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The Copenhagen Criteria for Sjögren’s Syndrome

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The Copenhagen criteria were based on a combination of objective tests—and not symptoms alone—of keratoconjunctivitis sicca.

First International Symposium on Sjögren’s Syndrome

Suggested Criteria for Classification

Annals of the Rheumatic Diseases 1990; 59: 110-121

Assessment of the European classification criteria for Sjögren’s syndrome in a series of clinically defined cases: results of a prospective multicentre study

Claudio Vitali, Stefano Bombardieri, Haralambos M Moutsopoulos, Joaquín Coll, Roberto Gerli, Pierre Y Harron, Louis Katz, Yrjö T Konttinen, Rolf Manthorpe, Olivier Meyer, Maria Mosca, Pieramico Omini, Raffaele A Pellerito, Yvon Penassou, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea Richards, Bernard Sauvage, Morten Schiodt, Maria Scuto, Stephen R Porter, Andrea 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Diagnostic criteria for a particular disease (so-called target disease) are needed if the target disease may be confused with other diseases (so-called confusable diseases) because of overlapping features. For a diagnosis, the target disease has to be recognized in a pool of confusable diseases (figure 4.1).

Theoretically, the target disease may be recognized in two ways: by recognition of the specific combination of features of the target disease or by exclusion of confusable diseases as the cause of the symptoms (figure 4.2). Ideally, for the diagnosis of the target disease, both methods should be used because:

- confusable diseases may be more common than the target disease; so if a confusable disease is present, recognition is mandatory as many can be treated;
- failure to diagnose a confusable disease (unclassifiable confusable disease, unknown confusable disease or false-negative diagnosis of a confusable disease) would automatically incorrectly yield a diagnosis of the target disease;
- patients may have a confusable disease plus the target disease.

If both methods are used, the diagnosis of the target disease is made on the basis of exclusion of confusable diseases and confirmation by the recognition of the presence of the specific combination of symptoms and signs of the target disease. If the main symptoms are not explained by a single diagnosis (confusable disease or target disease), a second diagnosis should be possible. This approach is useful in clinical practice as patients often have more than one disease. Recognition of confusable diseases is therefore considered to be an essential step in the diagnostic process.

In contrast to common belief, symptoms and signs for use in diagnostic criteria do not need to be specific for the target disease. On the contrary, if a specific symptom or sign existed for the target disease, a diagnosis would only require the presence of the
specific feature and diagnostic criteria would not be necessary. As is the case when individual people or music compositions are recognized, diseases can be recognized by their specific combination of features. For diseases, the combinations consist of the presence or absence of particular symptoms and signs and the results of a variety of clinical investigations. Many diseases, particularly the generalized autoimmune diseases, can manifest the same symptoms. This can make it difficult to establish the right diagnosis. An important question concerns the basis on which the diagnosis is made. Criteria have been drawn up to ensure that diagnoses are made on the same basis. Criteria are mutual agreements about how the diagnosis is made.

There is a high level of consensus regarding the basic definition of Sjögren’s syndrome: both the eyes and the mouth must be involved. However, many sets of criteria for Sjögren’s syndrome have been published in the literature (figure 4.6).1-11 There is more than one version of some of these sets. The sets differ with regard to the precise definition of what is considered abnormal, whether or not autoantibodies should be present and whether symptoms count.

**Sensitivity and specificity**

The terms sensitivity and specificity are often used to indicate the reliability of investigations and criteria. Let us assume that we wish to establish disease B. The sensitivity is the proportion or percentage of the people with disease B who have an abnormal test or meet the criteria. The specificity is the proportion or percentage of the people without disease B who have a normal test or do not meet the criteria.

A problem with designing criteria is that some kind of method has to be found (the gold standard) that allows the disease to be definitely diagnosed or definitely excluded. The opinion of a group of experts is often used as the gold standard.

**Generalized autoimmune diseases**

In generalized autoimmune diseases, two or more organs are involved, in contrast with organ-specific autoimmune diseases where one organ is involved.

**Diagnosis for clinical application**

When diagnosing individual patients in the consulting room, every endeavour will be made to reach the most appropriate diagnosis. Signs and symptoms that are not specifically required for the final diagnosis are allowed to be taken into consideration. The main purpose here is to arrive at a usable diagnosis as a basis for treatment, check-ups and assessment of the prognosis. This means that if the research criteria are used to establish an individual diagnosis, patients sometimes do not fulfil the criteria, whereas on the basis of other criteria - including the exclusion of other diagnoses - they do in fact have Sjögren’s syndrome.

**Overlapping features of diseases**

Figure 4.3 shows how disease B can be differentiated from diseases A and C. In situation 1 there is no overlap and disease B can easily be differentiated from diseases A and C. In situation 2 there are overlaps (indicated by *) and the decision has to be made as to whether patients with symptoms in these overlap areas should or should not be considered as having disease B.

When diagnosing individual patients (in the consulting room), situation 2a will be chosen. For the most definite diagnosis of B - for scientific research for instance - patients in the overlap area will not be considered as having disease B, even if it is quite probable that they do in fact have disease B.

Criteria are not definitive, but are continually being adapted in accordance with new insights and as new research data become available. Research criteria are often used in clinical situations and clinical criteria are sometimes used for research purposes, and both situations are wrong. However, even the correct use of clinical criteria in clinical situations and of research criteria for research purposes, represents a continuous source of errors and misunderstanding. But even more important is that in all these situations, results from scientific studies cannot be extrapolated to patient populations. The ESSIC criteria for the diagnosis of interstitial cystitis/bladder pain syndrome is an example of how these problems can be avoided (see the chapter on Urogenital disorders, paragraph interstitial cystitis/bladder pain syndrome).
times and the latest version was published in 2002, the so-called American-European criteria. They consist of 6 items (see table 4.1) that may be summarized as:

ocular symptoms, oral symptoms, eye tests, lip biopsy, imaging or function investigation of the salivary glands and antibodies in the blood.

In general terms, Sjögren’s syndrome can be diagnosed if 4 out of the 6 items are positive, see table 4.2 for details. A distinction is drawn between primary and secondary Sjögren’s syndrome. The term secondary means that a second generalized autoimmune disease is present. The diagnosis of secondary Sjögren’s syndrome can be established if only 3 of the 6 criteria items are present in addition to the other autoimmune disease.

The criteria are intended for scientific research. In comparison with other criteria, they have both advantages and disadvantages. Advantages are that they are accepted worldwide, are flexible and can therefore also be used for clinical diagnosis. A disadvantage is they draw a distinction between primary and secondary Sjögren’s syndrome. It would be more logical to apply one standard for the diagnosis of Sjögren’s syndrome, regardless of any other concomitant diseases. A second disadvantage

How to use diagnostic criteria?

In general, there is little point in carrying out the eye tests (item 3) in a patient who has no typical eye symptoms (item 1). Likewise, if a patient has no typical mouth or salivary gland symptoms (item 2), a lip biopsy (item 4) or other salivary gland test (item 5) is pointless.

In both situations the likelihood of finding abnormalities is minimal and not very relevant. There is likewise little point in continuing with investigations to diagnose Sjögren’s syndrome if it is clear that the patient can no longer score 4 items. The reason for this is that it is only worth while carrying out diagnostic tests for Sjögren’s syndrome if the probability exists of establishing a definite diagnosis (4 or more criteria items). If other possible causes have been excluded, characteristic symptoms give rise to the suspicion that it could be Sjögren’s syndrome. Carrying out further investigations simply to get a stronger suspicion is of little value. It is more logical to wait e.g. a year before taking another look at whether the patient meets the criteria. In the meantime - if the suspicion of Sjögren’s syndrome still exists - the patient should be treated in the same way as someone with a definite diagnosis.

The American-European criteria

For some years now, it has been the European criteria that have mainly been used to diagnose Sjögren’s syndrome. These have been revised a number of
Table 4.1 Revised international classification criteria for Sjögren’s syndrome \(^\text{10,11}\) (so-called American-European criteria)

I. **Ocular symptoms:** a positive response to at least one of the following questions:
   1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   2. Do you have a recurrent sensation of sand or gravel in the eyes?
   3. Do you use tear substitutes more than 3 times a day?

II. **Oral symptoms:** a positive response to at least one of the following questions:
   1. Have you had a daily feeling of dry mouth for more than 3 months?
   2. Have you had recurrently or persistently swollen salivary glands as an adult?
   3. Do you frequently drink liquids to aid in swallowing dry food?

III. **Ocular signs**—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
   1. Schirmer’s I test, performed without anaesthesia (≤ 5 mm in 5 minutes)
   2. Rose bengal score or other ocular dye score (≥ 4 according to Van Bijsterveld’s scoring system)

IV. **Histopathology:**
   In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1, defined as a number of lymphocytic foci which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes per 4 mm\(^2\) of glandular tissue

V. **Salivary gland involvement:** objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
   1. Unstimulated whole salivary flow (≤ 1.5 ml in 15 minutes)
   2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts
   3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. **Autoantibodies:** presence in the serum of the following autoantibodies:
   1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Table 4.2 Revised rules for classification \(^\text{10,11}\)

**For primary SS**
In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive

b. The presence of any 3 of the 4 objective criteria items (that is: items III, IV, V, VI)

c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

**For secondary SS**
In patients with a potentially associated disease (for instance another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

**Exclusion criteria:**
- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency disease (AIDS)
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

**Explanation of symbols**
- < less than
- ≤ less than or equal to
- > more than
is that a patient can fulfill the criteria even if both eye signs and eye symptoms are absent. If a patient has no ocular signs or symptoms, but does meet the criteria for salivary gland involvement, it would be better to call it focal lymphocytic sialoadenitis instead of Sjögren’s syndrome. This would then be comparable with patients who only have ocular signs and symptoms and for years have been indisputably diagnosed as having keratoconjunctivitis sicca.

Abnormal biopsy .... may be normal !
15% of healthy subjects without complaints of dryness of the mouth or eyes have an abnormal lip biopsy with focus scores ranging from 2 to 6.


Sequence of investigations
How should the criteria be applied in practice in order to make a diagnosis? There are no uniform rules for this. A logical method that is used by the author is described below.

It should first be established whether the eye and mouth symptoms are typical of Sjögren’s syndrome (see chapter 4.1, items 1 and 2).

Blood tests a should be carried out to detect other possible causes of the symptoms and also for antibodies against SSA/Ro and SSB/La.

Eye tests should also be arranged (Schirmer test, break-up time and rose bengal dye test, see also chapter 13).

Once all the results are known, 2, 3 or 4 items of the criteria will have been fulfilled (see figure 4.5).

The diagnosis is complete if 4 items are present, if 3 are present a lip biopsy may be arranged as a focus score of at least 1 will give a definite diagnosis. If 2
CHAPTER 4 DIAGNOSIS

JOOP P VAN DE MERWE - SJÖGREN'S SYNDROME: INFORMATION FOR PATIENTS AND PROFESSIONALS

**Missed diagnoses .....**

Almost 60% of patients diagnosed by experienced clinicians as Sjögren’s syndrome do not fulfill the American-European criteria for Sjögren’s syndrome.


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items are present, no further tests will be arranged because a definite diagnosis cannot be obtained. Patients regularly have fewer than 4 items of the criteria. If other causes of the signs and symptoms have been excluded, Sjögren’s syndrome may remain as the only probable explanation. Further treatment and check-ups should then be the same as in the case of people who fulfill all criteria.

**Specificity of the lip biopsy**

In 2002 a study was published on the findings in salivary gland biopsies of 54 healthy volunteers who had served as control subjects in various studies of salivary dysfunction.13 A biopsy with a focus score of more than 1 was regarded as positive (this is slightly different from the American-European criteria in which a focus score of 1 is also considered positive). The frequency of positive lip biopsies in the healthy subjects was 15%. The focus score ranged from 2 to 6 and none of the subjects had symptoms of dry mouth or dry eyes. The focus score showed no correlation with age, smoking, serologic findings or salivary flow in these subjects.

In a recent examination of inter-rater reliability for a group of 5 board-certified pathologists interpreting the same series of labial salivary gland biopsies, the agreement was found to be uniformly poor for judgments of diagnostic status, focus scores, and histological characteristics of biopsy specimens. This lack of reliability is troubling.17

**Sensitivity of the European criteria to diagnose Sjögren’s syndrome**

Diagnostic criteria are usually designed for the purpose of scientific studies and, therefore, cut-off points are chosen to obtain a high specificity, a choice that invariably results in a lower sensitivity. Brun et al.14 studied out-patients with a clinical diagnosis of Sjögren’s syndrome from a rheumatology department of a Norwegian university hospital. They compared how many of these patients fulfilled the 1993 preliminary European criteria in comparison with the modified preliminary criteria13 that are similar to the 2002 American-European criteria. The difference between these versions is that the modified and American-European criteria require a positive lip biopsy or the presence of antibodies to SSA/Ro and/or SSB/La, and that a positive ANA or rheumatoid factor is no longer part of the serology item. They found that of 203 patients with a clinical diagnosis of Sjögren’s syndrome, 57.1% satisfied the preliminary criteria and only 40.9% the modified (and thus also the American-European) criteria. Ramos-Casals et al.24 found that only 45% of Sjögren’s patients according to the 1993 criteria fulfilled the 2002 criteria.

The advantage of application of the modified and American-European criteria is that this results in more homogeneous and comparable patient populations in research. The disadvantage is that up to 60% of patients who could be diagnosed by experienced clinicians as Sjögren’s syndrome, do not get a diagnosis anymore, and no proper treatment in many cases. This is the reason that we proposed previously to use the name Sjögren’s like syndrome in patients who fulfill 3 items of the criteria and in whom no other explanation of the symptoms and signs can be found.16 This terminology is in line with the one used for patients with the antiphospholipid syndrome and 3 of the items of the diagnostic criteria for SLE (antiphospholipid syndrome with lupus-like syndrome). A better term, however, probably is incomplete Sjögren’s syndrome as the word "like" suggests that it only looks the same but is in reality different. See also the chapter on incomplete Sjögren’s syndrome.

**Noninvasive techniques to detect salivary gland changes**

Diagnostic methods to detect changes in the salivary glands include gland biopsies and x-ray sialography. These invasive methods may cause substantial complications for the patient. Noninvasive techniques such as ultrasonography (US) and magnetic resonance imaging (MRI) have been used to reliably characterize and diagnose Sjögren’s syndrome and offer promise as replacements for the earlier invasive and potentially harmful techniques.

**MRI sialography**

Tonami et al evaluated the effectiveness of MRI sialography of the parotid gland ducts in the diagnosis and staging of Sjögren syndrome.18 In control subjects, the main duct and the primary branching ducts of the parotid glands were clearly visible on MRI sialographic images. In patients with Sjögren syndrome, a punctate, globular, cavitary, or destructive appearance was well seen within the parotid glands. Findings obtained at

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*For practical reasons, blood tests are simultaneously carried out to check for abnormalities that are important to assess the severity of the Sjögren’s syndrome.*
Ultrasonography arose as the best performer, followed by sialography and salivary gland scintigraphy. 

El Miedany et al assessed the diagnostic value of parotid gland quantitative assessment using US as well as MRI in patients with Sjögren’s syndrome and to evaluate the possibility of using such modalities as a predictor of the histopathologic score of salivary gland biopsy in this group of patients. Patients and control subjects were scored according to the structural changes seen in both radiologic modalities. In addition, sialography and labial gland biopsy were done for all patients as well as the control subjects and scored according to the degree of affection.

Parenchymal inhomogenity (PIH) was seen in 93.6% of the patients studied by US, while nodular pattern was seen in 97.8% in the MRI study. The US and MRI results correlated significantly with the histopathologic score of the minor salivary glands (r =0.82, 0.84, respectively) as well as sialography score (r = 0.69, 0.60, respectively). There was good agreement between US and MRI findings (r = 0.87) in both SS cases and control subjects. The authors conclude that US and MRI are equally sensitive tools for the diagnosis of salivary involvement in patients with Sjögren’s syndrome. Quantitative assessment of US and MRI images seem to represent an advance in the diagnosis of Sjögren’s syndrome as they offer a good prediction of the pathology score of the salivary gland. MRI seems unnecessary as a routine diagnostic tool and should be considered as the second option in case of normal US.

Wernicke et al verified US criteria for examination of the major salivary glands in diagnosis of primary and secondary Sjögren’s syndrome. They selected 316 consecutive patients: 57 had primary Sjögren’s syndrome, 33 secondary Sjögren syndrome, 78 sicca symptoms, and 148 patients served as asymptomatic controls. Evident parenchymal inhomogeneity in 2 or more major salivary glands was detected by US in patients with primary and secondary Sjögren’s syndrome with a sensitivity of 63.1% and 63.6%, respectively. The specificity of this imaging approach was 98.7%. The volume of submandibular glands was reduced in patients with primary and secondary SS by about 30% compared to patients with sicca symptoms and asymptomatic controls. In patients with primary Sjögren’s syndrome, parenchymal inhomogeneity of the salivary glands was strongly associated with positivity for anti-SSA/Ro and/or anti-SSB/La antibodies. The authors conclude that US detection of parenchymal inhomogeneity of the major salivary glands and observation of reduced volume of the submandibular glands resulted in high specificities for diagnosis of primary and secondary Sjögren’s syndrome.

Obinata et al examined the reliability and correlation of sialography, salivary gland biopsy, and US for Sjögren syndrome and evaluated the usefulness of US as a diagnostic tool for Sjögren syndrome.

### Table 4.3 Grading of ultrasonography

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal glands</td>
</tr>
<tr>
<td>1</td>
<td>Small hypoechoic spots</td>
</tr>
<tr>
<td>2</td>
<td>Multiple scattered hypoechoic areas (2 mm)</td>
</tr>
<tr>
<td>3</td>
<td>Multiple hypoechoic areas (2-6 mm)</td>
</tr>
<tr>
<td>4</td>
<td>Multiple hypoechoic areas (6 mm)</td>
</tr>
</tbody>
</table>

MRI sialography correlated well with the results of labial gland biopsy.

Tonami concludes that MRI sialography has the potential to produce diagnostic findings in the parotid gland ducts of patients with Sjögren syn drome and speculates that this method will augment and possibly replace x-ray sialography.

Roberts et al used dynamic contrast-enhanced MR imaging and tracer kinetic modeling to quantify the microvascular pathophysiologic features of Sjögren’s syndrome. They found considerable heterogeneity in microvascular changes in the parotid gland in patients with Sjögren’s syndrome. The results demonstrate that dynamic MR tracer kinetic modeling parameters can enable quantification of the parotid gland microvascular characteristics related to the pathophysiologic features seen with Sjögren’s syndrome.

### Further reading

- Tzioufas AG, Moutsopoulos HM (2008)
- Tonami
- El Miedany et al
- Wernicke et al
- Salaffi et al
- Obinata et al
compared with sialography and histopathology. Seventy-three patients who underwent sialography, US, and salivary gland biopsy were included in this study. They found a statistically significant difference in the sensitivities of sialography and histopathology, in the specificities of sialography and US, and in the accuracies of sialography and both US and histopathology. The authors conclude that ultra-sonography can be used as a diagnostic tool for Sjögren’s syndrome, with its advantage of noninvasiveness and ease of use.

From these studies it may be concluded that ultrasonography - a simple, inexpensive, and non-invasive diagnostic tool that does not expose patients to radiation - seems an excellent replacement of older imaging techniques as well as lip biopsies for the diagnosis of Sjögren’s syndrome. Lip biopsies, however, remain important to differentiate Sjögren’s syndrome from confusable diseases such as sarcoidosis and malignant lymphomas in selected patients.

The American-European criteria critically reviewed

The criteria and rules as described in tables 4.1 and 4.2 are in contradiction with the approach given in figure 4.4 from the same paper in which a patient is classified as "no Sjögren" if typical mouth and eye complaints are absent.

It is remarkable and - in my opinion - an omission that the objective finding of one or two enlarged parotid glands at physical examination is not an (objective) item of the criteria. It counts as part of subjective item II when the patient confirms recurrent of persistent swollen salivary glands as an adult, but this item is already positive when the patient has the daily feeling of a dry mouth for more than three months. The physical finding of enlarged parotid(s) has a different meaning as compared to the symptoms of diminished function of the salivary gland and should score separately.

Sub-item II.1 (feeling of a dry mouth) is very common and nonspecific while the majority of Sjögren’s patients fulfill sub-item II.3. Therefore, II.1 can better be removed. But item II.3 is inappropriate as it refers to the habit of drinking during meals. It could better be replaced by the question "Do you need to drink liquids to be able to swallow dry food?". The need to drink to make swallowing food possible is probably an excellent physiological test for the saliva production of the parotid glands. Further studies should be done to see whether the salivary flow measurement (item V.1) has additional diagnostic value in this case, which I doubt.

Item V contains both expressions of diminished salivary gland function (sub-items V.1 and V.3) as well as anatomical abnormalities such as ductiectasia. Autoantibodies to SSA/Ro and SSB/La occur independently and are associated via autoimmune diseases such as Sjögren’s syndrome and subacute cutaneous lupus erythematodes. The probability that a patient suffers from Sjögren’s syndrome is much higher if autoantibodies are found to both SSA/Ro and SSB/La as compared to only one of them. Unfortunately, for the diagnostic criteria having antibodies to both SSA and SSB has no more weight than the presence of antibodies to only one of them.

In the author’s opinion, items for criteria should be clustered within five groups:

1. **Symptoms**
   - typical eye symptoms
   - typical mouth symptoms

2. **Diminished gland function**
   - abnormal Schirmer test
   - diminished salivary flow
   - abnormal scintigraphy

3. **Abnormal macroscopic anatomy**
   - parotid gland enlargement at physical examination
   - abnormal findings at ultrasonography
   - abnormal findings at sialography

4. **Abnormal microscopic anatomy**
   - abnormal focus scores as detected in tear glands or any salivary gland

5. **Autoantibodies**
   - autoantibodies to SSA (52kD)
   - autoantibodies to SSA (60 kD)
   - autoantibodies to SSB
   - rheumatoid factor with negative anti-CCP
   - a positive ANA with no evidence of SLE (?)

The weight for the diagnosis of each of these items should be determined with the aid of appropriate
statistical analysis.

This should be followed by typing of the disease to
guarantee that all patients who have Sjögren’s syndrome
according to expert opinions, as well as patients with
incomplete Sjögren’s syndrome, can be classified as
Sjögren’s syndrome with the addition of a particular
type. Typing of various subgroups of diseases has been
shown to be a successful approach in finding
optimal treatments for various malignancies. See
also the chapter on urogenital disorders, paragraph
on interstitial cystitis/bladder pain syndrome, for
an example of diagnostic criteria with typing of the
disease

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an out-patient clinic: classification of patients according to the
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