Classification Criteria for Serpiginous Choroiditis

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

• PURPOSE: To determine classification criteria for serpiginous choroiditis.
• DESIGN: Machine learning of cases with serpiginous choroiditis and 8 other posterior uveitides.
• METHODS: Cases of posterior uveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on diagnosis, using formal consensus techniques. Cases were split into a training set and a validation set. Machine learning using multinomial logistic regression was used on the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the infectious posterior uveitides / panuveitides. The resulting criteria were evaluated on the validation set.
• RESULTS: One thousand sixty-eight cases of posterior uveitides, including 122 cases of serpiginous choroiditis, were evaluated by machine learning. Key criteria for serpiginous choroiditis included (1) choroiditis with an ameboid or serpentine shape; (2) characteristic imaging on fluorescein angiography or fundus autofluorescence; (3) absent to mild anterior chamber and vitreous inflammation; and (4) the exclusion of tuberculosis. Overall accuracy for posterior uveitides was 93.9% in the training set and 98.0% (95% confidence interval 94.3, 99.3) in the validation set. The misclassification rates for serpiginous choroiditis were 0% in both the training set and the validation set.
• CONCLUSIONS: The criteria for serpiginous choroiditis had a low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 126–133. © 2021 Elsevier Inc. All rights reserved.)

Serpiginous choroiditis is a chronic posterior uveitis characterized by ameboid or serpentine choroidal inflammatory lesions with a characteristic fluorescein angiographic appearance, typically, though not always, extending from the edge of the optic nerve into adjacent retina. Untreated, it is a waxing and waning progressive disease, which results in chorioretinal damage and atrophy.[1] Several other names have been used in the past, including peripapillary choroidal sclerosis, helicoid peripapillary chorioretinal degeneration, geographic choroiditis, geographical choroidopathy, geographic helicoid peripapillary choroidopathy, and serpiginous choroidopathy.[1-5] The active lesions appear large, paucifocal, or less often multifocal; involve the choroid; and are gray-white or yellow. There is no to minimal anterior chamber and vitreous inflammation. Active lesions resolve over 1-2 months, leaving areas of retinal, retinal pigment epithelial (RPE), and choroidal atrophy. Newly active lesions appear at the border of the previous atrophic lesions. The development of contiguous active lesions at seemingly haphazard locations along the chorioretinal atrophy/scars gives rise to a serpent-like appearance, resulting in its name. Although the majority of lesions are connected and abut the optic disc, separate lesions, not adjacent to the disc, also occur.[1] The fluorescein angiogram demonstrates a classic appearance with early diffuse hypofluorescence of the lesions and late hyperfluorescence of the borders of the lesions (previously termed a "block early, stain late at the borders" appearance), which distinguishes serpiginous choroiditis from most other choroidopathies, such as acute posterior multifocal placoid pigment epitheliopathy (APMPPE), in which the fluorescein angiogram has a characteristic early diffuse hypofluorescence of the lesions and late diffuse hyperfluorescence of the lesions (originally described as "block early, stain late diffusely" appearance).[1,6,7] Choroidal neovascularization is an uncommon, but well-recognized, complication of serpiginous choroiditis.[1]

Serpiginous choroiditis is a rare entity, accounting for <5% of cases of posterior uveitis in case series from ter-

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

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2021.03.038

tiary care referral centers.[8] The etiology is unknown, but an autoinflammatory or autoimmune pathogenesis has been presumed. The reported pathology is that of choroidal lymphocytic inflammation in the areas of active disease with atrophy of the choroid and RPE and photoreceptor loss in the clinically atrophic areas. Scarring may extend into the retina, and focal areas of RPE hypertrophy correspond to pigment clumping sometimes seen at the lesion borders.[9] The course characterized by spread into contiguous choroid has led to the speculation that it may be infectious in nature, as has the detection by polymerase chain reaction of herpes simplex virus and varicella zoster virus in the aqueous humor, each in a single case of serpiginous choroiditis.[10] However, the reported success with immunosuppression, including alkylating agent therapy (which would worsen an infectious process, not control it), strongly suggests that it is not an infectious disease.[11-14] A similar-appearing disease, known as serpiginous-like tubercular choroiditis, occurs in the context of evidence of infection with tuberculosis (TB) and is treated with antituberculous therapy.[15]

Other imaging modalities may be of value in the management of serpiginous choroiditis. Indocyanine green angiography demonstrates hypofluorescent choroidal lesions throughout the angiogram and may show late hyperfluorescent borders. Indocyanine green angiography may demonstrate more extensive lesions than those seen clinically.[17,18] Fundus autofluorescence has been reported to be valuable in the management of serpiginous choroiditis. It demonstrates hypo-autofluorescent lesions in the area of scarring/atrophy; active lesions have hyper-autofluorescent borders, which resolve with treatment.[19] Optical coherence tomographic angiography of active lesions demonstrates an absence of choriocapillaris with variable outer retinal and RPE thickening, whereas in inactive lesions it demonstrates partial reappearance of the choriocapillaris. In atrophic lesions, these structures cannot be imaged.[20]

Because it is a rare disease, most treatment evidence comes from case series. Some investigators believe that oral corticosteroids shorten the duration of acute exacerbations but do not affect the long-term course.[1] Conversely, immunosuppression seems to control the disease and prevent exacerbations.[11-15] One comparative case series reported significantly better disease control with immunosuppression.[12] Discontinuation of nonalkylating agent immunosuppression may lead to recurrent disease, and the optimal duration of therapy is uncertain.[11,13,14] Alkylating agent therapy has been reported to induce long-term, sustained, drug-free remissions,[15] but this approach now is used sparingly owing to concerns about increased risks of malignancy associated with alkylating agent therapy.[21]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration that has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification. Among the diseases studied was serpiginous choroiditis.[22-28]

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in 4 phases, as previously described: (1) informatics, (2) case collection, (3) case selection, and (4) machine learning.[24-27]

• **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.[24]

• **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.[26,27] 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 article.[26,27] Because the goal was to develop classification criteria,[28] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[26,27]

• **MACHINE LEARNING:** The final database then was randomly separated into a learning set (~85% of the cases) and a validation set (~15% of the cases) for each disease, as described in the accompanying article.[27] Machine learning was used on the learning set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the learning set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm when compared to the consensus diagnosis. For serpiginous choroiditis, the diseases against which it was evaluated included APMPPE, birdshot chorioretinitis, multifocal choroiditis with panuveitis (MFCPU), multiple evanescent white dot syndrome, punctate inner choroiditis, sarcoidosis-associated posterior uveitis, syphilitic posterior uveitis, and TB posterior uveitis.

• **COMPARISON OF CASES WITH SERPIGINOUS CHOROIDITIS AND SERPIGINOUS-LIKE TUBERCULAR CHOROIDITIS:** Comparison of the characteristics of cases with serpiginous choroiditis and cases with serpiginous-like TB choroiditis was performed with the χ^2 test for categorical variables or the Fisher exact test when the count of a variable was less than 5. Continuous variables were summarized as medians and compared with the Wilcoxon rank sum test.

The study adhered to the principles of the Declaration of Helsinki. Institutional review boards at each participating

center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual institutional review boards.

RESULTS

One hundred fifty-seven cases of serpiginous choroiditis were collected, and 122 (78%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase These cases of serpiginous choroiditis were compared to cases of posterior uveitides, including 82 cases of APMPPE, 207 cases of birdshot chorioretinitis, 51 cases of multiple evanescent white dot syndrome, 138 cases of MFCPU, 144 cases of punctate inner choroiditis, 12 cases of sarcoid posterior uveitis, 35 cases of syphilitic posterior uveitis, and 277 cases of tubercular posterior uveitis (including 96 cases of serpiginous-like tubercular choroiditis). The details of the machine learning results for these diseases are outlined in the accompanying article.[27] The characteristics of cases with serpiginous choroiditis are listed in Table 1, and a comparison between serpiginous choroiditis and serpiginous-like TB choroiditis is listed in Table 2. Cases with serpiginous-like TB choroiditis involved patients who were younger, more likely to be Asian, less likely to have chronic disease, more likely to be unilateral, more likely to have higher grades of vitreous cells, and more likely to have multifocal lesions. The classification criteria developed after machine learning are listed in Table 3. Key features of the criteria include the ameboid or serpentine appearance of the lesions (Figure 1) and the characteristic fluorescein angiogram (Figure 2) or fundus autofluorescence demonstrating hypo-autofluorescent lesions with hyper-autofluorescent borders. The overall accuracies for posterior uveitides were 93.9% in the learning set and 98.0% (95% confidence interval 94.3, 99.3) in the validation set.[27] The misclassification rates for serpiginous choroiditis were 0% in both the learning set and the validation set.

DISCUSSION

The classification criteria developed by the SUN Working Group for serpiginous choroiditis have a low misclassification rate, indicating good discriminatory performance against other posterior uveitides.

The primary disease in the differential diagnosis of serpiginous choroiditis is serpiginous-like TB choroiditis.[16] Although patients with serpiginous-like TB choroiditis are more likely to be younger, have unilateral disease, have higher grades of vitritis, and have multifocal lesions, the features of the 2 diseases overlap sufficiently that the diagnosis cannot be made on morphologic appearance alone.[16]

TABLE 1. Characteristics of Cases of Serpiginous Choroiditis

Characteristic	Result
Number of cases	122
Demographics	
Age, median, years (25th, 75th percentile)	50 (38, 58)
Sex (%)	
Male	54
Female	46
Race/ethnicity (%)	
White, non-Hispanic	74
Black, non-Hispanic	3
Hispanic	2
Asian, Pacific Islander	2
Other	13
Missing	6
Uveitis history	
Uveitis course (%)	
Acute, monophasic	11
Acute, recurrent	0
Chronic	88
Indeterminate	1
Laterality (%)	
Unilateral	14
Unilateral, alternating	0
Bilateral	86
Ophthalmic examination	
Keratic precipitates (%)	
None	98
Fine	2
Anterior chamber cells, grade (%)	
0	92
½+	5
1+	2
2+	1
3+	0
4+	0
Anterior chamber flare, grade (%)	
0	98
1+	2
2+	0
3+	0
4+	0
Iris (%)	
Normal	98
Posterior synechiae	2
Iris nodules	0
Iris atrophy (sectoral, patchy, or diffuse)	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	16 (14, 18)
Proportion of patients with IOP > 24 mm Hg either eye (%)	2
Vitreous cells, grade (%)	
0	63
½+	21
1+	11

(*continued on next page*)

TABLE 1. (*continued*)

Characteristic	Result
2+	4
3+	1
4+	0
Vitreous haze, grade (%)	
0	90
½+	9
1+	1
2+	0
3+	0
4+	0
Chorioretinitis characteristics	
Lesion number (%)	
Unifocal (1 lesion)	5
Paucifocal (2-4)	67
Multifocal (≥5)	28
Lesion shape and character (%)	
Ameboid or serpentine	100
Oval or round	0
Placoid	0
Atrophic	13
Punctate	0
Lesion location (%)	
Posterior pole involved	96
Midperiphery and periphery only	4
Typical lesion size (%)	
<125 μm	0
125-250 μm	2
250-500 μm	6
>500 μm	91
Missing	1
Other features (%)	
Retinal vascular sheathing	1
Retinal vascular leakage	6
Choroidal neovascularization	2
Fluorescein angiogram demonstrating early diffuse hypofluorescent lesions and late hyperfluorescent lesion borders[a]	100

IOP = intraocular pressure.
[a]Based on review of 51 angiograms.

As such, all patients presenting with a serpiginoid appearance to the choroiditis should be tested for TB with either a tuberculosis skin test or interferon-γ release assay (eg, QuantiFERON gold, T-spot, etc). Although some patients in high-prevalence countries for TB might have serpiginous choroiditis and unrelated latent TB, in low-prevalence countries, such as the United States, a positive test for TB in the setting of a serpiginoid choroiditis would have a high positive predictive value for serpiginous-like TB choroiditis. Sarcoid nodules in the choroid may appear similar to serpiginous choroiditis, particularly if prior treatment has led to healing with atrophy; as such, sarcoidosis needs to be excluded.

Although classically serpiginous choroiditis lesions abut the optic disc, not all cases do. One study estimated that ~5% of eyes had lesions not adjacent to the disc.[14] For such lesions, the fluorescein angiogram (or fundus autofluorescence) can be very helpful in diagnosis. Occasionally cases of serpiginous choroiditis that are not adjacent to the disc may be mistaken for MFCPU, but the fluorescein angiogram and/or fundus autofluorescence are distinct. Relentless placoid choroiditis (sometimes termed ampiginous choroiditis) has lesions on ophthalmoscopy that are more similar to APMPPE than to serpiginous choroiditis, but has fluorescein angiograms more similar to serpiginous choroiditis (ie, block early, stain late at the borders).[29,30] The course is more often similar to serpiginous choroiditis than to APMPPE, as is the treatment. Whether relentless placoid choroiditis is a variant of serpiginous choroiditis or a distinct but related disease cannot be ascertained at this time, although many consider them distinct; as such, they should be classified separately until additional data clarify the issue.

The presence of any of the exclusions in Table 3 suggests an alternate diagnosis, and the diagnosis of serpiginous choroiditis should not be made in their presence. In prospective studies many of these tests will be performed routinely and the alternative diagnoses excluded, especially serpiginous-like tubercular choroiditis. However, in retrospective studies based on clinical care, not all of these tests may have been performed. In these studies the presence of an exclusionary criterion excludes serpiginous choroiditis, but the absence of such testing does not always exclude the diagnosis of serpiginous choroiditis if the criteria for the diagnosis are met, with the proviso that going forward TB should be excluded.

Classification criteria are employed to diagnose individual diseases for research purposes.[28] Classification criteria differ from clinical diagnostic criteria in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[28] 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 employed did not explicitly use sensitivity and specificity; instead, it minimized the misclassification rate. Because we were developing classification criteria and because the typical agreement between 2 uveitis experts on diagnosis is moderate at best,[27] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis. As such, there may be cases that clinicians would diagnose as serpiginous choroiditis that would not meet the criteria outlined in Table 3.

In conclusion, the criteria for serpiginous choroiditis outlined in Table 3 seem to perform sufficiently well for use as classification criteria in clinical research.[27]

TABLE 2. Comparison of Cases of Serpiginous Choroiditis With Cases of Serpiginous-like Tuberculous Choroiditis

Characteristic	Serpiginous Choroiditis	Serpiginous-like TB Choroiditis	*P* Value
Number of cases	122	96	
Demographics			
Age, median, years (25th, 75th percentile)	50 (38, 58)	32 (25, 43)	<.001
Sex (%)			.09
Male	54	66	
Female	46	34	
Race/ethnicity (%)			<.001
White, non-Hispanic	74	5	
Black, non-Hispanic	3	1	
Hispanic	2	1	
Asian, Pacific Islander	2	92[†]	
Other	13	0	
Missing	6	1	
Uveitis history			
Uveitis course (%)			<.01
Acute, monophasic	11	32	
Chronic	88	67	
Indeterminate	1	1	
Laterality (%)			<.01
Unilateral	14	45	
Bilateral	86	55	
Ophthalmic examination			
Keratic precipitates (%)			.93
None	98	100	
Any	2	0	
Anterior chamber cells, grade (%)			.78
0	92	94	
≥½+	8	6	
Anterior chamber flare, grade (%)			.93
0	98	98	
≥1+	2	2	
Iris (%)			.93
Normal	98	100	
Posterior synechiae	2	0	
Iris nodules	0	0	
IOP, involved eyes			
Median, mm Hg (25th, 75th percentile)	16 (14, 18)	16 (14, 18)	1.00
Percent patients with IOP > 24 mm Hg either eye	2		.26
Vitreous cells, grade (%)			.04
0	63	53	
½+	21	13	
≥1+	16	34	
Vitreous haze, grade (%)			.07
0	90	94	
≥½+	10	6	
Chorioretinitis characteristics			
Lesion number (%)			<.001
Unifocal (1 lesion)	5	0	
Paucifocal (2-4)	67	4	
Multifocal (≥5)	28	96	
Lesion shape and character (%)			
Ameboid or serpentine	100	99	.74
Lesion location (%)			.41
Posterior pole involved	96	91	
Midperiphery and periphery only	4	9	
Typical lesion size (%)			.50
<250 μm	2	0	
250-500 μm	6	9	
>500 μm	91	99	
Missing	1	1	
Other features (%)			
Retinal vascular occlusion	0	0	1.00
Retinal vascular sheathing or leakage	7	2	.12
Choroidal neovascularization	2	0	.26

IOP = intraocular pressure; TB = tuberculosis.

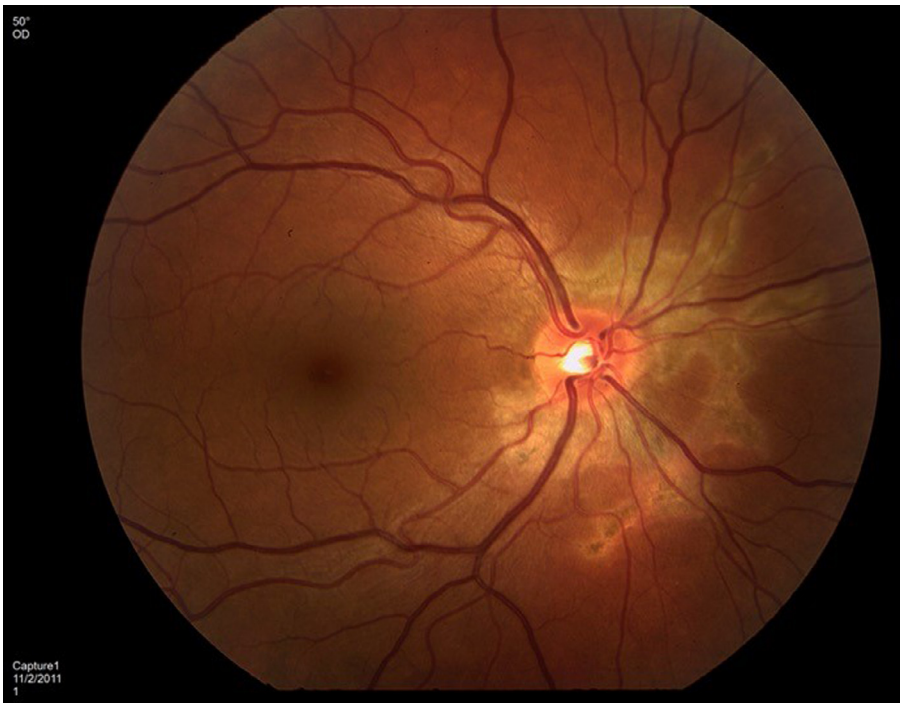

FIGURE 1. Fundus photograph of a case of serpiginous choroiditis, demonstrating the ameboid chorioretinal lesions.

TABLE 3. Classification Criteria for Serpiginous Choroiditis

Criteria
1. Paucifocal or multifocal choroiditis with an ameboid or serpentine shape[a]
AND
2. Characteristic imaging
a. Fluorescein angiogram with early diffuse hypofluorescent lesions and late hyperfluorescent lesion borders OR
b. Fundus autofluorescence with hypo-autofluorescent lesions with hyper-autofluorescent borders
AND
3. Absent-to-minimal anterior chamber and vitreous inflammation
Exclusions
1. Positive serologic test for syphilis using a treponemal test
2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata)
3. Evidence of infection with *Mycobacterium tuberculosis*, either
a. Histologically or microbiologically confirmed infection with *M. tuberculosis*[b] OR
b. Positive interferon-γ release assay[c] OR
c. Positive tuberculin skin test[d]

[a]Lesions do not need to be contiguous with the optic disc.
[b]For example, biopsy-, fluorochrome stain–, culture-, or polymerase chain reaction–based assay.
[c]For example, QuantiFERON gold or T-spot.
[d]For example, purified protein derivative; a positive result should be >10 mm induration.

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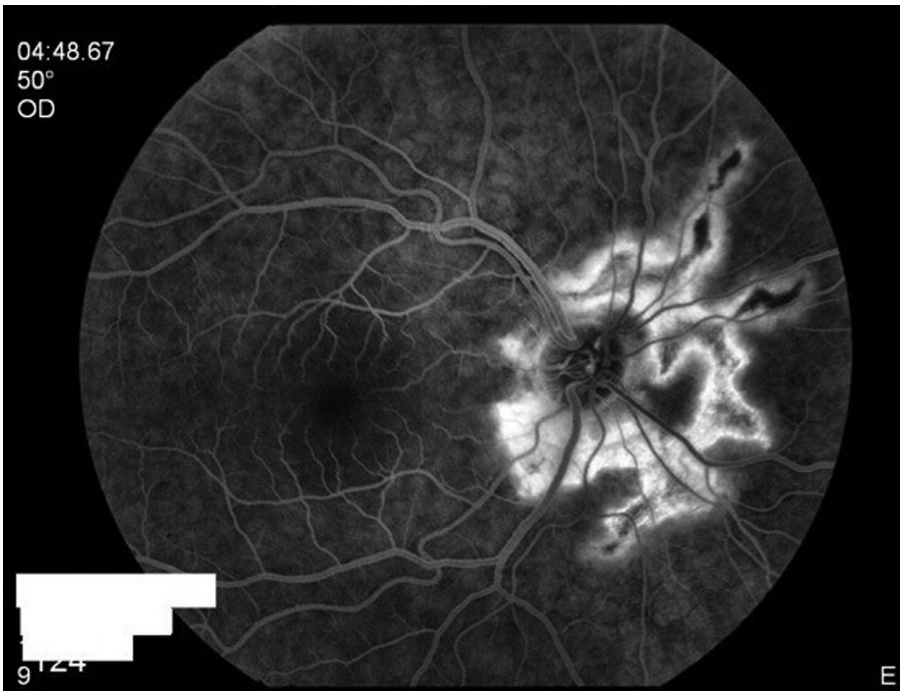

FIGURE 2. Fluorescein angiogram of a case of serpiginous choroiditis, demonstrating the characteristic late staining at the borders.

Funding/Support: Supported by grant R01 EY026593 from the National Eye Institute, the National Institutes of Health, Bethesda, Maryland, USA; the David Brown Fund, New York, New York, USA; the Jillian M. And Lawrence A. Neubauer Foundation, New York, New York, USA; and the New York Eye and Ear Foundation, New York, New York, USA. Financial Disclosures: Douglas A. Jabs: none; Antoine Brezin: none; Ralph Levinson: none; Neal Oden: none; Alan G. Palestine: none; Narsing A. Rao: none; Jennifer E. Thorne: Dr Thorne engaged in a portion of this research as a consultant and was compensated for the consulting service; Brett E. Trusko: none; Albert Vitale: none; Susan E. Wittenberg: none. All authors attest that they meet the current ICMJE criteria for authorship.

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