
## design of criteria for diagnosis

*presentation:*

1. criteria: different types and different functions
2. classification criteria: why and how
3. how it was done for systemic vasculitis and generalized autoimmune diseases
4. an example: Sjögren's syndrome
5. suggested approach for IC

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## 1

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SPECIAL ARTICLE

### CRITERIA FOR RHEUMATIC DISEASE

Different Types and Different Functions

JAMES F. FRIES, MARC C. HOCHBERG, THOMAS A. MEDSGER, JR., GENE G. HUNDER, CLAIRE BOMBARDIER, and the AMERICAN COLLEGE OF RHEUMATOLOGY DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE

Because most rheumatic diseases lack a single distinguishing feature, the presence of a combination of clinical and, sometimes, laboratory manifestations is needed to identify a specific disease. Criteria sets that have been derived by a careful analysis of a selected group of patients subsequently provide a

approaches to understanding the etiology and course of these chronic, progressive, multifactorial, and often poorly defined diseases. Criteria sets provide a uniform language, thus aiding (or facilitating) comparisons of patient populations between studies. Most importantly, they provide a conceptual structure for

Arthritis Rheum 1994;37:454-62

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**Table 1. Types and purposes of criteria***

| Type | Purpose |
|---|---|
| **Classification criteria** | To separate those with a specific disease from those without the disease |
| **Subclassification criteria** | To separate diseases or subsets within a disease cluster |
| **Prognostic criteria** | To separate subjects with good or potentially favorable outcomes from those with bad outcomes |
| **Status indexes** | To assess present disease activity or accumulated damage from the disease |
| **Activity indexes** (implies reversibility) | To estimate current disease activity status |
| **Damage indexes** (implies irreversibility) | To estimate accumulated damage from the disease |
| **Outcome criteria** | To measure the overall impact of a disease and to serve as dependent variables for clinical studies |

* Fries JF *et al.* Arthritis Rheum 1994;37:454-62

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## CLASSIFICATION CRITERIA*

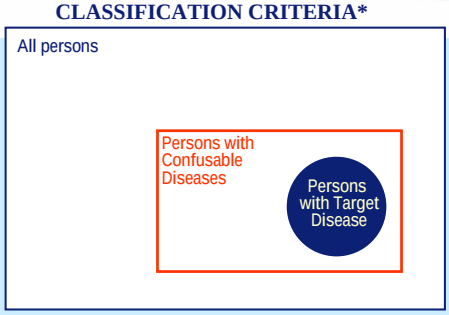


Figure 1. Classification criteria separate patients with the disease from the general population or from patients with potentially confusable conditions.

* Fries JF *et al.* Arthritis Rheum 1994;37:454-62

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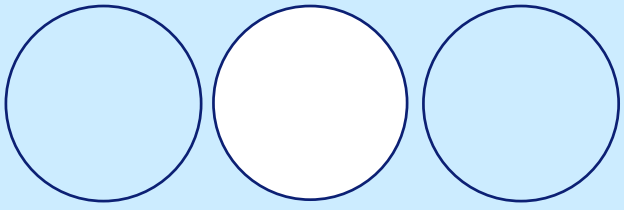
## 2 are classification criteria needed for the diagnosis of disease IC ?



disease A IC disease B

not in this situation !

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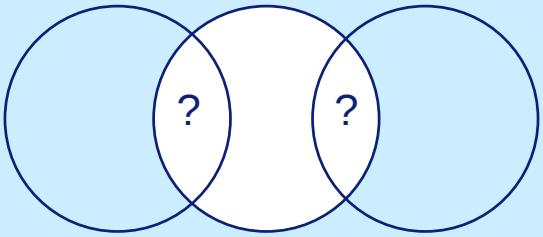
## classification criteria are needed if diseases have overlapping features

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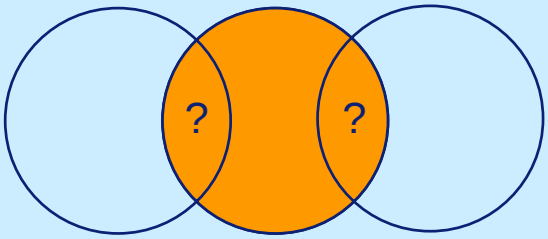
## clinical practice: diagnosis is necessary high sensitivity ➔ low specificity

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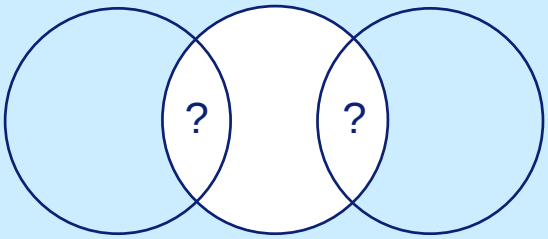
## scientific studies

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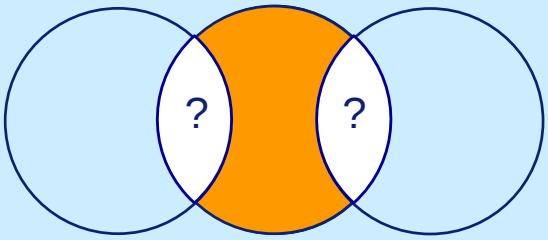
## scientific studies: definite disease high specificity ➔ low sensitivity

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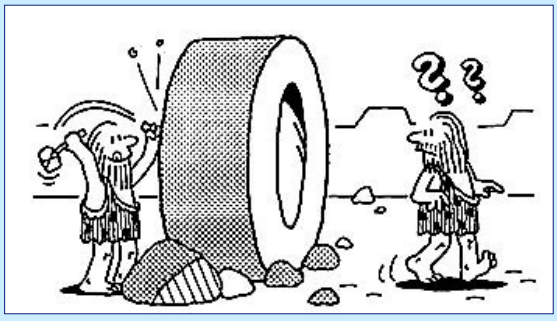
## do we need to invent the wheel ?



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## 3 classification of systemic vasculitis and generalized autoimmune diseases

*examples:*

| systemic vasculitis | generalized autoimmune diseases |
|---|---|
| • Wegener's granulomatosis<br>• polyarteritis nodosa<br>• microscopic polyangiitis<br>• Churg-Strauss syndrome<br>• giant cell arteritis<br>• Takayasu disease<br>• hypersensitivity vasculitis<br>• Henoch-Schönlein purpura | • systemic lupus erythematosus<br>• MCTD<br>• systemic sclerosis<br>• CREST syndrome<br>• Sjögren's syndrome<br>• antiphospholipid syndrome<br>• subacute cutaneous LE |

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## classification of vasculitis and generalized autoimmune diseases

*common features (and features in common with IC)*

- causes unknown
- strong overlap between diseases in each group
- many different opinions on definition and classification
- diagnosis has implications for treatment



## classification of systemic vasculitis and generalized autoimmune diseases

*examples of diseases with classification rules*:

| systemic vasculitis | generalized autoimmune diseases |
|---|---|
| • Wegener's granulomatosis | • systemic lupus erythematosus |
| • polyarteritis nodosa | • MCTD |
| • microscopic polyangiitis | • systemic sclerosis |
| • Churg-Strauss syndrome | • CREST syndrome |
| • giant cell arteritis | • Sjögren's syndrome |
| • Takayasu disease | • antiphospholipid syndrome |
| • hypersensitivity vasculitis | • subacute cutaneous LE |
| • Henoch-Schönlein purpura | |



## classification of systemic vasculitis and generalized autoimmune diseases

- classification rules have been broadly accepted

- classification rules:
  algorithms created with statistical methods based on the way how experts diagnose the disease and differentiate it from overlapping diseases



STATISTICAL APPROACHES TO CLASSIFICATION

Methods for Developing Classification and Other Criteria Rules

DANIEL A. BLOCH, LINCOLN E. MOSES, and BEAT A. MICHEL

During the 1980s, the American College of Rheumatology (ACR) (formerly, the American Rheumatism Association) published several papers on classification criteria for rheumatic diseases (1-5). This issue of *Arthritis and Rheumatism* includes classification criteria for 7 forms of vasculitis. The ACR has also developed separate classification criteria for osteoarthritis of the hand (6) and for osteoarthritis of the hip (manuscript submitted). Subcommittees of the ACR are developing "prognostic stratification" criteria as well.

Over the years, researchers have asked us

rules derived are not those presented by Hunder et al (7) as the official ACR classification criteria rules for GCA. Our use of the vasculitis data set is for illustrative purposes only. We chose to include more predictors than the ACR rules to allow more insight into the characteristics of alternative methods. In this article, we confine our attention to 8 predictors considered by ACR subcommittee members to be important for classification purposes. These are defined in Table 1. All predictors (called "criteria") take only 2 values, corresponding to present or absent, and definable as 1 or 0. Most of the

Arthritis Rheum 1990;33:1137-44

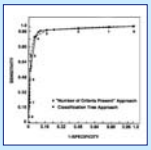


## classification methods

1. "number of items present rule"

$$Y = Z_1 + Z_2 + .... + Z_r$$

*if any 1 or more* of a list of r items are present in a patient, then classify the patient as having the disease*



* optimal cut-off points are selected with ROC-curves

Arthritis Rheum 1990;33:1137-44



## classification methods

1. "number of items present rule"

*pro*
- simple definitions (+/-): easy application

*con*
- simple definitions (+/-):
  - all items are given *equal* weight
  - all items *must* be dichotomous (+/-)

➔ *little insight into the characteristics of a classified patient group*

Arthritis Rheum 1990;33:1137-44

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➔ *little insight into the characteristics of a classified patient group*

useful for daily clinical practice ? yes
useful for scientific studies ? more or less

Arthritis Rheum 1990;33:1137-44



## classification methods

2. linear discriminant function

$$Y_L = a_0 + a_1 Z_1 + a_2 Z_2 + .... + a_r Z_r$$

*if $Y_L > c$ then classify the patient as having the disease*

similar to method 1 if $a_0=0$ and $a_x=1$

Arthritis Rheum 1990;33:1137-44



## classification methods

2. linear discriminant function

*pro*
- items may have a different weight
- items may be polychotomous or continuous

Arthritis Rheum 1990;33:1137-44



## classification methods

3. multiple logistic regression

$$\ln\left[\frac{Pr(W=1)}{1-Pr(W=1)}\right] = b_0 + b_1 Z_1 + b_2 Z_2 + .... + b_r Z_r$$

*Pr(W=1)* is the estimated probability that the subject has the disease

Arthritis Rheum 1990;33:1137-44



## classification methods

3. multiple logistic regression

*pro*
- items may have a different weight
- items may be polychotomous or continuous
- provides estimated probabilities for each subject to have the disease

Arthritis Rheum 1990;33:1137-44



## classification methods

4. classification tree

is constructed by repeated splits of groups into 2 descendant subgroups

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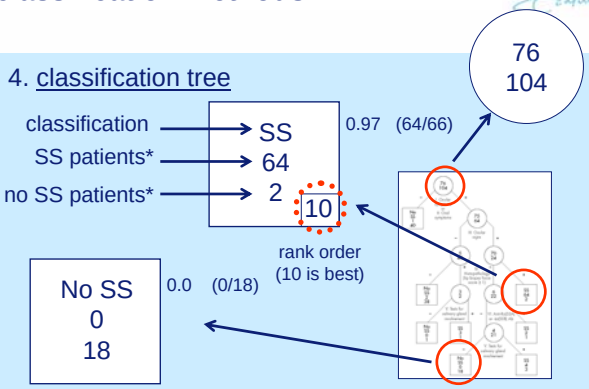
## classification methods

4. classification tree




* diagnosis according to the expert clinicians



## classification methods

4. classification tree

*pro*
- items may be polychotomous or continuous
- nonparametric: no refererence to a model for the relationship between classification items and disease status
- high information content - classified groups of subjects in studies may be referred to the exact classifying subgroup of the tree

Arthritis Rheum 1990;33:1137-44



## classification methods

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- items may be polychotomous or continuous
- nonparametric: no refererence to a model for the relationship between classification items and disease status
- high information content - classified groups of subjects in studies may be referred to the exact classifying subgroup of the tree

useful for daily clinical practice ? more or less

useful for scientific studies ? excellent

Arthritis Rheum 1990;33:1137-44



## 4 how it was done in Sjögren's syndrome (1)

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CONSENSUS REPORT

Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group

C Vitali, S Bombardieri, R Jonsson, H M Moutsopoulos, E L Alexander, S E Carsons, T E Daniels, P C Fox, R I Fox, S S Kassan, S R Pillemer, N Talal, M H Weisman, and the European Study Group on Classification Criteria for Sjögren's Syndrome

Ann Rheum Dis 2002;61:554–558

Classification criteria for Sjögren's syndrome (SS) were developed and validated between 1989 and 1996 by the European Study Group on Classification Criteria for SS, and broadly accepted. These have been re-examined by consensus group members, who have introduced some modifications, more clearly defined the rules for classifying patients with primary or secondary SS, and provided more precise exclusion criteria.

multiple sites. The involvement of lachrymal and salivary glands results in the typical features of dry eye and salivary dysfunction (xerostomia). However, one third of the patients present with systemic extraglandular manifestations. Finally, SS can be seen alone (primary SS) or in association with other autoimmune rheumatic disease (secondary SS).[2] Thus, the diagnostic approach to SS is rather complicated because it must include two different goals: firstly, assessment of the ocular and salivary components, and secondly, differentiation

Ann Rheum Dis 2002;61:554-8



## "number of criteria present rule" (1)

**Table 2** Revised international classification criteria for Sjögren's syndrome

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 lymph... pert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent ... contain more than 50 lymphocytes) per 4 mm² of glandular tissue[18]

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive ... diagnostic tests:
1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts[19]
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer[20]

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

**2 subjective items**

**4 objective items**

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## "number of criteria present rule" (2)

**Table 3** Revised rules for classification

*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 (Histop... 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 ... 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)

**rules for classification**

**exclusion criteria**

Ann Rheum Dis 2002;61:554-8

## classification tree

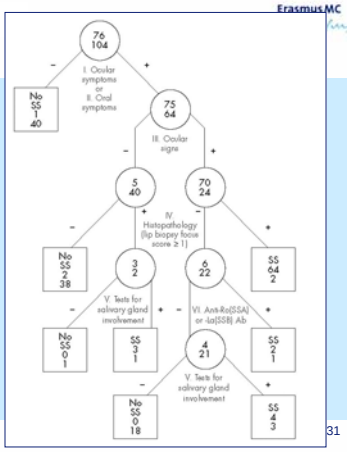

Figure 2 Classification tree performance of the classification criteria for SS. Schematic representation of the classification tree for the classification of primary SS. Within each circle the number of patients with primary SS (upper value) and the number of controls without SS (lower value) are reported. The boxes show the numbers of subjects who could be classified either as having SS or not having SS (No SS). The variable used in each node of the tree to discriminate between patients and controls is reported beneath the circles. Following the entire sequence allowed us to classify correctly 73/76 patients with primary SS (sensitivity 96.1%) and 98/104 disease controls (specificity 94.2%).

Ann Rheum Dis 2002;61:554-8

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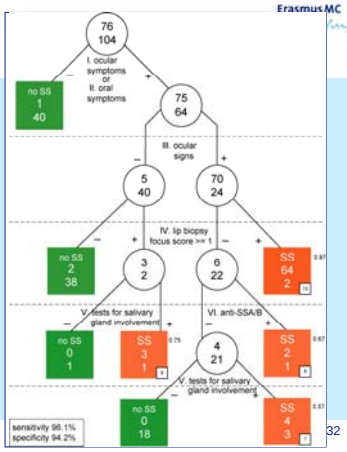
## classification tree

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## classification criteria

Classification criteria often serve as diagnostic criteria. This is particularly true when the sensitivity and specificity of classification criteria are both close to 100%. In this case, classification criteria could be used as diagnostic criteria. This is rather unusual at the beginning of the disease, when the typical signs and symptoms are often lacking or are not entirely expressed. Classification criteria are therefore not perfect for use in diagnosis and a certain proportion of patients may be misclassified, particularly in the early stages of the disorder. Thus, classification cannot be considered the medical standard for a diagnosis and the expert doctor is the only person who can establish a definitive diagnosis for any individual patient. However, classification criteria for disease syndromes can be used to ensure the standardisation of the diagnosis in patients taking part in clinical studies, and to facilitate the analysis of results and the comparison of patients between institutions.[1]

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## how it was done in Sjögren's syndrome (2)

The *European Study Group on Classification for Sjögren's Syndrome* started in 1988 and published in:

1989 selection of questions and tests
1993 preliminary criteria
1996 validation in a prospective multicentre study
2002 revision by the *American-European Consensus Group*

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## 5 suggested approach in a multicentre study

1. collect what information (symptoms and signs) is used/needed - by experts - to diagnose IC and differentiate IC from confusable diseases (for both women and men)
2. collection of data from patients with IC and patients with confusable diseases (controls) to define classification criteria for IC
3. validation with new patient groups

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## suggested approach in a multicentre study

1. collect what information (symptoms and signs) is used/needed - by experts - to diagnose IC and differentiate IC from confusable diseases (for both women and men)
2. collection of data from patients with IC and patients with confusable diseases (controls) to define classification criteria for IC

The same database can be used to create *"number of items present rule"* for clinical diagnoses and a *"classification tree"* for scientific studies

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## suggested approach in a multicentre study

1. **collect what information (symptoms and signs) is used/needed - by experts - to diagnose IC and differentiate IC from confusable diseases (for both women and men)**
2. collection of data from patients with IC and patients with confusable diseases (controls) to define classification criteria for IC
3. …

For 1 a lot of work has already been done in Copenhagen 2003 !

Nordling J *et al.* European Urology 2004; 45:662-9

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## summary & conclusions (1)

1. the first thing we need is classification criteria based on
   - diagnoses (by experts)
   - items used (by experts) for diagnosis and exclusion of confusable diseases

   (later: prognostic, status and outcome criteria)
2. extensive knowledge is available on the use of classification criteria with systemic vasculitis and generalized autoimmune diseases

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## summary & conclusions (2)

3. classification methods
   *with the same patient data several rules can be obtained*

   *optimal rules*:

   for clinical practice: "*number of items rule*"
   (easy to memorize and easy to use)

   for scientific studies: *classification tree*
   (exact description of patient population)

   *but both can be used in either situation*

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## summary & conclusions (3)

4. classification criteria are conceptually the same as diagnostic criteria (both aimed at a correct diagnosis)
5. classification criteria are not perfect and a proportion of patients may be misclassified (the expert's diagnosis is perfect by definition)
6. sensitivity and specificity are interchangeable properties of desicion making processes; cut-off point can be chosen to obtain a high sensitivity or a high specificity, depending on clinical or scientific applications, respectively
7. if classification criteria have a high sensitivity and a high specificity they can be used as diagnostic criteria in clinical situations

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## do we need to reinvent the wheel ?


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