ACR / EULAR classification criteria for Systemic Sclerosis

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Goals Presentation

- To explain difference between diagnosis and classification
- To explain neccessity of classification criteria in SSc
- To get you familiarized with the ACR-EULAR class. criteria

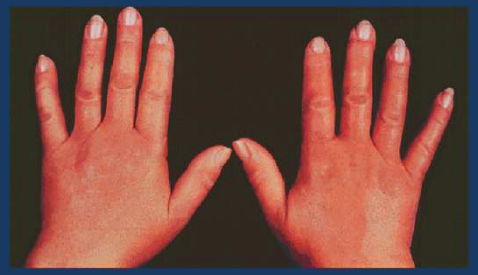
Systemic Sclerosis

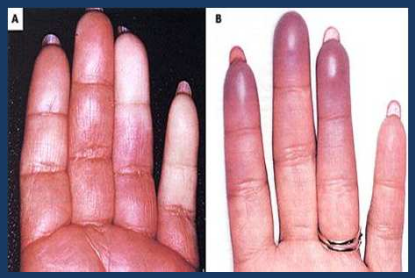
- **Rare disease:** **prevalence 1 in 10.000**
- **Clinical symptoms:** **heterogeneous**

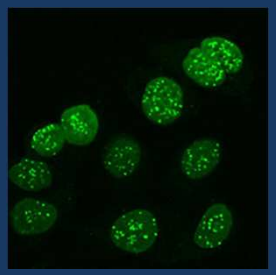
  non specific ------ more specific
- **Main symptom:** **skin thickening**

Syndrome Systemic Sclerosis

- No single diagnostic test for systemic sclerosis
- Recognition of SSc as a syndrome-type disease
  - Easy if fully developed
  - Difficult if early in disease process
  - Expert clinical opinion



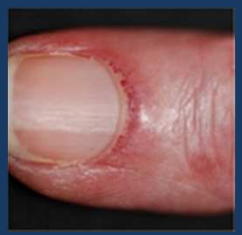




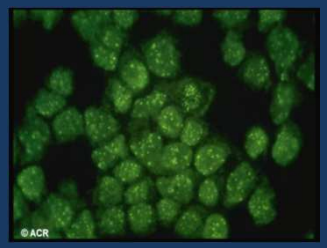
Pathogenic process in SSc

Organ damage

Excessive collagen production and deposition



Vascular damage



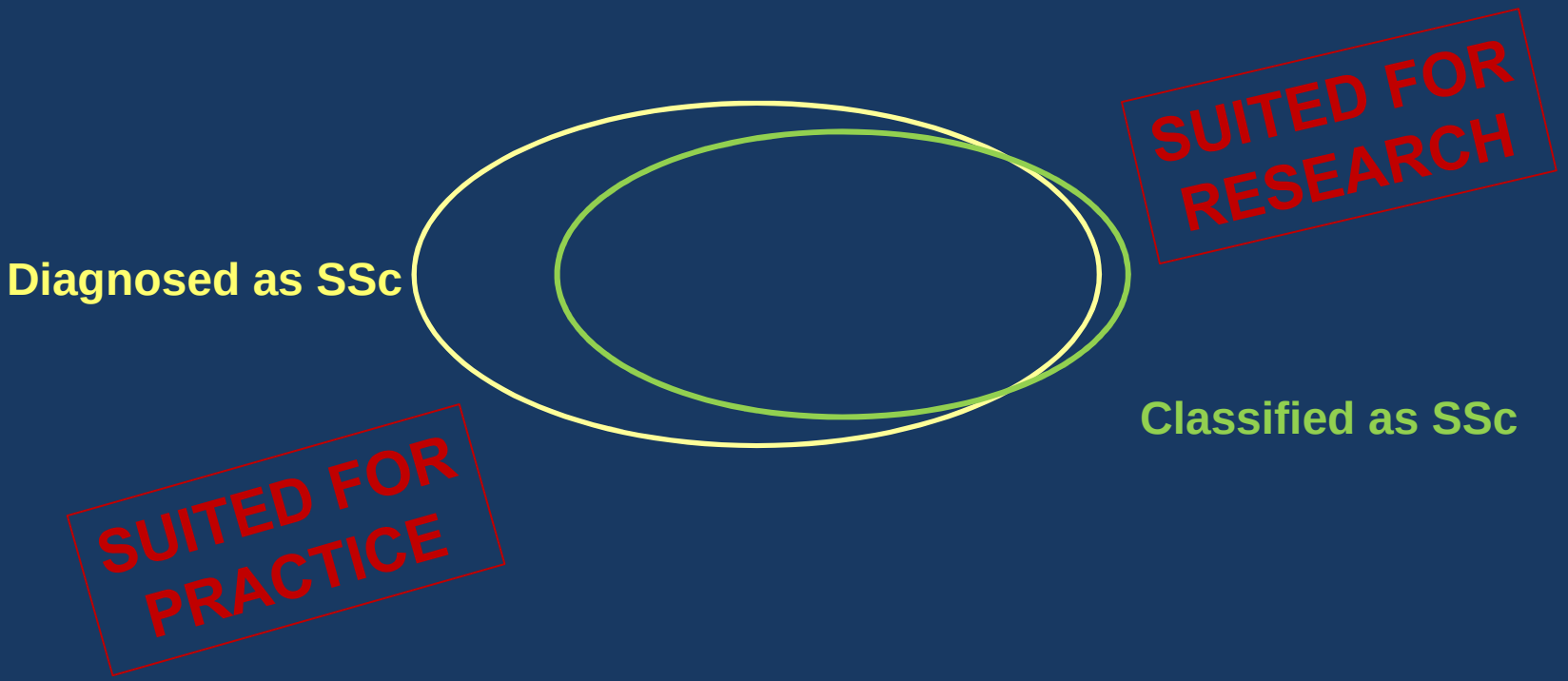
Inflammation/ Autoimmunity

Diagnosis ‘versus’ Classification

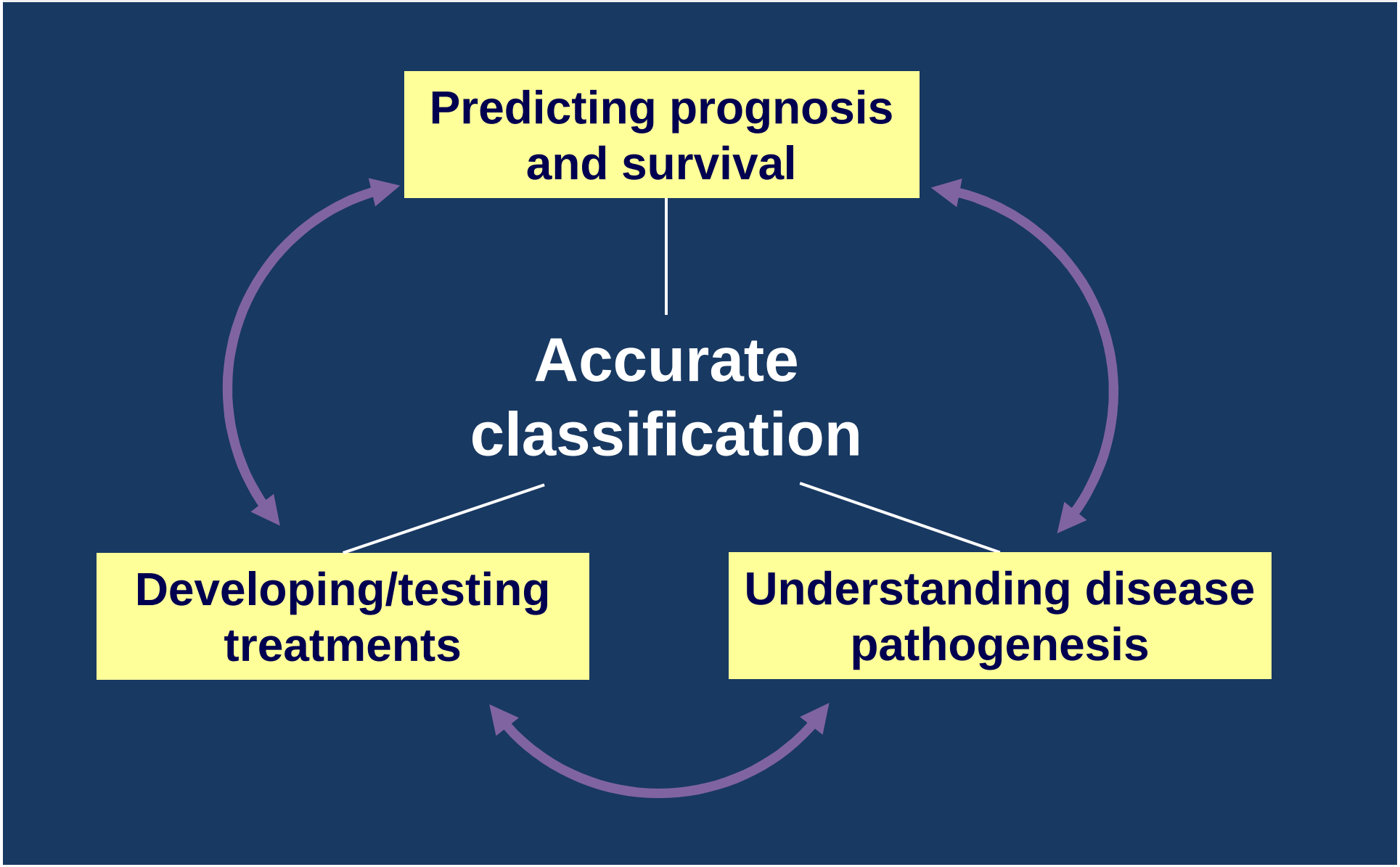
- *Diagnosis* for treating and preventing an illness, educating the patient, and for prognosis
- *Classification* for inclusion patients in studies
  - Classification criteria are not synomynous with diagnostic criteria
  - Conclusions from clinical studies using classification criteria should apply to patients with the diagnosis

Diagnosis ‘versus’ Classification

- Classification and diagnostic criteria ideally become the same



Need for classification in SSc: heterogeneous



1980 ACR Preliminary criteria for the classification of SSc

- Major criterion: - proximal scleroderma
- Minor criteria: - pulmonary fibrosis on chest X-ray
  - sclerodactyly
  - digital ulcers or pitting scars

The major criterion or 2 of the minors = ‘systemic sclerosis’

Arthritis Rheum. 1980;23(5):581-90

1988 Subclassification limited - diffuse

LeRoy et al: limited and diffuse subtypes

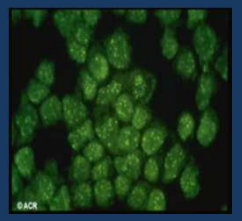
Skin involvement:

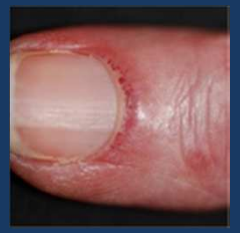
- Limited: face and distal to elbows and knees
- Diffuse: proximal to elbows and knees and/or trunk

J Rheumatol. 1988;15(2):202-5

Limitations of the 1980 ACR classification

- No disease specific auto-antibodies
- No nailfold capillaroscopy
- Developed in definite and mostly diffuse patients



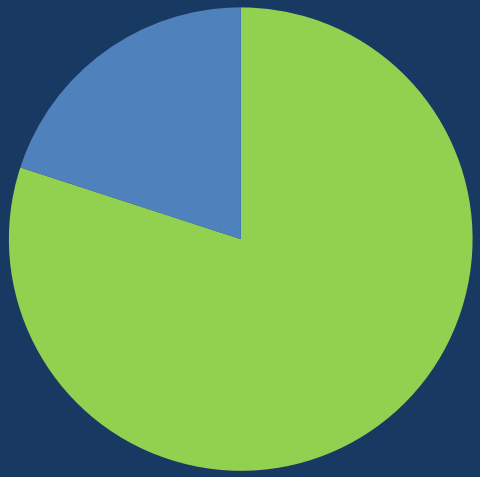


→ patients with limited and early disease are missed

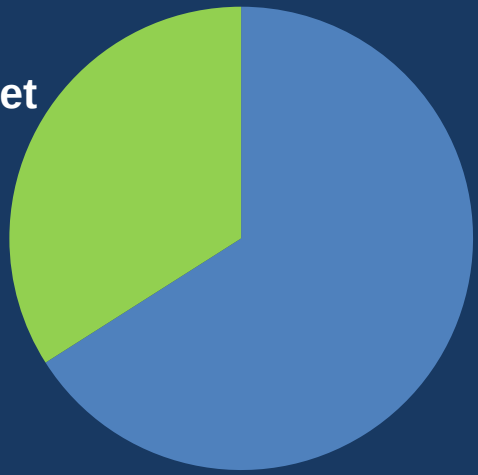
LeRoy et al: J Rheumatol. 1988;15(2):202-5

Limitations of the ACR classification

- Pittsburgh cohort of 639 patients with SSc[1]
  - 20% of limited SSc patients did not meet ACR criteria



- French Canadian cohort of 259 patients with SSc[2]
  - 66% of limited SSc patients did not meet ACR criteria



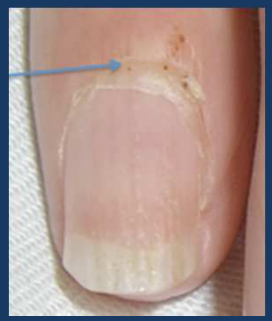
ACR criteria met
ACR criteria not met

- Many SSc patients diagnosed by expert clinicians would be excluded based on ACR criteria

1. Hachulla E, et al. Clinical Rev Allergy Immunol 2010; 2011 Apr;40(2):78-832
2. Lonzetti LS, et al. Arthritis Rheum 2001; 44:735-6

Nailfold capillaroscopy in SSc classification

- Simple and non-invasive
- Distinguishes primary from secondary Raynaud's[1]
- Detects microvascular damage and dysfunction, which are the earliest morphological and functional markers of SSc[2]
- Associated with disease subset and severity[3]
- Capillaroscopic changes are associated with complications such as PF, PH and DU[4]



1. Cutolo M, *et al*. *Best Pract Res Clin Rheumatol* 2005; 19:437-52.
2. Cutolo M, *et al*. *Nat Rev Rheumatol* 2010; 6:578-87.
3. Caramaschi P, *et al*. *Rheumatol (Oxford)* 2007; 46:1566-9.
4. Joven B, *et al. EULAR* 2006; FRI0360.

Systemic sclerosis related autoantibodies

Autoantigen recognised	Percentage of patients	SSc type	Clinical associations
Nuclei	95%	Both	
Centromere	10–20%	lcSSc	CREST syndrome, digital loss, PAH, PBC
Topoisomerase I (Scl-70)	15–25%	dcSSc	Interstitial lung disease, cardiac disease
RNA polymerase I, II, III	10–25%	dcSSc	Renal crisis, cardiac disease, tendon friction rubs
U3-RNP (fibrillarin)	5–45%	dcSSc	African-American males, pulmonary disease
Th/To RNP	5%	lcSSc	
U1-RNP	5–35%	lcSSc	Mixed connective tissue disease
PM-Scl	4%	SSc with myositis	

Van Ingen et al: EULAR on Line Course

2001 Early SSc classification criteria

Leroy and Medsger

- **SSc**: Raynaud's *objectively* documented
  + SSc-type nailfold capillary pattern
  or SSc-specific autoantibodies

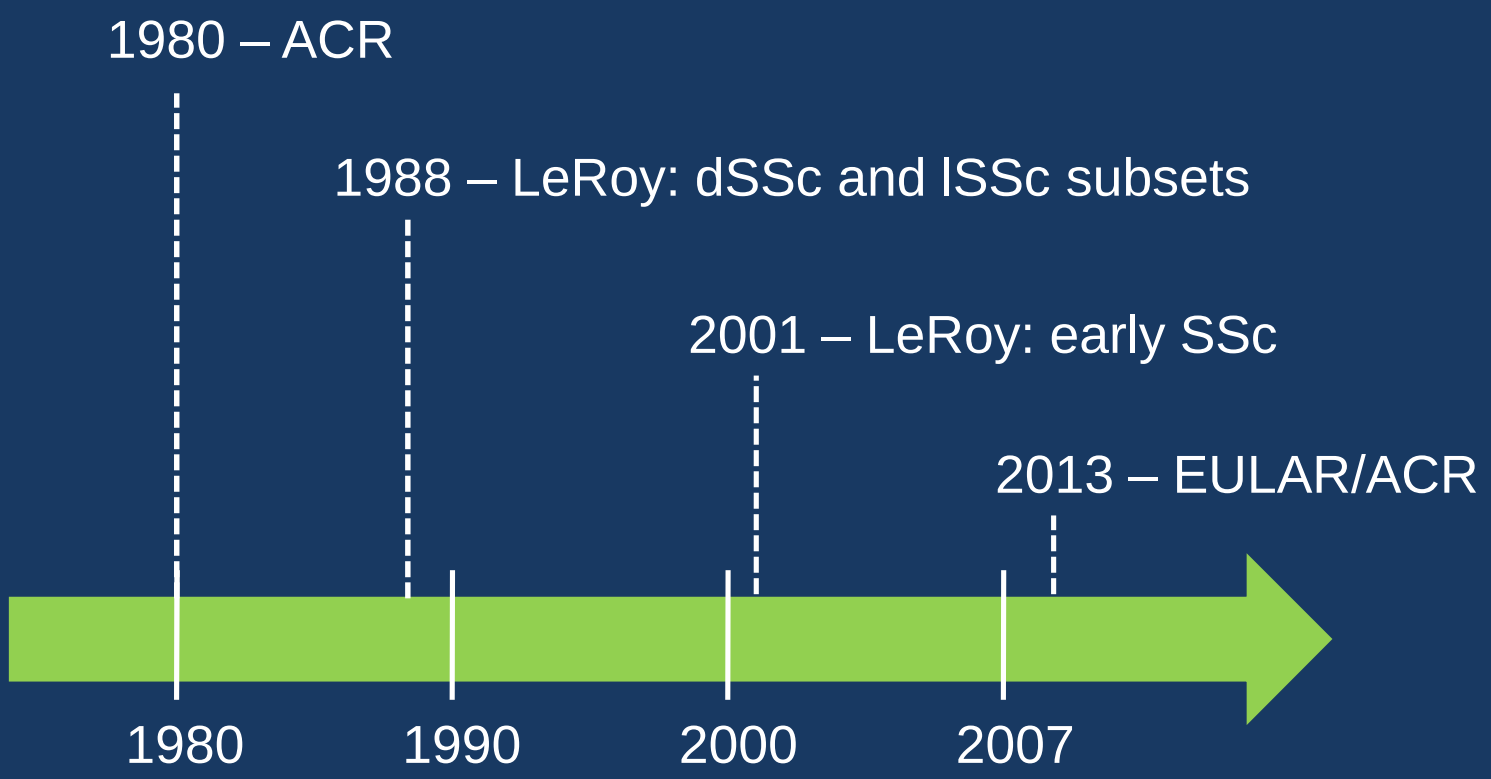
  Raynaud's *subjectively* documented
  + SSc-type nailfold capillary pattern
  and SSc-specific autoantibodies

- **lcSSc** Criteria for SSc + Distal cutaneous changes
- **dcSSc** Criteria for SSc + Proximal cutaneous changes

→ No validation!

Leroy and Medsger J Rheumatol 2001;28:1573-1576.

History of SSc classification schemes



dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; lSSc: limited SSc

New ACR-EULAR SSc classification criteria

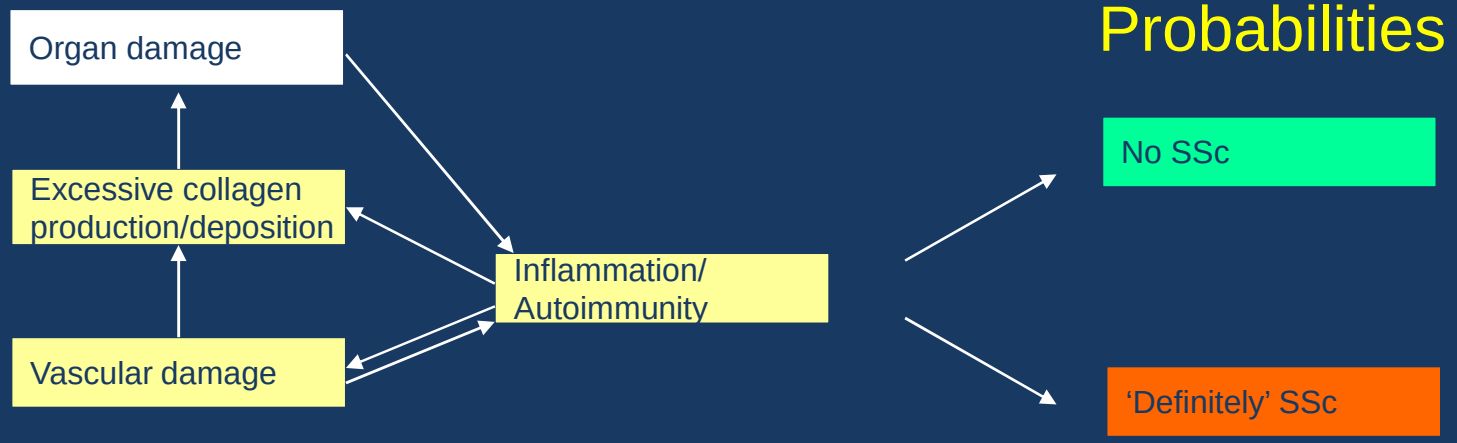
→ **Task force: Goals**

- To develop SSc classification criteria jointly by ACR and EULAR
- to enable identification of individuals with SSc for inclusion in clinical studies
- being more sensitive and specific than previous criteria

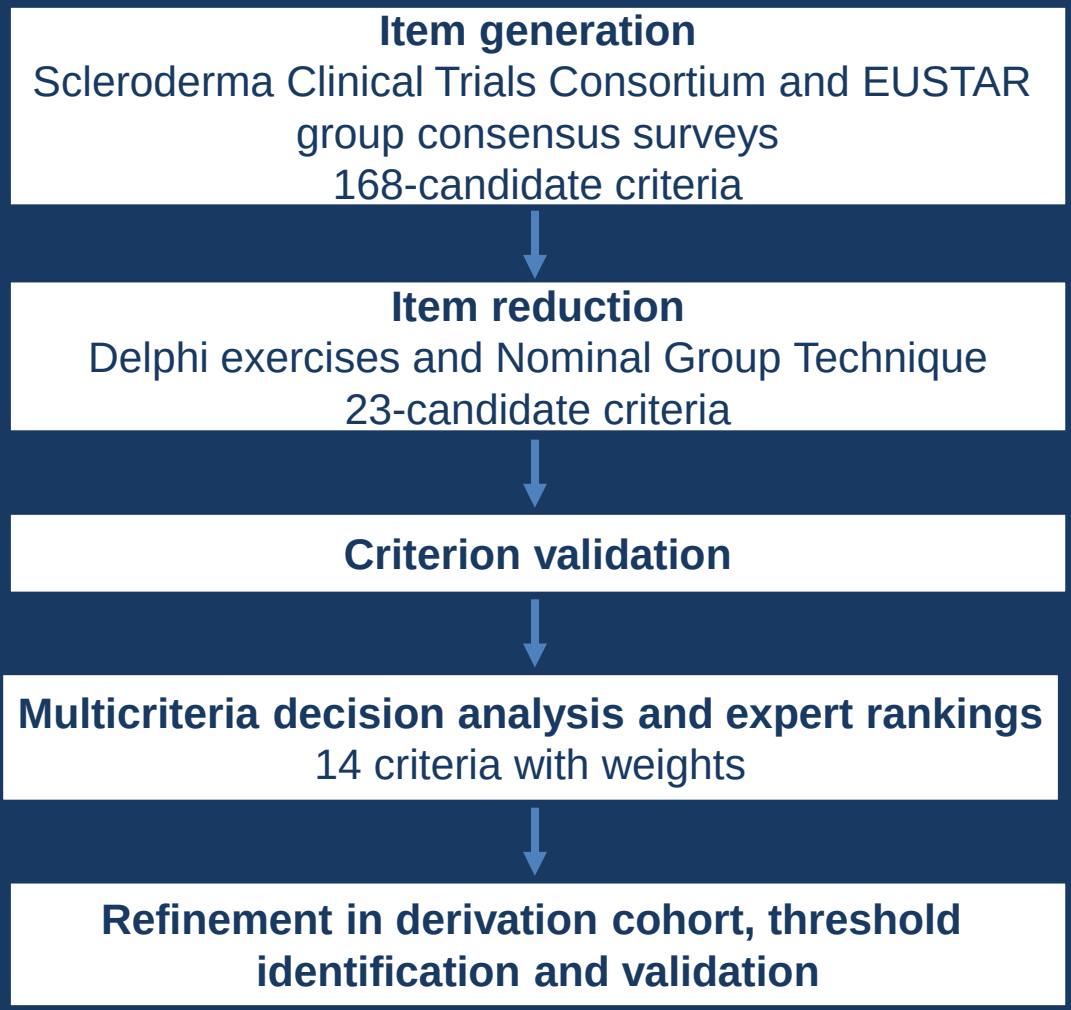
New ACR-EULAR SSc classification criteria

Prerequisites

1) Classify SSc patients in early and in late stage
2) Include vascular, immunologic and fibrotic manifestations
3) Feasible to use in clinical practice
4) In accordance with the way diagnosis is made in clinical practice



New ACR-EULAR SSc classification criteria



Van den Hoogen F, et al. Ann Rheum Dis 2013; 172:1747-55.
Van den Hoogen F, et al. Arthritis Rheum 2013; 65:2737-47.

	Item	rank		Item	rank
1.	Presence of scleroderma	9	13.	Calcinosis	7
2.	Positive antI-topo I	9	14.	Telangiectasia	6
3.	Positive anticentromere	9	15.	Puffy fingers	6
4.	Positive anti-RNA polymerase III	9	16.	Pulm. Art. hypertension	6
5.	Abnormal nailfold pattern	8	17.	Positive ANA	5
6.	Fingertip ulcers / scars	8	18.	Contractures fingers	5
7.	Renal crisis	7	19.	Positive anti-Pm-Scl	5
8.	Raynaud's phenomenon	7	20.	Reduced FVC	5
9.	Interstitial lung disease/fibrosis	7	21.	Reduced DL_{CO}	4
10.	Tendon or bursal friction rubs	7	22.	Gastro-intestinal reflux	4
11.	Fingertip pulp loss/acreosteolysis	7	23.	Dysphagia	4
12.	Esophageal dilatation (X-ray/CT)	7			

ACR-EULAR SSc classification criteria

Criteria domain*	Sub-criteria	Weight#
Skin thickening (count the higher of the three)	Skin thickening of the fingers of both hands extending proximal to the MCP joints	9
	Puffy fingers	2
	Whole finger, distal to MCP joint	4
Fingertip lesions (count the higher of the two)	Digital tip ulcers	2
	Pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung involvement	PAH and/or ILD	2
Raynaud's phenomenon		3
SSc-related antibodies	Any of ACA, ATA (anti-Scl 70), ARA	3

*Item should be scored as present if it has occurred at any time during the disease course

#The weight of each item that is present should be added together to obtain a total score. A total score of 9 or more is classified as SSc

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ACR-EULAR SSc classification criteria

To whom can it be aplied?

Applicable to any patient considered for inclusion in a SSc study

Not applicable to:

- Patients having a systemic sclerosis-like disorder *better explaining* their manifestations, such as:

- nephrogenic sclerosing fibrosis
- scleromyxedema
- porphyria
- graft versus host disease
- scleredema diabeticorum
- erythromyalgia
- lichen sclerosis
- diabetic chierarthropathy

- Patients with '*skin thickening sparing the fingers*'

ACR-EULAR SSc classification criteria

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits - a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other reasons such as inflammatory dactylitis.
Finger tip ulcers or pitting scars	Ulcers or scars distal to or at the PIP joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasia(e) in a scleroderma like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or large matt-like telangiectasia(e). Telangiectasiae are visible macular dilated superficial blood vessels; which collapse upon pressure and fill slowly when pressure is released; distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with SSc	Enlarged capillaries and/or capillary loss with or without peri-capillary hemorrhages at the nailfold and may be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis on HRCT or chest radiograph, most pronounced in the basilar portions of the lungs, or presence of 'Velcro' crackles on auscultation not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self report or reported by a physician with at least a two-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
Scleroderma specific antibodies	Anti-centromere antibody or centromere pattern on antinuclear antibody (ANA) testing; anti-topoisomerase I antibody (also known as anti-Scl70 antibody); or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

A comparison between previous classification criteria and the 2013 ACR-EULAR classification criteria for SSc

	Derivation sample (n=200)		Validation sample (n=405)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ACR SSc criteria	0.80 (0.72 to 0.87)	0.77 (0.68 to 0.84)	0.75 (0.70 to 0.80)	0.72 (0.64 to 0.79)
2001 LeRoy/Medsger SSc criteria	0.76 (0.68 to 0.84)	0.69 (0.68 to 0.84)	0.75 (0.70 to 0.80)	0.78 (0.70 to 0.85)
2013 ACR/EULAR SSc criteria	0.95 (0.90 to 0.98)	0.93 (0.86 to 0.97)	0.91 (0.87 to 0.94)	0.92 (0.86 to 0.96)

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; SSc, systemic sclerosis.

The ACR-EULAR classification criteria performed better than
- the ACR 1980 criteria for SSc
- the 2001 LeRoy/Medsger SSc criteria

Performance: in SSc cases and controls

	Validation sample (N=405)		Validation sample ≤ 3 years disease duration (N=100)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ACR SSc Criteria	0.75 (0.70, 0.80)	0.72 (0.64, 0.79)	0.75 (0.70, 0.80)	0.72 (0.63, 0.79)
2001 LeRoy and Medsger criteria	0.75 (0.70, 0.80)	0.78 (0.70, 0.85)	0.80 (0.69, 0.88)	0.76 (0.53, 0.92)
2013 ACR-EULAR SSc Criteria	0.91 (0.87, 0.94)	0.92 (0.86, 0.96)	0.91 (0.83, 0.96)	0.90 (0.70, 0.99)

ACR-EULAR classification criteria for SSc

- Perform better than the 1980 ACR criteria
- Good performance, also in patients with
  - limited disease
  - short disease duration
- Are relatively simple to apply to individual subjects
- Are ACR-EULAR endorsed for inclusion of patients with ‘definite’ SSc in studies
- Validation in other cohorts is encouraged

New ACR-EULAR SSc classification criteria

Criteria domain*	Sub-criteria	Weight#
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Fingertip lesions (count the higher of the two)	Digital tip ulcers	2
	Pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung involvement	PAH and/or ILD	2
Raynaud's phenomenon		3
SSc-related antibodies	Any of ACA, ATA (anti-Scl 70), ARA	3

TOTAL=9

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Lung involvement	PAH and/or ILD	2
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SSc-related antibodies	Any of ACA, ATA (anti-Scl 70), ARA	3

TOTAL=12

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TOTAL=8

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New ACR-EULAR SSc classification criteria

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Telangiectasia		2
Abnormal nailfold capillaries		2
Lung involvement	PAH and/or ILD	2
Raynaud's phenomenon		3
SSc-related antibodies	Any of ACA, ATA (anti-Scl 70), ARA	3

TOTAL=7

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Take home message

If a patient fulfils ACR-EULAR classification criteria:

diagnosis of systemic sclerosis almost certain

If a patient does not fulfil ACR-EULAR classification criteria:

diagnosis of SSc is not excluded

Goals Presentation

- To explain difference between diagnosis and classification
- To explain neccessity of classification criteria in SSc
- To get you familiarized with the ACR-EULAR class. criteria

ACKNOWLEDGEMENTS

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