

Association of Dry Eye Tests With Extraocular Signs Among 3514 Participants in the Sjögren's Syndrome International Registry



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• **PURPOSE:** To identify a screening strategy for dry eye patients with a high likelihood of having Sjogren syndrome (SS) through the evaluation of the association of ocular surface tests with the extraocular signs used for the diagnosis of SS.

• **DESIGN:** Multicenter cross-sectional study.

• **METHODS:** The Sjogren's International Clinical Collaborative Alliance (SICCA) registry enrolled 3514 participants with SS or possible SS from 9 international academic sites. Ocular surface evaluation included Schirmer I testing, tear breakup time (TBUT), and staining of the cornea (0–6 points) and conjunctiva (0–6 points). Multivariate logistic regression analysis was performed to identify predictive factors for (1) histopathologic changes on labial salivary gland (LSG) biopsies (positive = focus score of ≥ 1 focus/4 mm²) and (2) positive anti-SSA/B serology.

• **RESULTS:** The adjusted odds of having a positive LSG biopsy were significantly higher among those with an abnormal Schirmer I test (adjusted OR = 1.26, 95% CI 1.05–1.51, $P = .014$) and positive conjunctival staining (for each additional unit of staining 1.46; 95% CI 1.39–1.53, $P < .001$) or corneal staining (for each additional unit of staining 1.14; 95% CI 1.08–1.21, $P < .001$). The odds of having a positive serology were

significantly higher among those with an abnormal Schirmer I test (adjusted OR = 1.3; 95% CI 1.09–1.54, $P = .004$) and conjunctival staining (adjusted OR = 1.51; 95% CI 1.43–1.58, $P < .001$).

• **CONCLUSIONS:** In addition to corneal staining, which was associated with a higher likelihood of having a positive LSG biopsy, conjunctival staining and abnormal Schirmer I testing are of critical importance to include when screening dry eye patients for possible SS, as they were associated with a higher likelihood of having a positive LSG biopsy and serology. (Am J Ophthalmol 2016;172:87–93. © 2016 Elsevier Inc. All rights reserved.)

SJÖGREN SYNDROME (SS) IS THE SECOND MOST common autoimmune disease, affecting nearly 4 million Americans, with an estimated prevalence of 0.5%–5%.¹

Although the disease is common, diagnosis is often delayed by an average time of 6.5 years from symptom onset,^{2–4} and the majority of SS patients are undiagnosed.⁵ Diagnostic delays are of great clinical significance, as studies have consistently identified SS as an independent risk factor for non-Hodgkin lymphoma.^{4,6,7} Early detection of SS is important because patients who are started on biological agent treatment within the first 5 years of disease onset may be more likely to respond to treatment than those with delayed initiation of therapy.^{8–10}

Clinically, SS is characterized by hypofunction of the salivary and lacrimal glands, which typically leads to dry mouth and dry eye,¹¹ although it may affect any organ system in the body. Because SS affects many organ systems, collaboration among multiple medical specialties is required and often contributes to delays in diagnosis. Currently, there are 2 sets of criteria used for the diagnosis of SS: the American-European Consensus Group (AECG) criteria¹² and the more recent set of classification criteria developed by the Sjögren's International Collaborative Clinical Alliance (SICCA) group and provisionally endorsed by the American College of Rheumatology

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(ACR).¹³ The ACR criteria define SS as requiring 2 out of 3 of the following signs: (1) positive serology (anti-SSA/SSB positivity or positive rheumatoid factor [RF] and antinuclear antibodies [ANA] $\geq 1:320$); (2) presence of focal lymphocytic sialadenitis (FLS) with a focus score (FS) $\geq 1/4$ mm² on a labial salivary gland (LSG) biopsy (“positive LSG biopsy”); or (3) an ocular staining score (OSS) ≥ 3 .¹³ Recently, a revised set of classification criteria (ACR/European League Against Rheumatism) has been proposed in an attempt to reconcile differences between the AECG and ACR/SICCA criteria (Shiboski CH, American College of Rheumatology 2015).

Because dry eye is one of the most common symptoms of SS, patients often first seek care from eye care providers, who can potentially play a key role in reducing time from symptom onset to diagnosis. Previous studies have shown that up to 10% of dry eye patients have SS.¹⁴ However, because of the high prevalence of dry eye disease,^{15,16} it is not practical or economically feasible for ophthalmologists to refer all dry eye patients for an SS evaluation. In addition, screening is challenging, as there is currently no universal standard regarding which dry eye patients should undergo a comprehensive evaluation for SS (that includes a rheumatologic evaluation with specific blood work, and an LSG biopsy).

Historically, assessment of dry eye symptoms alone has not been helpful in screening patients for SS, as multiple autoimmune diseases may present with dry eye symptoms without any known symptoms specific for SS-related dry eye.^{17–19} Similarly, severity of symptoms is not a helpful distinguishing factor, as SS-related dry eye patients experience a wide range of symptoms ranging from asymptomatic dry eye to severe dysfunction and decreased quality of life. Furthermore, there is limited evidence regarding specific ocular signs that in isolation can reliably distinguish SS-related from non-SS-related dry eye for the purpose of identifying SS patients.²⁰ Thus historically, ocular symptoms and signs in isolation have been poorly predictive of extraocular objective signs required for the diagnosis of SS patients, in particular positive serology and a positive LSG biopsy.^{12,21,22} However, although ocular signs in isolation may not be useful for diagnosing SS (in the absence of a systemic evaluation), ocular signs may be useful for *screening* dry eye patients and deciding who should undergo a comprehensive evaluation for SS.

Therefore, the goal of the present study is to explore the association of individual ocular surface diagnostic tests (Schirmer I test, tear breakup time [TBUT], ocular surface staining of the cornea and conjunctiva) with extraocular objective diagnostic tests for SS, thus gaining insight about their potential role in the clinical evaluation algorithm that may be used by ophthalmologists in screening dry eye patients for possible SS. The comprehensive data collected as part of the SICCA study offered a unique opportunity to explore this objective.

METHODS

• **STUDY DESIGN AND POPULATION:** Enrollment in the SICCA cohort study occurred between 2004 and 2012 in 9 international academic sites in Argentina, China, Denmark, Japan, India, the United Kingdom, and the United States.²² Institutional Review Board approval of the study protocol was obtained from all centers before the start of the study, and informed consent was obtained from all subjects. The objectives of the SICCA registry, funded primarily by the National Institute of Dental and Craniofacial Research, were to (1) develop new classification criteria for SS, and (2) establish a data and biospecimen repository that would be accessible by investigators worldwide for future studies on the pathogenesis, phenotypic features, and genotypic features of the disease. The data-driven consensus methodology used in the development of classification criteria, and the role of a panel of expert clinicians representing the 3 specialties involved in the diagnosis and management of SS, have been previously described.¹³ Expert panel members in the SICCA group agreed that the classification criteria should pertain to a target population of patients who may have signs and symptoms suggestive of SS, and be referred to specialists involved in the diagnosis and management of SS, namely rheumatologists, ophthalmologists, or oral medicine specialists.¹¹ It was agreed that no diagnostic criteria or labels would be used for enrollment and that all participants in the cohort would undergo the same set of standardized tests and evaluations, including eye examination, labial salivary gland biopsy, and serologic testing (anti-SS A or anti-SS B antibodies or RF positivity in combination with elevated ANA). Thus, patients reporting dry eye symptoms or those who lacked dry eye symptoms but had either extraocular symptoms or signs that may be suggestive of SS were included in the study.

Specifically, to be eligible for the SICCA registry, participants had to be 21 years of age and were required to have 1 or more of the following: (1) symptoms of dry eyes or dry mouth; (2) bilateral parotid enlargement; (3) recent increase in dental caries; (4) a previous suspicion or diagnosis of SS; (5) elevated serology of ANA, positive rheumatoid factor (RF), anti-SS A antibodies, or anti-SS B antibodies; or (6) diagnoses of rheumatoid arthritis or systemic lupus erythematosus. Eligibility criteria were intended to target individuals with signs or symptoms of SS, not the general population *and* not patients exclusively reporting dry eye symptoms. These represent patients who may have been referred to an ophthalmologist by a rheumatologist or oral medicine specialist in the absence of dry eye symptoms. Exclusion criteria included known diagnoses of the following: hepatitis C, HIV infection, sarcoidosis, amyloidosis, active tuberculosis, graft-vs-host disease, autoimmune connective tissue diseases other than rheumatoid arthritis or systemic lupus erythematosus, or past head and neck radiation treatment.

Further exclusion criteria specific to the eye included current treatment with daily eye drops for glaucoma, corneal surgery in the last 5 years to correct vision, cosmetic eyelid surgery in the last 5 years, or physical or mental condition interfering with successful participation in the study. Contact lens wearers were asked to discontinue use 7 days prior to SICCA examination. We did not exclude participants taking prescription drugs that may affect salivary or lacrimal secretion, but we recorded their use and asked that they discontinue use 1 day prior to the SICCA examination.

• **VARIABLES AND MEASURES:** *SICCA registry ocular examination.* The sequence and details of the SICCA eye examination protocol have previously been described by the SICCA group,²³ and are only briefly described here. Because ocular surface staining with the vital dyes fluorescein and lissamine green may disrupt tear film stability, Schirmer I test (without anesthesia) was performed first. Next, TBUT, grading of corneal staining with fluorescein (0.5% drops), and grading of conjunctival staining with lissamine green (1% drops) were performed, in that order. Ocular surface staining assessments were performed within a specified time frame before the dye had sufficient time to diffuse and the intensity of the staining could be compromised.

Outcome variables. The outcome variables, positive serology and positive LSG biopsy, were defined as follows: (1) positive serology as determined by the presence of SSA or SSB antibodies or RF positivity and ANA titer $\geq 1:320$; (2) LSG biopsy with a diagnosis of FLS and a focus score of ≥ 1 focus/4 mm². These extraocular outcomes are the other objective tests typically used for the diagnosis of SS, in addition to the ocular surface staining. Thus, they are studied here because they represent the basis of SS classification criteria that was recently endorsed by the ACR.¹³

• **STATISTICAL ANALYSES:** Summary statistics (proportions for categorical variables; means with 95% confidence intervals [CI] for continuous variables) were used to describe the SICCA participant characteristics with respect to the various objective tests measured (ocular, oral, serologic).

We used logistic regression models to quantify the marginal association between ocular surface diagnostic test results and each of our 2 outcomes (positive LSG biopsy and positive serology). Variables for the ocular test results were defined as follows: (1) binary indicator of an unanesthetized Schirmer I test score ≤ 5 mm; (2) binary indicator of a TBUT score < 10 seconds; (3) conjunctival component of the OSS (graded 0–6 for the conjunctival portion of the grading system) (4); corneal component of the OSS (graded 0–6 for the corneal portion of the grading system); and (5) binary indicator of an OSS score ≥ 3 . *P* values of less than .05 were deemed statistically significant for regression

TABLE 1. Sjögren Syndrome–Related Characteristics in the Sjogren’s International Collaborative Clinical Alliance (SICCA) Registry (N = 3514)^a

Diagnostic Tests	N (%)
Ocular eye tests	
Schirmer I test	
Schirmer I test ≤ 5 mm	1026 (31.7)
Schirmer I test > 5 mm	2213 (67.7)
Tear breakup time	
< 10 seconds	2868 (84.5)
≥ 10 seconds	528 (15.5)
Ocular staining score (mean) ^b	
Conjunctival score	2.99 (2.92–3.06)
Corneal score	2.16 (2.10–2.22)
Total OSS score	5.15 (5.03–5.27)
Salivary gland biopsy	
Focus score ≥ 1	1305 (39.1)
Focus score < 1	2032 (60.9)
Positive serology	
SSA or SSB antibodies	
Present	1296 (38.3)
Not present	2086 (61.7)
RF and ANA titer $\geq 1:320$	
Present	1382 (40.9)
Not present	2000 (59.1)

ANA = antinuclear antibodies; OSS = ocular staining score; RF = rheumatoid factor.

^aBecause of missing data, some of the denominators used to compute the proportions above may differ from 3514.

^bConfidence intervals are provided here; this was included as a continuous variable in the regression.

results. To investigate the independent contribution of the ocular measures in predicting the 2 outcomes, we fitted 2 additional logistic models including the first 4 ocular variables defined above, as well as participant age and race.

All statistical analyses were performed using Stata 10.0 (StataCorp. 2007. Stata Statistical Software: Release 10; StataCorp LP, College Station, Texas, USA) and R (v. 3.0 for MacIntosh; R Foundation for Statistical Computing, Vienna, Austria). Participants with missing values were excluded from the analysis. Missing data occurred as follows: Schirmer score 5.4%, abnormal LSG focus scores 4.8%, and all other variables had smaller fractions of missing data.

RESULTS

• **SAMPLE CHARACTERISTICS:** Data from a total of 3514 participants were available from the SICCA registry (Table 1). The proportion of participants with an abnormal Schirmer score (defined as ≤ 5 mm/5 min) was 32%. The majority of participants (85%) had an abnormal TBUT

TABLE 2. Unadjusted Association of Ocular Surface Tests in Relation to Positive Serology or Positive LSG biopsy in the Sjogren's International Collaborative Clinical Alliance (SICCA) Registry (N = 3514)^a

Diagnostic Tests	Unadjusted Odds Ratio: Positive Serology (95% CI)	P Value	Unadjusted Odds Ratio: Positive LSG Biopsy (95% CI)	P Value
Ocular eye tests				
Schirmer I test ≤ 5 mm/min ^b	2.37 (2.04–2.75)	<.001	2.44 (2.1–2.85)	<.001
TBUT <10 seconds ^b	2.48 (2–3.07)	<.001	2.17 (1.75–2.68)	<.001
Ocular staining score				
Conjunctival OSS score ^b	1.55 (1.49–1.6)	<.001	1.57 (1.51–1.63)	<.001
Corneal OSS score ^b	1.43 (1.27–1.49)	<.001	1.52 (1.45–1.58)	<.001
Abnormal OSS score ^b	1.28 (1.26–1.31)	<.001	1.31 (1.28–1.34)	<.001

CI = confidence interval; LSG = labial salivary gland; OSS = ocular staining score.

^aBecause of missing data, some of the denominators used to compute the calculations above may differ from 3514.

^bStatistically significant result.

(defined as <10 seconds). The mean conjunctival OSS score was 3 points (95% CI = 2.92–3.06) and the mean corneal OSS score was 2.2 (95% CI = 2.10–2.22). The mean total OSS score was 5.2 (95% CI = 5.03–5.27). The cohort also had the following features: 39.1% had a focus score greater than or equal to 1, 38.3% had a positive SSA or SSB, and 40.9% had positive RF and ANA titer $\geq 1:320$.

• **BIVARIATE ANALYSES EXPLORING THE ASSOCIATION BETWEEN EYE-RELATED PHENOTYPIC FEATURES AND POSITIVE SEROLOGY AND BIOPSY:** *Positive serology.* In the bivariate analysis of the independent predictors (Table 2), increased odds of positive serology was associated with abnormal Schirmer test (OR = 2.37, 95% CI = 2.04–2.75, $P < .0001$) and abnormal TBUT (OR = 2.48, 95% CI = 2.0–3.07, $P < .0001$). For ocular staining scores, increased odds of positive serology was associated with conjunctival OSS scores (OR = 1.55, 95% CI = 1.49–1.6, $P < .0001$), corneal OSS scores (OR = 1.43, 95% CI = 1.37–1.49, $P < .0001$), and an abnormal total OSS score (OR = 1.28, 95% CI = 1.26–1.31, $P < .0001$).

Positive labial salivary gland biopsy. Similarly, increased odds for having a positive LSG biopsy was associated with abnormal Schirmer score (OR = 2.44, 95% CI = 2.1–2.85, $P < .0001$) and abnormal TBUT (OR = 2.17, 95% CI = 1.75–2.68, $P < .0001$). Increased odds of positive LSG biopsy was further associated with conjunctival OSS scores (OR = 1.57, 95% CI: 1.51–1.63, $P < .0001$), corneal OSS scores (OR = 1.52, 95% CI: 1.45–1.58, $P < .0001$), and an abnormal OSS score (OR = 1.31, 95% CI = 1.28–1.34, $P < .0001$).

• **MULTIVARIATE ANALYSIS:** We fit separate models to explore dry-eye test results as potential explanatory variables of (1) a positive LSG biopsy or (2) positive

TABLE 3. Logistic Regression Models Fit to Explore Dry-Eye Test Results as Potential Explanatory Variables of Positive Labial Salivary Gland Biopsy and Positive Serology Among Participants in the Sjogren's International Collaborative Clinical Alliance (SICCA) Registry

	Adjusted Odds Ratio (95% CI) ^a	P Value
LSG biopsy (N = 3153)		
TBUT <10 seconds	0.76 (0.58–0.99)	.043
Schirmer I test ≤ 5 mm/5 min	1.26 (1.05–1.51)	.014 ^b
Conjunctival component of OSS	1.46 (1.39–1.53)	<.001 ^b
Corneal component of OSS	1.11 (1.05–1.18)	<.001 ^b
Serology (N = 3232)		
TBUT <10 seconds	1.1 (0.83–1.42)	.572
Schirmer I test ≤ 5 mm/5 min	1.3 (1.12–1.61)	.002 ^b
Conjunctival component of OSS	1.51 (1.43–1.59)	<.001 ^b
Corneal component of OSS	0.98 (0.93–1.05)	.586

CI = confidence interval; LSG = labial salivary gland; OSS = ocular staining score; TBUT = tear breakup time.

^aAdjusted for age and race.

^bStatistically significant.

anti-SSA/B serology. We included 4 independent variables in our models, as follows: abnormal TBUT, abnormal Schirmer test, corneal staining score, and conjunctival staining score. Unadjusted multivariate model results are presented in the Supplemental Table (Supplemental Material available at [AJO.com](http://ajoo.com)).

We then fit separate models, adjusting for age and race (Table 3). The odds of a positive focus score on LSG biopsy were significantly higher among those with an abnormal Schirmer test (adjusted OR = 1.26; 95% CI 1.05–1.51, $P = .014$). In addition, the odds of a positive focus score on LSG biopsy were also significantly higher among those with positive conjunctival staining or corneal staining.

Specifically, the adjusted odds ratio for having a positive focus score on LSG biopsy for each additional point of the conjunctival staining score was 1.46 (95% CI 1.39–1.53, $P < .001$) and for 1 unit of corneal staining score was 1.11 (1.05–1.18, $P < .001$). In contrast, the odds of a positive focus score on LSG biopsy were significantly lower for those with an abnormal TBUT (adjusted OR 0.76; 95% CI 0.58–0.99; $P = .043$).

The odds of a positive serology were significantly higher among those with an abnormal Schirmer test (adjusted OR = 1.3; 95% CI 1.12–1.61, $P = .002$) and conjunctival staining (adjusted OR = 1.51; 95% CI 1.43–1.59, $P < .001$), but not for those with corneal staining (adjusted OR = 0.983; 95% CI 0.93–1.05, $P = .586$) or abnormal TBUT (adjusted OR = 1.1; 95% CI 0.83–1.42, $P = .572$).

DISCUSSION

WE EXAMINED THE ASSOCIATIONS BETWEEN INDIVIDUAL ocular tests for dry eye in relation to objective tests assessing extraocular signs for SS in the SICCA registry. When each dry eye diagnostic test was assessed individually, we found that a positive LSG biopsy and positive anti-SSA/B serology were each significantly associated with all dry eye tests, including Schirmer test, TBUT, corneal staining, and conjunctival staining.

However, when all 4 dry eye diagnostic tests were included in a multivariate model adjusted for age and race, we demonstrated that the adjusted OR for a positive LSG biopsy for 1 unit of conjunctival staining score was 1.46 and for 1 unit of corneal staining score was 1.16. In other words, the odds of having a positive LSG biopsy increased by approximately 50% for each unit increase in conjunctival staining and approximately 16% for each unit increase in corneal staining. The odds of having a positive LSG biopsy were also significantly higher among those with an abnormal Schirmer test. Surprisingly, we found the odds of having a positive LSG biopsy were lower among those with an abnormal TBUT; however, this finding was of borderline significance. In addition, there is no known biologic basis for this association and further studies are needed to explore this finding.

In addition, we found that the odds of having positive serology were significantly higher for those with an abnormal Schirmer test or conjunctival staining, but not for those with corneal staining or an abnormal TBUT. Although we found independent associations for TBUT with extraocular tests, this variable did not significantly contribute to providing information necessary for predicting positive extraocular findings for SS in either of our final models.

Dry eye symptoms are one of the most common reasons patients seek care from an ophthalmologist, with an *estimated 11 percent of dry eye patients having underlying SS*.¹⁴

The majority of SS patients first seek medical care for dry eye symptoms, but many are misdiagnosed as having non-autoimmune-related dry eye. Because dry eye disease is highly prevalent in the general population and SS evaluations are costly, complex, and time-consuming, it is not practical or economically feasible to refer all dry eye patients for SS evaluation.^{15,16} Ophthalmologists are severely hampered by the absence of evidence-based screening tools that reliably distinguish SS-related from non-SS-related dry eye patients, resulting in under-referrals and increased delays in the diagnosis of SS.

The results of our study indicate that both Schirmer I testing and conjunctival staining with lissamine green are critical tests to include when screening dry eye patients for possible SS, as both of these dry eye tests were associated with predicting both a positive serology and positive LSG biopsy. In addition, corneal staining with fluorescein was significantly associated with having a positive LSG biopsy.

Although many ophthalmologists commonly use fluorescein staining of the cornea in their evaluation of dry eye patients,^{24,25} few routinely assess ocular surface staining of the conjunctiva. For example, it has been reported that only 4.9%–10% of eye care professionals routinely assess staining of the conjunctiva.^{24,25} This underutilization of conjunctival staining may contribute to the under-referral of dry eye patients for SS evaluation.

Our results highlight the importance of including conjunctival staining when screening dry eye patients, as significant positive staining is associated with 2 of the nonocular diagnostic criteria for SS (positive LSG biopsy and serology), and therefore is highly suggestive of SS. This is consistent with the findings of others who have noted the importance of conjunctival staining for the evaluation of both SS-related and non-SS-related dry eye. For example, Caffery and associates found that rose bengal staining of the temporal conjunctiva was the most important ocular sign in distinguishing primary SS from non-SS dry eye.²⁰ In contrast, others have noted more nasal than temporal staining of the conjunctiva in SS patients.²⁶ Future studies comparing SS to non-SS dry eye patients are needed to further elucidate specific patterns of conjunctival staining that may distinguish these 2 groups.

Other studies have also supported the important role of the conjunctiva in the pathogenesis of dry eye disease. Proinflammatory markers such as lymphatic endothelial markers, increased cytokine transcripts, chemokines, adhesion molecules, and major histocompatibility complex (MHC) class II–positive dendritic cells are abundantly positive in conjunctiva of dry eye patients.^{27–30} In addition, Solomon and associates found that the conjunctival epithelium may be the source of increased interleukin-1 expression, likely leading to a cascade of proinflammatory events.²⁹ Inflammation in the conjunctiva may in turn trigger pathologic inflammatory changes in the cornea, such as through the induction of MHC class II expression in corneal dendritic cells, which are thought to play an

important role in autoimmune responses.³¹ Further studies focused on the conjunctiva of SS patients are needed to further elucidate these relationships and the role they play in SS-related ocular surface disease.

Our findings should be interpreted in light of the strengths and limitations of our study. The large sample size available for this analysis was a major strength for this study. With a large number of participants, systematic biases away from the null can be prevented and thus our results were less likely to overestimate associations between dependent and independent variables.³² Given that the registry is composed of individuals from 9 international sites, the generalizability of these results may be significant across different patient populations. However, these results may only be generalizable to patients suspected of SS, rather than to all dry eye patients, given the inclusion criteria used for recruitment into the SICCA cohort.¹³ Our study also has additional limitations. One limitation is potential intergrader variability, which is multiplied by the large number of evaluators participating in the ocular examinations. However, it was recently reported that there was high intergrader agreement among trained ophthalmologists in the SICCA study.³³ Therefore, intergrader variability was unlikely to have had a large effect on our re-

sults. Another limitation is that there was some overlap in the cohorts used to develop the OSS criteria and the SICCA/ACR classification criteria—thus resulting in some circularity in the analysis of the usefulness of tests. In addition, this study may have limited generalizability in clinical practice in that the ocular surface examination must be done in a specific order, using the timelines provided for each test. Finally, our study did not examine the utility of combining ocular signs with symptoms (ocular and systemic) for screening for SS. Future studies would be helpful in determining if a combination of specific ocular signs and symptoms has an increased utility in screening dry eye patients for SS rather than the assessment of ocular signs alone.

In summary, we examined the associations of individual dry eye test results with extraocular findings for SS. Our findings suggest that in addition to corneal staining, both Schirmer I testing and conjunctival staining are critical tests that should always be included when screening dry eye patients to determine whether a further evaluation for SS is warranted. Given the strong association between SS and lymphoproliferative disease, ophthalmologists serve an integral role in screening for this debilitating and potentially life-threatening syndrome.

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