

# Sjögren Syndrome

## Laboratory Support of Diagnosis

### CLINICAL BACKGROUND

Sjögren syndrome is an autoimmune disease characterized by lymphocyte infiltration of exocrine glands, which manifests as dry eyes and mouth.<sup>1</sup> The syndrome is estimated to be between 9 and 20 times more common in women than in men and typically presents in the 4<sup>th</sup> or 5<sup>th</sup> decade of life.<sup>1</sup> The disease can present by itself (primary) or in association with another underlying autoimmune condition (secondary), commonly rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).<sup>2</sup> Sjögren syndrome may occur as part of a triad that includes primary biliary cirrhosis (PBC) and autoimmune thyroid disease.<sup>1,2</sup> Patients with Sjögren's syndrome also have an overall increased risk for malignancies, specifically non-Hodgkin lymphoma and thyroid cancer.<sup>3</sup>

Although dry eyes are the hallmark of the condition, initial symptoms can be nonspecific and may include mild dry

mouth, arthralgias, and fatigue.<sup>1</sup> These nonspecific symptoms, coupled with a general lack of awareness of the disease, can delay diagnosis up to 7 years.<sup>4</sup> Prompt diagnosis, however, is important as early treatment can prevent progression to complete loss of lacrimal and salivary gland function and extraglandular involvement including synovitis, interstitial lung disease, neuropathy, vasculitis, and renal disease.<sup>1</sup>

### INDIVIDUALS SUITABLE FOR TESTING

- Individuals suspected of having Sjögren syndrome
- Individuals suspected of having an autoimmune condition associated with Sjögren syndrome

### TEST AVAILABILITY

Test availability is shown in **Table 1**.

**Table 1. Tests Used to Diagnose Sjögren Syndrome and Associated Disorders**

Test Code	Test Name	Clinical Use
249 <sup>a</sup>	ANA Screen, IFA, with Reflex to Titer and Pattern	Diagnose Sjögren syndrome and other rheumatic conditions, including RA and SLE
90077 <sup>a</sup>	ANA Screen, IFA, with Reflex to Titer and Pattern (Sjögren's Panel 1) Includes ANA screen (IFA) with reflex to titer and pattern; also includes rheumatoid factor and SS-A and SS-B antibodies.	Diagnose Sjögren syndrome with or without RA
19880(X) <sup>a</sup>	ANA Screen, IFA, with Reflex to Titer and Pattern (Sjögren's Panel 2) Includes ANA screen (IFA) with reflex to titer and pattern; mitochondrial antibody screen with reflex to titer; rheumatoid factor; and SS-A, SS-B, and thyroid peroxidase antibodies.	Diagnose Sjögren syndrome and assess for concurrent PBC or autoimmune thyroid disease
93748	Early Sjogren's Syndrome Profile Includes carbonic anhydrase 6 IgG, IgM, IgA; parotid secretory protein IgG, IgM, IgA; and salivary gland protein (SP1) IgG, IgM, IgA.	Diagnose Sjögren syndrome at an early stage
259 <sup>a</sup>	Mitochondrial Antibody with Reflex to Titer	Diagnose PBC
4418	Rheumatoid Factor	Diagnose Sjögren syndrome, RA, and PBC
7832	Sjögren's Antibodies (SS-A, SS-B)	Diagnose Sjögren syndrome
38568	Sjögren's Antibody (SS-A)	Diagnose Sjögren syndrome
38569	Sjögren's Antibody (SS-B)	Diagnose Sjögren syndrome
5081	Thyroid Peroxidase Antibodies (TPO)	Diagnose autoimmune thyroid disease

ANA, antinuclear antibody; IFA, immunofluorescence assay; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS-A, Sjögren syndrome-related antigen A; and SS-B, Sjögren syndrome-related antigen B.

<sup>a</sup> Reflex tests are performed at an additional charge and are associated with an additional CPT code(s).

## TEST SELECTION

While a number of different diagnostic criteria for Sjögren syndrome have been proposed, Sjögren’s International Collaborative Clinical Alliances Cohort/American College of Rheumatology criteria require at least 2 of the following to diagnose Sjögren syndrome: 1) positive Sjögren syndrome-related antigen A (SS-A, ie, Ro) and/or Sjögren syndrome-related antigen B (SS-B, ie, La) antibodies or positive rheumatoid factor (RF) and antinuclear antibodies (ANA); 2) positive minor salivary gland biopsy with a focus score  $\geq 1/4$  mm<sup>2</sup>; and 3) keratoconjunctivitis sicca with an ocular staining score  $\geq 3$ .<sup>1</sup>

Salivary gland biopsy, however, is not commonly performed in clinical practice; thus, autoantibody detection plays a large role in the diagnosis. The key antibodies (SS-A, SS-B, RF, and ANA) can be complemented with mitochondrial and thyroid peroxidase antibodies to rule-in or rule-out the presence of concurrent PBC and autoimmune thyroid disease.

Autoantibodies to carbonic anhydrase 6 (CA6), salivary gland protein 1 (SP-1), and parotid secretory protein (PSP) have recently been identified in patients meeting Sjögren syndrome criteria. These 3 antibodies may assist in establishing a diagnosis of Sjögren syndrome earlier in the course of the disease, potentially leading to earlier treatment and reduced risk of end organ damage.<sup>1,5</sup>

## INTERPRETATION

Antibodies to SS-A and SS-B are consistent with a diagnosis of Sjögren syndrome<sup>1</sup> but may also be seen in autoimmune thyroiditis,<sup>6</sup> SLE,<sup>7</sup> PBC,<sup>8</sup> and RA.<sup>1</sup> Absence of SS-A and SS-B antibodies does not rule out Sjögren syndrome, especially early in the disease course.<sup>1,6-8</sup> These antibodies are often not identified until significant end organ damage has occurred.<sup>1</sup>

SS-A antibodies are found in up to 74% of patients with Sjögren syndrome, while SS-B antibodies are found in up to 52%.<sup>1</sup>

The presence of ANA and RF antibodies is consistent with Sjögren syndrome. Up to 85% of those with the syndrome have ANA antibodies, while up to 74% have RF antibodies.<sup>1</sup> These antibodies are also seen in other autoimmune diseases (eg, RA, SLE), so their presence is not sufficient for a diagnosis.

Antibodies to CA6 and/or SP-1 are also consistent with Sjögren syndrome.<sup>5</sup> Of patients with idiopathic dry mouth and dry eyes for <2 years, 76% had antibodies to CA6 and/or SP-1, while only 31% had antibodies to SS-A and/or SS-B.<sup>5</sup> SP-1 has also been identified in 19% of Sjögren patients that are SS-A/SS-B negative.<sup>9</sup> These data, in conjunction with mouse studies, seem to indicate that CA6 and SP-1 appear earlier in the disease and thus can be used to diagnose Sjögren syndrome at an earlier stage.<sup>5,10</sup>

PSP antibodies have been identified in 18% of patients with Sjögren syndrome, and are rarely seen in normal controls.<sup>5</sup> They have also been identified in 10% of patients with RA.<sup>5</sup> If these early data are confirmed, PSP antibody presence may help identify patients with Sjögren syndrome who lack antibodies more commonly associated with the disease.<sup>5</sup>

Mitochondrial and thyroid peroxidase antibodies can help identify Sjögren syndrome patients with concurrent PBC and/or autoimmune thyroid disease.

The frequencies of the various autoantibodies in Sjögren syndrome and other autoimmune diseases are shown in **Table 2**. As some diagnostic criteria for Sjögren syndrome rely heavily on clinical signs and symptoms, laboratory results should be interpreted in light of a patient’s clinical findings.<sup>1</sup>

**Table 2. Antibody Frequency in Sjögren Syndrome and Associated Disorders<sup>1,5,6,8,11-14</sup>**

Condition	Antibody Frequency, %								
	SS-A	SS-B	ANA	RF	CA6	SP-1	PSP	Mitochondrial	TPO
Sjögren syndrome	33-74	23-52	59-85	36-74	54	54	18	5	9 (1°) 17 (2°)
SLE	30	10	98	20					
RA	15	20	24	50	10	0	10		7
PBC	50		50	70				95	
Autoimmune thyroid	10 <sup>a</sup>		35						83

1°, primary Sjögren syndrome; 2°, secondary Sjögren syndrome; ANA, antinuclear antibodies; CA6, carbonic anhydrase 6; PBC, primary biliary cirrhosis; PSP, parotid secretory protein; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SP-1, salivary gland protein 1; TPO, thyroid peroxidase.

<sup>a</sup> Of ANA positive patients with autoimmune thyroid disease.

## References

1. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. *Clin Epidemiol.* 2014;6:247-255.
2. Tincani A, Andreoli L, Cavazzana I, et al. Novel aspects of Sjögren's syndrome in 2012. *BMC Med.* 2013;11:93. doi: 10.1186/1741-7015-11-93.
3. Liang Y, Yang Z, Qin B, et al. Primary Sjogren's syndrome and malignancy risk: a systematic review and meta-analysis. *Ann Rheum Dis.* 2014;73:1151-1156.
4. Improving diagnosis and outcomes of Sjögren's disease through targeting dry eye patients: a continuing medical education enduring material. *Ocul Surf.* 2015;13:S1-S33.
5. Shen L, Suresh L, Lindemann M, et al. Novel autoantibodies in Sjögren's syndrome. *Clin Immunol.* 2012;145:251-255.
6. Tektonidou MG, Anapliotou M, Vlachoyiannopoulos P, et al. Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. *Ann Rheum Dis.* 2004;63:1159-1161.
7. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med.* 2004;164:1275-1284.
8. Selmi C, Meroni PL, Gershwin ME. Primary biliary cirrhosis and Sjögren's syndrome: autoimmune epithelitis. *J Autoimmun.* 2012;39:34-42.
9. Shen L, Kapsogeorgou EK, Yu M, et al. Evaluation of salivary gland protein 1 antibodies in patients with primary and secondary Sjogren's syndrome. *Clin Immunol.* 2014;155:42-46.
10. Suresh L, Malyavantham K, Shen L, et al. Investigation of novel autoantibodies in Sjogren's syndrome utilizing sera from the Sjogren's International Collaborative Clinical Alliance Cohort. *BMC Ophthalmol.* 2015;15:38. doi: 10.1186/s12886-015-0023-1.
11. Tunc R, Gonen MS, Acbay O, et al. Autoimmune thyroiditis and anti-thyroid antibodies in primary Sjogren's syndrome: a case-control study. *Ann Rheum Dis.* 2004;63:575-577.
12. Witte T, Hartung K, Sachse C, et al. Rheumatoid factors in systemic lupus erythematosus: association with clinical and laboratory parameters. SLE study group. *Rheumatol Int.* 2000;19:107-111.
13. Eriksson C, Engstrand S, Sundqvist KG, et al. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. *Ann Rheum Dis.* 2005;64:403-407.
14. Cozzani E, Drosera M, Gasparini G, et al. Serology of lupus erythematosus: correlation between immunopathological features and clinical aspects. *Autoimmune Dis.* 2014;2014:321359. doi: 10.1155/2014/321359.

