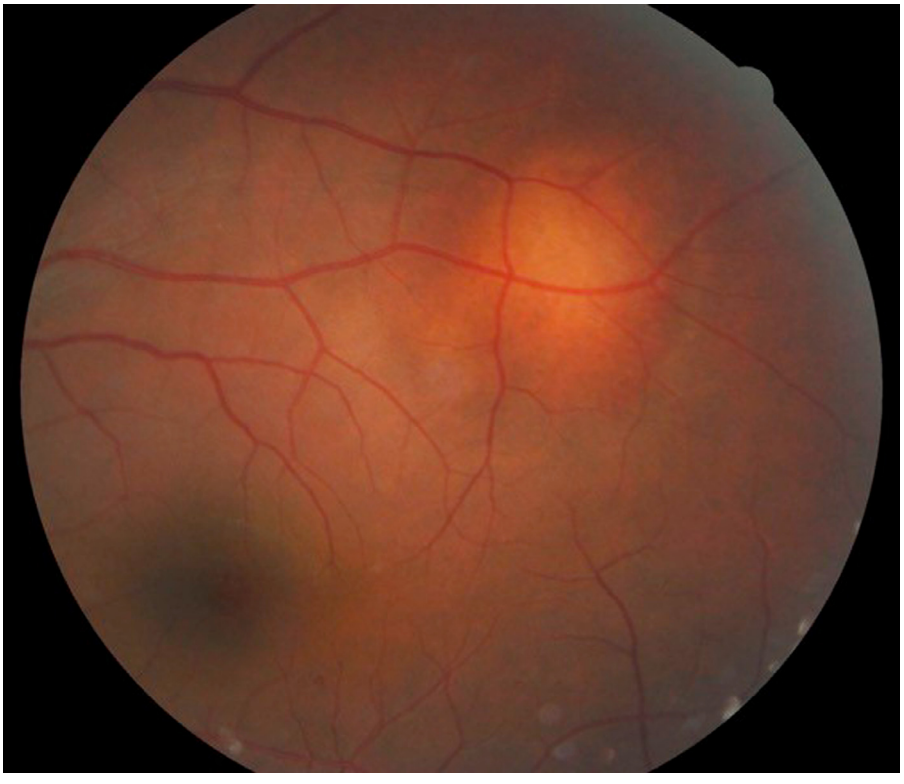

FIGURE 3. Sarcoidosis-associated uveitis with a focal choroidal nodule.

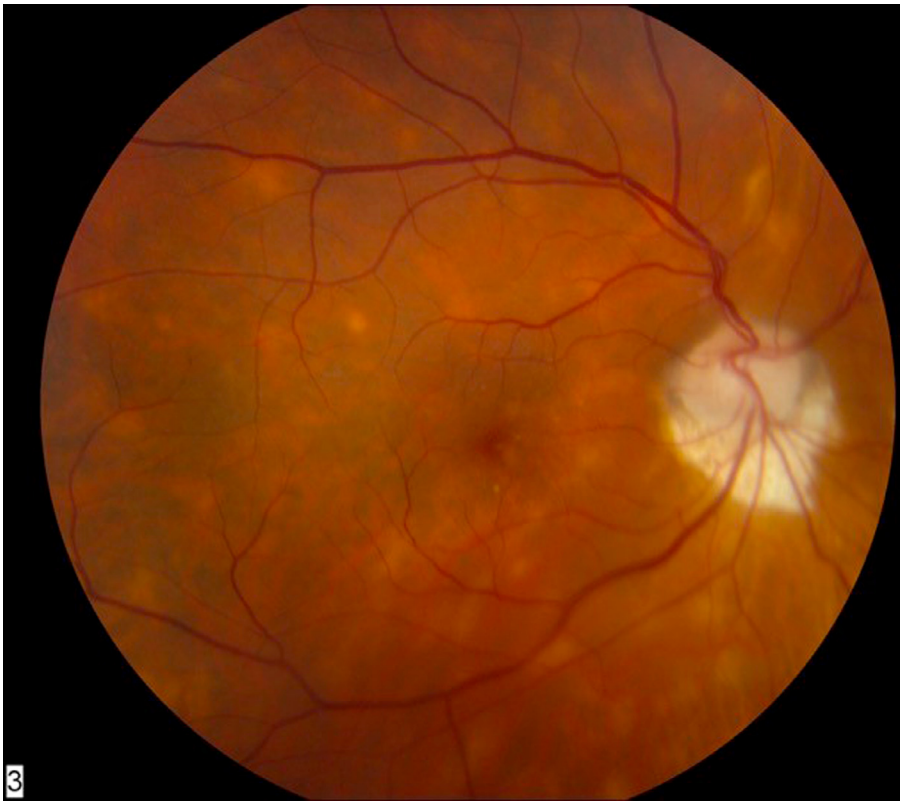

FIGURE 4. Sarcoidosis-associated uveitis with multifocal choroiditis.

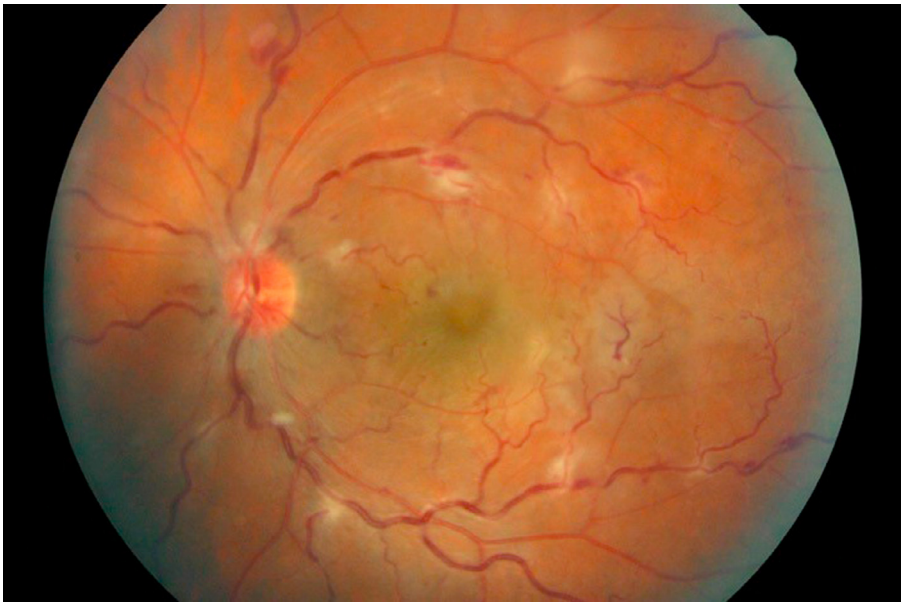

FIGURE 5. Sarcoidosis-associated uveitis with retinal vascular sheathing.

scribed: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.[13-16]

• **INFORMATICS:** As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a standardized, menu-driven hierarchical case collection instrument.[13]

• **CASE COLLECTION AND CASE SELECTION:** De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease, as previously described.[13-16] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques described in the accompanying articles.[15,16] Because the goal was to develop classification criteria,[17] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[15,16]

• **MACHINE LEARNING:** The final database was analyzed by anatomic class; cases for each class were randomly separated into a training set (~85% of the cases) and a validation set (~15% of the cases) for each disease, as described in the accompanying article.[16] Relevant cases of sarcoidosis-associated uveitis were analyzed in the anterior uveitides, intermediate uveitides, and panuveitides. Machine learning was used in the training sets to determine criteria that minimized misclassification. The criteria then were tested in the validation sets; for both the training sets and the validation sets, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm compared to the consensus diagnosis.

Cases of sarcoidosis-associated anterior, intermediate, and panuveitis were evaluated in the machine learning for anterior uveitides (cytomegalovirus anterior uveitis, herpes simplex virus anterior uveitis, juvenile idiopathic arthritis-associated anterior uveitis, syphilitic anterior uveitis, spondyloarthritis/HLA-B7-associated anterior uveitis, tubulointerstitial nephritis with uveitis, and varicella zoster virus anterior uveitis), intermediate uveitides (multiple-sclerosis-associated intermediate uveitis, pars planitis, intermediate uveitis, non-pars planitis type, and syphilitic intermediate uveitis), and panuveitides (Behçet disease, syphilitic panuveitis, sympathetic ophthalmia, Vogt-Koyanagi-Harada disease, tuberculous panuveitis), respectively. Although "isolated" posterior sarcoidosis-associated uveitis cases were included in the machine learning of posterior uveitides, there were too few cases (n = 12) for reliable statistical inferences.

RESULTS

A total of 383 cases of sarcoidosis-associated uveitis were collected, and 278 cases (73%) achieved supermajority agreement in the diagnosis during the "selection" phase and were used in the machine learning phase. They were compared to 971 other anterior uveitides, 537 other intermediate uveitides, and 910 other panuveitides. Details of the machine learning results for these diseases are outlined in the accompanying article.[16] The characteristics of cases with sarcoid-associated uveitis are listed in Table 1. Biopsy confirmation of the diagnosis of sarcoidosis was obtained in 58%, and 79% had bilateral hilar adenopathy on chest imaging. Bilateral hilar adenopathy was detected in 72% of 242 cases with reported chest radiography results and 82% of 164 cases with reported chest CT scan results. Of 156 cases with both chest radiography and chest CT results reported, 116 had bilateral hilar adenopathy on both imaging modalities, 24 cases had no evidence of bilateral hilar adenopathy of both imaging modalities, and 16 cases had bilateral hilar adenopathy identified on chest CT imaging but not chest radiography. The characteristics of cases of sarcoid-associated uveitis by anatomic class are listed in Table 2. The criteria developed after machine learning are listed in Table 3. The key features of the criteria are a compatible uveitic syndrome and evidence of sarcoidosis. Evidence of sarcoidosis was either biopsy results demonstrating non-caseating granulomata or chest imaging (either chest radiography or chest CT) demonstrating bilateral hilar adenopathy. The overall accuracies by anatomic class were anterior uveitides, training set 97.5% and validation set 96.7% (95% confidence interval [CI]: 92.4-98.6); intermediate uveitides, training set 99.8% and validation set 99.3% (95% CI: 96.1-99.9); and panuveitides, training set 96.3% and validation set 94.0% (95% CI: 89.0-96.8).[16] The overall accuracy of the diagnosis of sarcoidosis-associated uveitis in the validation set was 99.6% (95% CI: 98.8-99.9). The following misclassification rates for sarcoid-associated uveitis in the training set were: 3.2% against anterior uveitides, 2.6% intermediate uveitides, and 1,2% non-infectious panuveitides. There were too few cases of isolated posterior sarcoidosis-associated uveitis for formal testing, although they were included in the testing against the other diseases. In the validation set, the misclassification rates were 0% against anterior uveitides, 0% intermediate uveitides, and 0% non-infectious panuveitides.

DISCUSSION

The classification criteria developed by the SUN Working Group for sarcoidosis-associated uveitis had a low misclassification rate, indicating good discriminatory performance against other uveitides.

The diagnosis of sarcoidosis is most straight forward when there is compatible pulmonary disease and a "confirmatory" biopsy demonstrating non-caseating granulomata. In regions where tuberculosis in not endemic, patients with asymptomatic bilateral hilar adenopathy or bilateral hilar adenopathy and uveitis nearly always have sarcoidosis when a pulmonary biopsy is performed.[18] However, in regions where tuberculosis is endemic or in patients from endemic regions (with >6 months residence there), tuberculosis needs to be excluded, as both diseases may produce a similar picture on chest imaging.[19] In those situations, if the pa-

TABLE 1. Characteristics of Patients With Sarcoid Uveitis

Characteristic	Result
Number of cases	278.0
Demographics	
Median IQR (25th 75th), y	49.0 (39, 61)
Men, %	29.0
Women, %	71.0
Race/ethnicity, %	
White, non-Hispanic	37.0
Black, non-Hispanic	26.0
Hispanic	1.0
Asian, Pacific Islander	24.0
Other	9.0
Missing	3.0
Uveitis history	
Uveitis course, %	
Acute, monophasic	5.0
Acute, recurrent	7.0
Chronic	80.0
Indeterminate	8.0
Laterality, %	
Unilateral	18.0
Unilateral, alternating	1.0
Bilateral	82.0
Ophthalmic examination	
Keratic precipitates, %	
None	52.0
Fine	18.0
Round	6.0
Stellate	0.0
Mutton-fat	23.0
Anterior chamber cells, %	
Grade 0	15.0
½+	24.0
1+	28.0
2+	25.0
3+	7.0
4+	1.0
Hypopyon, %	1.0
Anterior chamber flare, %	
Grade 0	60.0
1+	30.0
2+	9.0
3+	1.0
4+	0.0
Iris, %	
Normal	64.0
Posterior synechiae	27.0
Iris nodules	12.0
Sectoral iris atrophy	0.0
Patchy iris atrophy	1.0
Diffuse iris atrophy	0.0
Heterochromia	0.0
IOP-involved eyes	
Median IQR (25th, 75th), mm Hg	16.0 (13, 19)
Proportion of patients with IOP>24 mm Hg in either eye, %	10.0
Vitreous cells, %	
Grade 0	31.0
½+	21.0
1+	31.0
2+	14.0
3+	3.0
4+	0.0
Vitreous haze, %	
Grade 0	61.0
½+	11.0
1+	20.0
2+	5.0
3+	2.0
4+	0.0
Vitreous snowballs, %	17.0
Pars plana snowbanks, %	1.0
Choroidal nodule, %	2.0
Multifocal choroiditis, %	30.0
Retinal vascular sheathing, %	18.0
Anatomic class, %	
Anterior uveitis	40.0
Intermediate uveitis	19.0
Posterior uveitis	4.0
Panuveitis	37.0
Evidence of sarcoidosis, %	
Non-caseating granuloma on tissue biopsy [a]	58.0
Bilateral hilar adenopathy of chest imaging[b]	79.0
Non-specific tests for sarcoidosis, %	
ACE	52
Lysozyme	12.0

ACE = angiotensin-converting enzyme; IOP = intraocular pressure; IQR = interquartile range.

[a] 161 of 161 patients' biopsy results were positive, demonstrating non-caseating granulomata.

[b] 174 of 242 patients (72%) had a chest radiograph with bilateral hilar adenopathy, and 134 of 164 patients (82%) undergoing computerized tomography had bilateral hilar adenopathy.

(*continued on next page*)

tient has evidence of latent tuberculosis (eg, the tuberculin skin test is positive or an interferon-γ-release assay [IGRA] is positive), the only way to confirm the diagnosis is to perform a biopsy. In the SUN database, 6.1% of cases of TB uveitis had bilateral hilar adenopathy on chest imaging, of whom 76% were from Asian countries (and therefore presumably from a tuberculosis-endemic country).[20] A study of patients with uveitis and a positive IGRA in a non-endemic country suggested that when a biopsy (or bronchoalveolar lavage) was performed, ~75% of those patients would have sarcoidosis and not tuberculosis.[21] Nevertheless, 36% of the patients with uveitis and bilateral hilar adenopathy in this study did not undergo additional testing and were presumed to have ocular tuberculosis. As such, patients with a uveitis compatible either with sarcoidosis or with

TABLE 2. Characteristics of Sarcoid Uveitis by Anatomic Class of the Uveitis

Characteristic/Anatomic Class	Anterior Uveitis	Intermediate Uveitis	Posterior Uveitis	Panuveitis
Number of cases	112	52	12	102
Demographics				
Median IQR (25th 75th) age, y	46.0 (37, 55)	5,246.0 (43, 67)	5,346.0 (50, 64)	5146.0 (35, 63)
Men, %	24.0	29.0	33.0	33.0
Women, %	76.0	71.0	67.0	67.0
Race/ethnicity, %				
White, non-Hispanic	30.0	63.0	42.0	31.0
Black, non-Hispanic	49.0	6.0	0.0	15.0
Hispanic	0.0	2.0	0.0	2.0
Asian, Pacific Islander	7.0	13.0	33.0	45.0
Other	7.0	12.0	25.0	4.0
Missing	7.0	4.0	0.0	3.0
Uveitis history				
Uveitis course, %				
Acute, monophasic	10.0	0.0	0.0	3.0
Acute, recurrent	14.0	2.0	0.0	3.0
Chronic	63.0	96.0	92.0	78.0
Indeterminate	13.0	2.0	8.0	16.0
Laterality, %				
Unilateral	24.0	19.0	42.0	7.0
Unilateral, alternating	2.0	0.0	0.0	0.0
Bilateral	74.0	81.0	58.0	93.0
Ophthalmic examination				
Keratic precipitates, %				
None	46.0	75.0	92.0	43.0
Fine	19.0	15.0	8.0	20.0
Round	8.0	0.0	0.0	8.0
Stellate	1.0	0.0	0.0	0.0
Mutton-fat	27.0	10.0	0.0	29.0
Anterior chamber cells, %				
Grade 0	4.0	35.0	75.0	12.0
½+	25.0	27.0	17.0	24.0
1+	32.0	13.0	8.0	32.0
2+	30.0	19.0	0.0	24.0
3+	7.0	6.0	0.0	8.0
4+	2.0	0.0	0.0	1.0
Hypopyon, %	1.0	0.0	0.0	0.0
Anterior chamber flare, %				
Grade 0	63.0	81.0	100.0	42.0
1+	29.0	15.0	0.0	39.0
2+	6.0	2.0	0.0	18.0
3+	2.0	0.0	0.0	1.0
4+	0.0	2.0	0.0	0.0
Iris, %				
Normal	61.0	60.0	100.0	66.0
Posterior synechiae	33.0	29.0	0.0	23.0
Iris nodules	13.0	10.0	0.0	16.0
Sectoral iris atrophy	0.0	0.0	0.0	0.0
Patchy iris atrophy	1.0	2.0	0.0	2.0
IOP-involved eyes				
Median IQR (25th, 75th) mm Hg	16.0 (13, 19)	16.0 (14, 18)	15.0 (14, 17)	16.0 (13, 18)
Percentage of patients with IOP >24 mm Hg in either eye	8.0	8.0	0.0	16.0
Vitreous cells, %				

(*continued on next page*)

TABLE 2. (*continued*)

Characteristic/Anatomic Class	Anterior Uveitis	Intermediate Uveitis	Posterior Uveitis	Panuveitis
Grade 0	55.0	10.0	25.0	17.0
½+	27.0	21.0	17.0	14.0
1+	14.0	52.0	33.0	39.0
2+	3.0	15.0	25.0	24.0
3+	1.0	2.0	0.0	6.0
Vitreous haze, %				
Grade 0	86.0	46.0	42.0	44.0
½+	6.0	17.0	17.0	14.0
1+	5.0	29.0	33.0	28.0
2+	1.0	4.0	8.0	11.0
3+	1.0	4.0	0.0	3.0
Vitreous snowballs, %	0.0	58.0	8.0	26.0
Pars plana snowbanks, %	0.0	4.0	0.0	0.0
Choroidal nodule, %	0.0	0.0	17.0	5.0
Multifocal choroiditis, %	0.0	0.0	92.0	73.0
Retinal vascular sheathing, %	0.0	27.0	49.0	28.0
Evidence of sarcoidosis, %				
Non-caseating granuloma on tissue biopsy	60.0	54.0	58.0	59.0
Bilateral hilar adenopathy of chest imaging	82.0	85.0	75.0	74.0
Non-specific tests for sarcoidosis, %				
ACE	45.0	51.0	58.0	59.0
Lysozyme	14.0	0.0	0.0	17.0

ACE = angiotensin-converting enzyme; IOP = intraocular pressure; IQR = interquartile range.

tubercular uveitis (eg, chronic anterior uveitis with iris nodules), bilateral hilar adenopathy, and a positive tuberculin skin test or IGRA cannot be reliably diagnosed without biopsy or microbiologic confirmation of the diagnosis.

Although a patient with uveitis reasonably may be presumed to have sarcoidosis when there is a compatible clinical picture and chest imaging, not all patients with ocular sarcoidosis will have abnormal chest radiograph results or CT scans.[22] Hence, there have been attempts to create diagnostic criteria and to evaluate serological tests for sarcoidosis, including the serum angiotensin-1-converting enzyme (ACE) level and the serum lysozyme level.[23] The International Workshop on Ocular Sarcoidosis (IWOS) published criteria in 2009.[24] The IWOS criteria included 4 levels of certainty: definite (biopsy-confirmed); presumed (bilateral hilar adenopathy and uveitis); probable (neither biopsy-confirmed nor bilateral hilar adenopathy, but fulfilling several ocular and systemic criteria, the latter relating to anergy and serological tests); and possible ocular sarcoidosis. Evaluation of the IWOS criteria by an international group demonstrated problems with the performance of the IWOS criteria,[11] which subsequently were revised ("Revised IWOS Criteria") but kept the different levels of certainty.[25] The SUN criteria for sarcoidosis-associated uveitis are similar to the definite and presumed ocular sarcoidosis classes of the IWOS criteria. The SUN criteria for sarcoidosis-associated uveitis did not include probable and possible cases of IWOS criteria-diagnosed ocular sarcoidosis, because only ~62% of those with probable ocular sarcoidosis using the IWOS criteria will have sarcoidosis when a biopsy is performed[22,24] (and presumably a lower percentage of possible cases), which reflects the difference between classification criteria developed by the SUN Working Group and diagnostic criteria developed by the IWOS Group.

The presence of any of the exclusions in Table 3 suggests an alternate diagnosis, and the sarcoidosis-associated uveitis should not be diagnosed in their presence. In prospective studies, many of those tests will be performed routinely and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of those tests may have been performed. Hence the presence of an exclusionary criterion excludes pars planitis, but the absence of such testing does not always exclude the diagnosis of sarcoidosis-associated uveitis if the criteria for the diagnosis are met. The exception is that, in areas where tuberculosis is endemic or in patients emigrating from areas in which tuberculosis is endemic, tuberculosis should be excluded.

Neither elevated serum ACE nor elevated serum lysozyme levels were selected by the machine learning for the SUN criteria set of sarcoidosis-associated uveitis. Sensitivity of an elevated serum ACE for detecting sarcoidosis has been reported to vary from 22%-84% and 42%-60% of elevated serum lysozyme.[10,23,24,26,27] Positive

TABLE 3. Classification Criteria for Sarcoid Uveitis

Criteria
1. Compatible uveitic picture, either
a. Anterior uveitis or
b. Intermediate or anterior/intermediate uveitis or
c. Posterior uveitis with either choroiditis (paucifocal choroidal nodule[s] or multifocal choroiditis) or
d. Panuveitis with choroiditis or retinal vascular sheathing or retinal vascular occlusion
And
2. Evidence of sarcoidosis, either
a. Tissue biopsy demonstrating non-caseating granulomata or
b. Bilateral hilar adenopathy on chest imaging
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence of infection with *Mycobacterium tuberculosis*,[a] either
a. Histologically- or microbiologically-confirmed infection with M. tuberculosis[b] OR
b. Positive interferon-ɣ release assay (IGRA)[c] or
c. Positive tuberculin skin test[d]

[a]Routine exclusion of tuberculosis is not required in areas where tuberculosis is non-endemic but should be performed in areas where tuberculosis is endemic or in tuberculosis-exposed patients. With evidence of latent tuberculosis in a patient with a uveitic syndrome compatible with either sarcoidosis or tubercular uveitis and bilateral hilar adenopathy, the classification as sarcoid uveitis can be made only with biopsy confirmation of sarcoidosis (and therefore exclusion of tuberculosis).

[b]For example, biopsy, fluorochrome stain, culture, or polymerase chain reaction-based assay.

[c]For example, Quantiferon-gold or T-spot.

[d]For example, a purified protein-derivative skin test positive result should be >10 mm induration.

predictive values reported for elevated serum ACE have ranged from 18%-90% and 12% for an elevated level of serum lysozyme.[10,25,28,29] The highest value for the positive predictive value of ACE was derived from a case series enriched for sarcoidosis, and more than one-half of the cases had probable or possible IWOS criteria-diagnosed ocular sarcoidosis.[27] Had the percentage of sarcoidosis cases been at the more typical 5% level, the positive predictive value would have dropped to 52%. As such, neither the SUN process nor published studies support the inclusion of these serological tests in classification criteria.

More recently, serum-soluble interleukin-2 receptor (sIL-2R) has been evaluated as a possible diagnostic test for sarcoidosis.[27] Case series data suggest high sensitivity and specificity (98% and 94%, respectively). In a sarcoidosis-enriched population of patients with uveitis, the positive predictive value was 77%,[27] but in a population of patients with uveitis, where sarcoidosis accounted for 5% of cases, the positive predictive value would be 46%. Although the SUN database did not have sIL-2R data for evaluation, the positive predictive values suggest that it may have a limited role in classification criteria. However, in both situations, the negative predictive value would be 99%, suggesting that it may be a reasonable test for excluding sarcoidosis in those clinical settings where the test is available.

Because sarcoidosis is in the differential diagnosis of most classes of uveitis, its exclusion is an important part of the criteria for many other uveitic diseases.[8] Although serologic tests to date have performed too poorly to be used for diagnosing sarcoidosis, as noted above, they may potentially have value for excluding sarcoidosis, and some clinical centers use a 2-step approach by screening with an ACE and obtaining chest imaging only in those with an elevated ACE or present with high suspicion. Reported negative predictive values have ranged from 87%-97%.[10,23,26,28] Because the agreement among uveitis experts on uveitic diagnoses is moderate at best,[15] prospective series using standardized classification criteria should be used to evaluate this strategy.

The identification of bilateral hilar adenopathy by chest imaging is important in establishing the diagnosis of sarcoidosis, but other findings by chest imaging (eg, nodular disease, interstitial pneumonitis without bilateral hilar adenopathy) are not specific and should not be used to diagnose sarcoidosis without biopsy confirmation.[18,19] Conventionally, screening has been performed with chest radiography and chest CT scanning used in cases of equivocal chest radiographs or cases with high suspicion on other grounds. Nevertheless, there are data to suggest that chest CT scanning may be superior for the detection of bilateral hilar adenopathy.[29,30] Whether chest CT scanning should replace chest radiography as a screening tool is an open question, and the SUN data do not provide a definitive answer. However, among cases with both chest imaging results, chest radiography detected 88% of the cases of bilateral hilar adenopathy seen on chest CT imaging, suggesting that for "screening" purposes, the more conventional approach may be adequate. In a retrospective case series of 709 patients with uveitis, among whom 10.7% had sarcoidosis, chest CT had superior sensitivity to chest radiography, but the positive predictive value for both modes was 100%, and the negative predictive values for chest radiographs were 94.4% and 98.2% for chest CTs, again suggesting that the chest radiograph may be adequate as a screening tool.[28] Nevertheless, there may be selected clinical situations in which a chest CT is preferred.[30] Prospective studies involving both chest imaging techniques and using standardized classification criteria may resolve this issue.

Classification criteria are used to diagnose individual diseases for research purposes.[17] Classification criteria differ from clinical diagnostic criteria, in that, although both seek to minimize misclassification, when a tradeoff is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[17] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process used did not explicitly

use sensitivity and specificity; instead it minimized the misclassification rate. Because the focus of this study was to develop classification criteria and because the typical agreement between 2 uveitis experts on diagnosis was moderate at best,[15] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such, some cases which clinicians would diagnose with sarcoidosis-associated uveitis will not be so classified by classification criteria.

In conclusion, the criteria for sarcoidosis-associated uveitis outlined in Table 3 appear to perform sufficiently well for use as classification criteria in clinical research.

CREDIT ROLES

Douglas A. Jabs, MD, MBA: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing–Original draft, Writing–Review and editing, Visualization, Supervision, Project administration, Funding acquisition. **Nisha R. Acharya, MD:** Investigation, Writing–Review and editing. **Alastair K. Denniston, PhD, MRCP, FRCOphth:** Investigation, Writing–Review and editing. **Susan L. Lightman, PhD, FRCP, FRCOphth:** Investigation, Writing–Review and editing. **Peter McCluskey, MD:** Investigation, Data curation, Writing–Review and editing. **Neal Oden, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing–Review and editing. **Annabelle A. Okada, MD, DMSc:** Investigation, Writing–Review and editing. **Alan G. Palestine, MD:** Investigation, Writing–Review and editing. **Jennifer E. Thorne, MD, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing–Review and editing. **Brett E. Trusko, PhD, MBA:** Methodology, Software, Resources, Data curation, Investigation, Writing–Review and editing. **Albert Vitale, MD:** Investigation, Writing–Review and editing.

TOC

A formalized approach was used to develop classification criteria, including informatics-based case collection, consensus-technique-based case selection, and machine learning, classification criteria for sarcoidosis-associated uveitis. Key criteria included a compatible uveitic syndrome and evidence of sarcoidosis using either a tissue biopsy demonstrating non-caseating granulomata or chest imaging demonstrating bilateral hilar adenopathy. The resulting classification criteria had a low misclassification rate.

Funding/Support: The Standardization of Uveitis Nomenclature (SUN) Working Group was supported by National Eye Institute/National Institutes of Health grant R01 EY026593; the David Brown Fund; the Jillian M. and Lawrence A. Neubauer Foundation; and the New York Eye and Ear Foundation.

REFERENCES

1. Statement on SarcoidosisJoint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and the ERS Executive Committee, February 1999. *Am J Resp Crit Care Med*. 1999;160(2):736–755.
2. Sepah YJ, Agarwal A, Jabs DA, Nguyen QD. Sarcoidosis. In: Schachat AP, Wilkinson CP, Hinton DR, Sada SVR, Wiedemann P, eds. *Ryan's Retina*. Sixth edition. New York: Elsevier; 2018:1572–1585.
3. Baughman RP, Teirsten AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Resp Crit Care Med*. 2001;164(10 Pt 1):1885–1889.
4. Ungprasert P, Tooley AA, Crowson CS, Matteson EL, Smith WM. Clinical characteristics of ocular sarcoidosis: a population-based study 1976-2013. *Ocular Immunol Inflamm*. 2019;27(3):389–395.
5. Henderly DE, Genstler AJ, Smith RE, Rao NA. Changing patterns of uveitis. *Am J Ophthalmol*. 1987;103(2):131–136.
6. Jabs DA, Busingye J. Approach to the diagnosis of the uveitides. *Am J Ophthalmol*. 2013;156(2):228–236.
7. Obenauf CD, Shaw HE, Syndor CF, Klintworth GK. Sarcoidosis and its ophthalmic manifestations. *Am J Ophthalmol*. 1978;86(5):648–655.
8. Jabs DA, Johns CJ. Ocular involvement in chronic sarcoidosis. *Am J Ophthalmol*. 1986;102(3):297–301.
9. Rothova A. Ocular involvement in sarcoidosis. *Br J Ophthalmol*. 2000;84(1):110–116.
10. Birnbaum AD, Oh FS, Chakrabarti A, Tessler HH, Goldstein D. Clinical features and diagnostic evaluation of biopsy-proven ocular sarcoidosis. *Arch Ophthalmol*. 2011;129(4):409–413.
11. Acharya NR, Browne EN, Rao N, Mochizuki Mfor the International Ocular Sarcoidosis Working Group. Distinguishing features of ocular sarcoidosis in an international cohort of uveitis patients. *Ophthalmology*. 2018;125(1):119–126.
12. Jabs DA, Rosenbaum JT. Nussenblatt RB, the Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Report of the first international workshop. *Am J Ophthalmol*. 2005;140(3):509–516.

13. Trusko B, Thorne J, Jabs D, et al. Standardization of Uveitis Nomenclature Working Group. The SUN Project. Development of a clinical evidence base utilizing informatics tools and techniques. *Methods Inform Med*. 2013;52(3):259–265.
14. Okada AA, Jabs DA. The SUN Project. The future is here. *Arch Ophthalmol*. 2013;131(6):787–789.
15. Jabs DA, Dick A, Doucette JT, et al. on behalf of the Standardization of Uveitis Nomenclature Working Group. Interobserver agreement among uveitis experts on uveitic diagnoses: the Standard of Uveitis Nomenclature experience. *Am J Ophthalmol*. 2018;186:19–24.
16. The Standardization of Uveitis Nomenclature (SUN) Working GroupDevelopment of classification criteria for the uveitides. *Am J Ophthalmol*. 2021 Apr 10 Online ahead of print.
17. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria. *Arthritis Care Res*. 2015;67(7):891–897.
18. Winterbauer RH, Belic N, Moores KD. Clinical interpretation of bilateral hilar adenopathy. *Ann Intern Med*. 1973;78(7):65–71.
19. Babu K, Shukla SB, Philips M. High resolution chest computerized tomography in the diagnosis of ocular sarcoidosis in a high TB endemic population. *Ocular Immunol Inflamm*. 2017;25(2):253–258.
20. Standardization of Uveitis Nomenclature (SUN) Working GroupClassification criteria for tubercular uveitis. *Am J Ophthalmol*. 2021 Apr 9 Online ahead of print.
21. LaDista NR, van Velthoven ME, Ten Dam-vanLoon NH, et al. Clinical manifestations of patients with intraocular inflammation and positive Quanteriferon-TB gold in-tube test in a country non-endemic for tuberculosis. *Am J Ophthalmol*. 2014;137(4):754.
22. Ohara K, Okubo A, Kamata K, Sasaki H, Kobayashi J, Kitamura S. Transbronchial lung biopsy in the diagnosis of suspected ocular sarcoidosis. *Arch Ophthalmol*. 1993;111(5):642–644.
23. Baarsma GS, La Hey E, Glasius E, de Vries J, Kilstra A. The predictive value of serum angiotensin converting enzyme and lysozyme levels in the diagnosis of ocular sarcoidosis. *Am J Ophthalmol*. 1987;104(3):211–217.
24. Herbort CP, Mochizuki M, Rao NA. the members of the Scientific Committee of the First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: results of the First International Workshop on Ocular Sarcoidosis (IWOS). *Ocular Immunol Inflamm*. 2009;17(3):160–169.
25. Mochizuki M, Smith JR, Takase H, Kaburaki T, Acharya NR, Rao NA. for the International Workshop on Ocular Sarcoidosis Study Group. *Br J Ophthalmol*. 2019 ePub ahead of print.
26. Niederer RL, Al-Janabi A, Lightman SL. Tomkins-Netzer O. Serum angiotensin-converting enzyme has a high negative predictive value in the investigation for systemic sarcoidosis. *Am J Ophthalmol*. 2018;194:82–87.
27. Gundlach E, Hoffman MM, Prasse A, Heinzelman S. Interleukin-2 receptor and angiotensin converting enzyme as markers for ocular sarcoidosis. *PLoS One*. 2016;11.
28. Niederer RL, Sims JL. Utility of screening investigations for systemic sarcoidosis in undifferentiated uveitis. *Am J Ophthalmol*. 2019;206:149–153.
29. Kosmorsky GS, Meisler DM, Rice TW, Meziane MA, Lowder CY. Chest computed tomography and mediastinoscopy in the diagnosis of sarcoidosis-associated uveitis. *Am J Ophthalmol*. 1998;126(1):132–134.
30. Han YS, Rivera-Grana E, Salek S, Rosenbaum JT. Distinguishing uveitis secondary to sarcoidosis from idiopathic disease: cardiac implications. *JAMA Ophthalmol*. 2018;136(2):109–115.