CURRENT OPINION

Novel classifications for systemic sclerosis: challenging historical subsets to unlock new doors

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CURRENT OPINION

Detection, screening, and classification of interstitial lung disease in patients with systemic sclerosis

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introduction

- Systemic sclerosis (SSc) : A heterogeneous disease
- wide spectrum of clinical presentations : impact on the different classification criteria for SSc
- The historical dichotomy limited/diffuse subsets based on cutaneous involvement has been challenged
- This review aims to highlight recent studies that have proposed new innovative approaches to decipher this heterogeneity

ACR classification criteria : 1990

- proposed criteria for SSc : one major criterion or at least two minor criteria

➢ Major criterion :

✓ proximal cutaneous sclerosis

➢ Minor criteria :

✓ Sclerodactyly

✓ Digital ischemia : digital pitting scars of fingertips or loss of substance of the distal finger pad

✓ Bibasilar pulmonary fibrosis

LeRoy's classification : 1988

➢ Diffuse cutaneous SSc :

- ✓ Onset of Raynaud's phenomenon within 1 year of onset skin changes
- ✓ Truncal and acral skin involvement
- ✓ Presence of tendon friction rubs
- ✓ Early and significant incidence of ILD, oliguric renal failure, diffuse GI disease and myocardial involvement
- ✓ Absence of anticentromere antibodies
- ✓ **Antitopoisomerase antibodies**
- ✓ **Nailfold capillary** dilatation and capillary destruction

➢ Limited cutaneous SSc :

- ✓ Raynaud's phenomenon for years
- ✓ Limited Skin involvement
- ✓ A significant late incidence of pulmonary hypertension, with or without ILD, skin calcifications and telangiectasia
- ✓ A high incidence of **anticentromere antibodies** (70–80%)
- ✓ Dilated **nailfold capillary** loops, usually without capillary dropout

LeRoy and Medsger classification criteria : 2001

Limited SSc (lSSc)	Limited cutaneous SSc	Diffuse cutaneous SSc
Raynaud's phenomenon objectively documented by :	Criteria for lSSc	Criteria for lSSc
1. Direct observation of any of the two :	Plus	Plus
a. Pallor (well demarcated whitening of acral skin)	Distal cutaneous	Proximal cutaneous
b. Cyanosis (dusky blueness which disappears on rewarming)	Changes	Changes
c. Suffusion (well demarcated redness)		
or		
2. Direct measurement of response to cold by:		
a. Abnormal widefield nailfold capillaroscopy		
b. Nielsen test or equivalent		
plus any one:		
SSc-type nailfold capillary pattern		
or		
SSc selective autoantibodies		
If Raynaud's Phenomenon is subjective only:		
both SSc capillary pattern and SSc selective autoantibodies (in titre > 1:100) are required to define lSSc		

- **EUSTAR (2011)** Proposed two steps for referral of patients in expert centers.

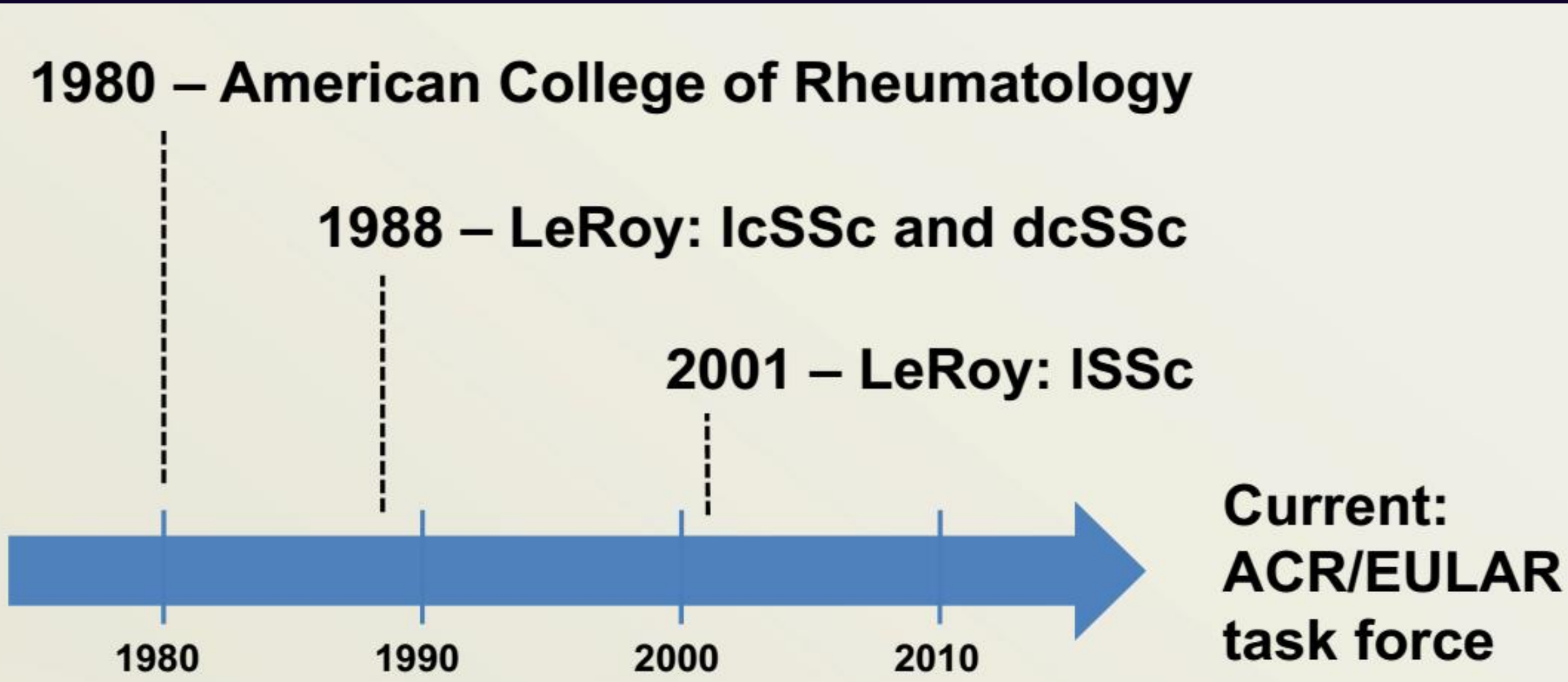
- ✓ **Suspicion of very early SSc** : Raynaud's phenomenon, puffy fingers, antinuclear antibodies

- ✓ **Diagnosis of very early SSc** : previous criteria with abnormal capillaroscopy with scleroderma pattern or positive anticentromere antibodies or positive antitopoisomerase-1 antibodies

ACR/EULAR classification criteria : 2013

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

Classification schemes– Overview

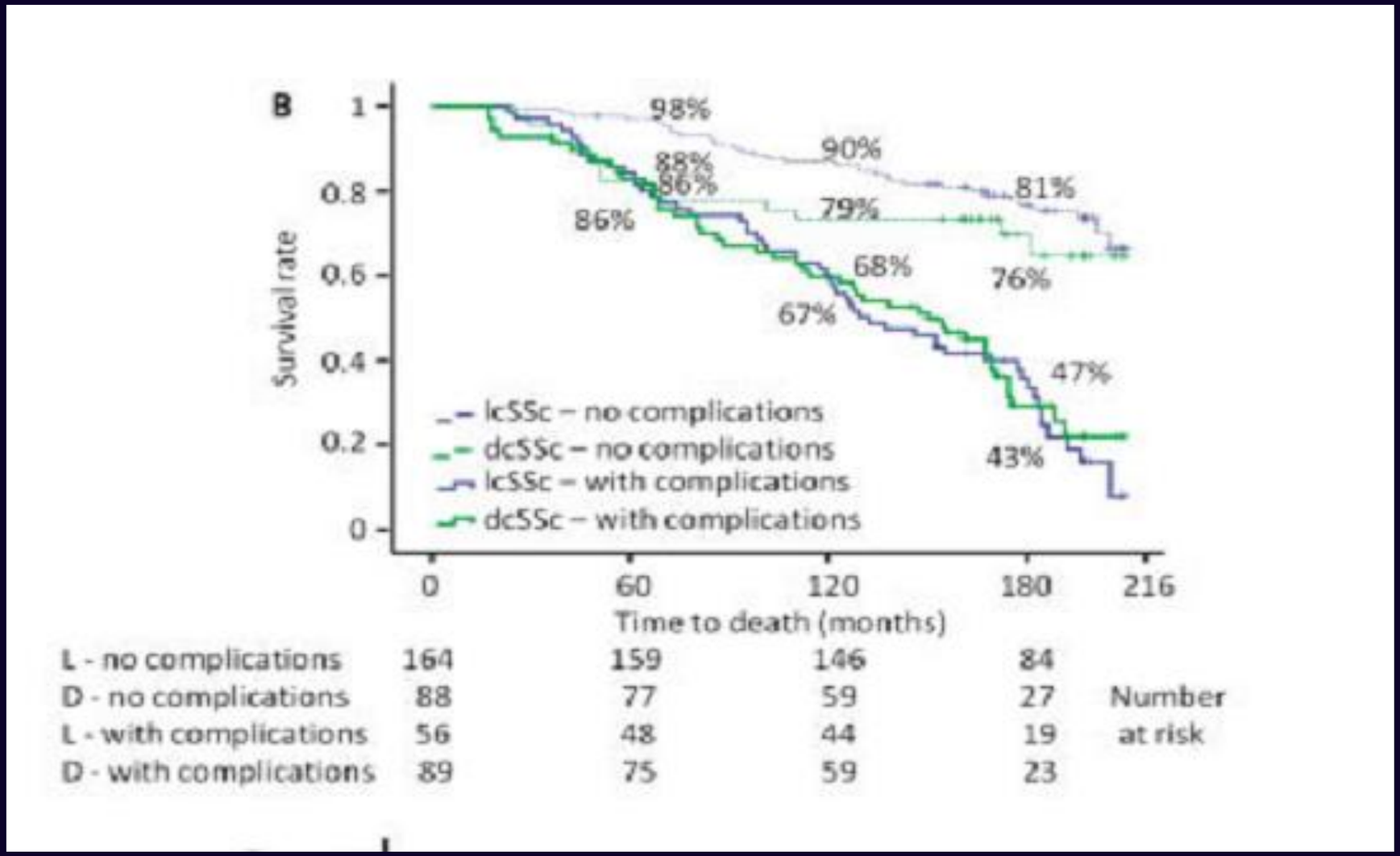


RECENT PROPOSALS TO CLASSIFY SSc

- Considerations on skin, organ involvement and autoantibodies
- Systemic sclerosis-overlap syndromes
- Clinical trajectories over time
- High-throughput omics technologies
- Radiomics

Considerations on skin, organ involvement and autoantibodies

- in a study of 398 consecutive patients followed for 15 years , Nihtyanova et al showed that the **presence of organ damage was a powerful prognosis factor in both lcSSc and dcSSc.**



*Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, Wells AU, Denton CP. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis & rheumatology. 2014 Jun;66(6):1625-35.

Considerations on skin, organ involvement and autoantibodies

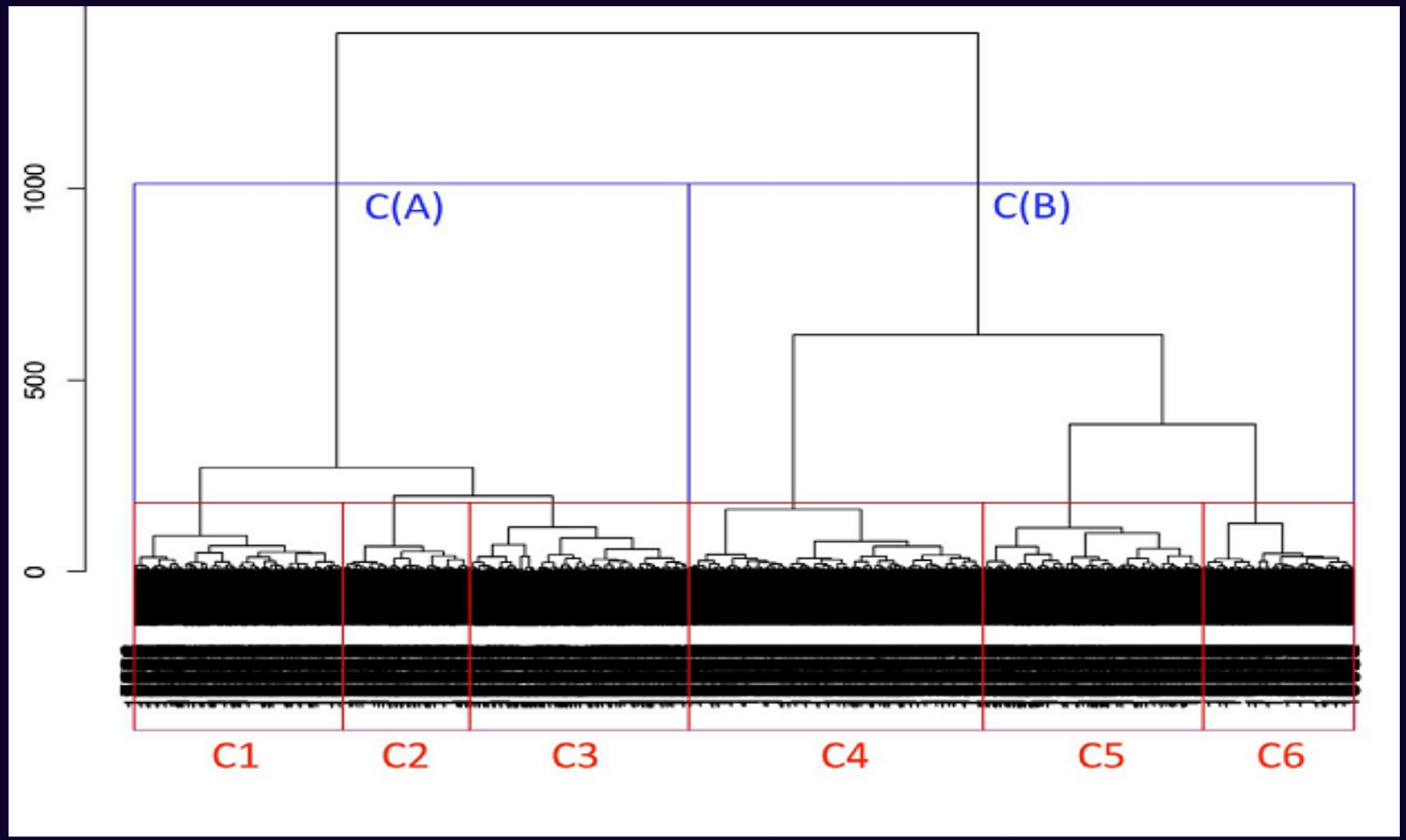
- A study by the Canadian Scleroderma Research Group (2007) : Demographic characteristics and visceral involvement were more associated with **serological status** than with skin extension.

- Another study (2012) : Kranenburg et al. have also shown that organ damage and survival differed between patients with antitopo-I-positive lcSSc and patients with antitopo-I negative lcSSc or antitopo-I positive dcSSc.

- Another study (2012) : The significance of **serologic profiles** has also been highlighted by Patterson et al. who characterized five major groups of patients with specific clinical and serological associations in a cohort of 505 Australian SSc patients.

Considerations on skin, organ involvement and autoantibodies

- A recent EUSTAR study (2019) : to distinguish and characterize homogeneous groups of SSc patients (6927 SSc patients)
- the presence of **organ damage** and **serological profiles** markedly impacted survival regardless of cutaneous involvement



*Sobanski V, Giovannelli J, Allanore Y, Riemekasten G, Airò P, Vettori S, Cozzi F, Distler O, Matucci-Cerinic M, Denton C, Launay D. Phenotypes determined by cluster analysis and their survival in the prospective European scleroderma trials and research cohort of patients with systemic sclerosis. Arthritis & Rheumatology. 2019 Sep;71(9):1553-70.

Considerations on skin, organ involvement and autoantibodies

- In a recent study (2020) Nihtyanova et al. described the **associations between autoantibodies, clinical presentation and outcomes** in a cohort of 1325 SSc individuals.

- they propose **a novel SSc classification scheme** including seven groups :

✓ ACA + lcSSc,
✓ antitopo-I + lcSSc,
✓ antitopo-I + dcSSc,
✓ anti-RNA polymerase 3 antibodies +
✓ antiU3RNP +
✓ other antibodies lcSSc
✓ other antibodies dcSSc

*Nihtyanova SI, Sari A, Harvey JC, Leslie A, Derrett-Smith EC, Fonseca C, Ong VH, Denton CP. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis & Rheumatology. 2020 Mar;72(3):465-76.

Considerations on skin, organ involvement and autoantibodies

- This proposed new classification enabled **more precise risk stratification** of patients, compared with the dichotomy dcSSc/lcSSc.

- The authors also confirmed the strong association between **ACA** and low incidence rates of major organ-based complications and mortality. Regarding pulmonary hypertension, they found a similar incidence in the ACA + group and in the SSc cohort overall, challenging the classical association between ACA and pulmonary hypertension

- **Conclusion :** These findings highlight the **importance of autoantibodies , cutaneous subset, and disease duration** when assessing morbidity and mortality in patients with SSc. Our novel classification scheme may improve disease monitoring and benefit future clinical trial designs in SSc.

- **Nihtyanova SI, Sari A, Harvey JC, Leslie A, Derrett-Smith EC, Fonseca C, Ong VH, Denton CP. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis & Rheumatology. 2020 Mar;72(3):465-76.**

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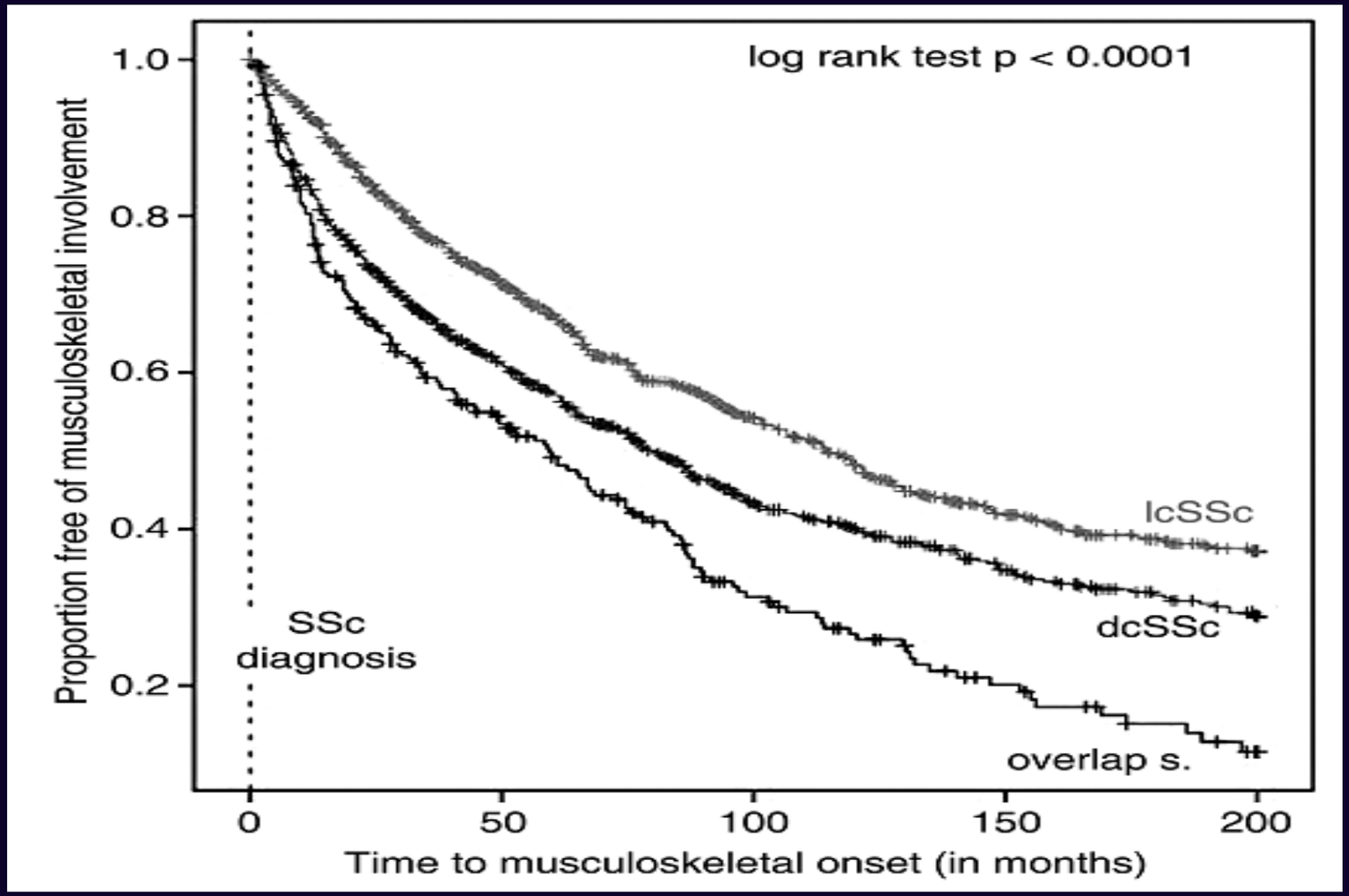
systemic sclerosis-overlap syndromes

- On the basis of the study (2015) of 3240 patients from the German SSc Registry overlapping patients had :
- ✓ More (and earlier) **musculoskeletal involvement**,
- ✓ developed **cardiac and pulmonary damage** earlier than lcSSc but later than dcSSc
- ✓ **specific antibody profiles** (anti-U1RNP, anti-PM/Scl, anti-SS-A/SS-B)



*Moinzadeh P, Aberer E, Ahmadi-Simab K, Blank N, Distler JH, Fierlbeck G, Genth E, Guenther C, Hein R, Henes J, Herich L. Disease progression in systemic sclerosis-overlap syndrome is significantly different from limited and diffuse cutaneous systemic sclerosis. Annals of the rheumatic diseases. 2015 Apr 1;74(4):730-7.

systemic sclerosis-overlap syndromes

- **whole blood gene expression** profiling could also differentiate SSc from overlapping forms, suggesting that the later could be a distinct subset (2020 study)

*Moinzadeh P, Frommolt P, Franitza M, Toliat MR, Becker K, Nürnberg P, Nihtyanova SI, Ahrazoglu M, Belz D, Hunzelmann N, Abraham D. Whole blood gene expression profiling distinguishes systemic sclerosis-overlap syndromes from other subsets. Journal of the European Academy of Dermatology and Venereology. 2020 May;34(5):e236-8.

RECENT PROPOSALS TO CLASSIFY SSc

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- **Clinical trajectories over time**
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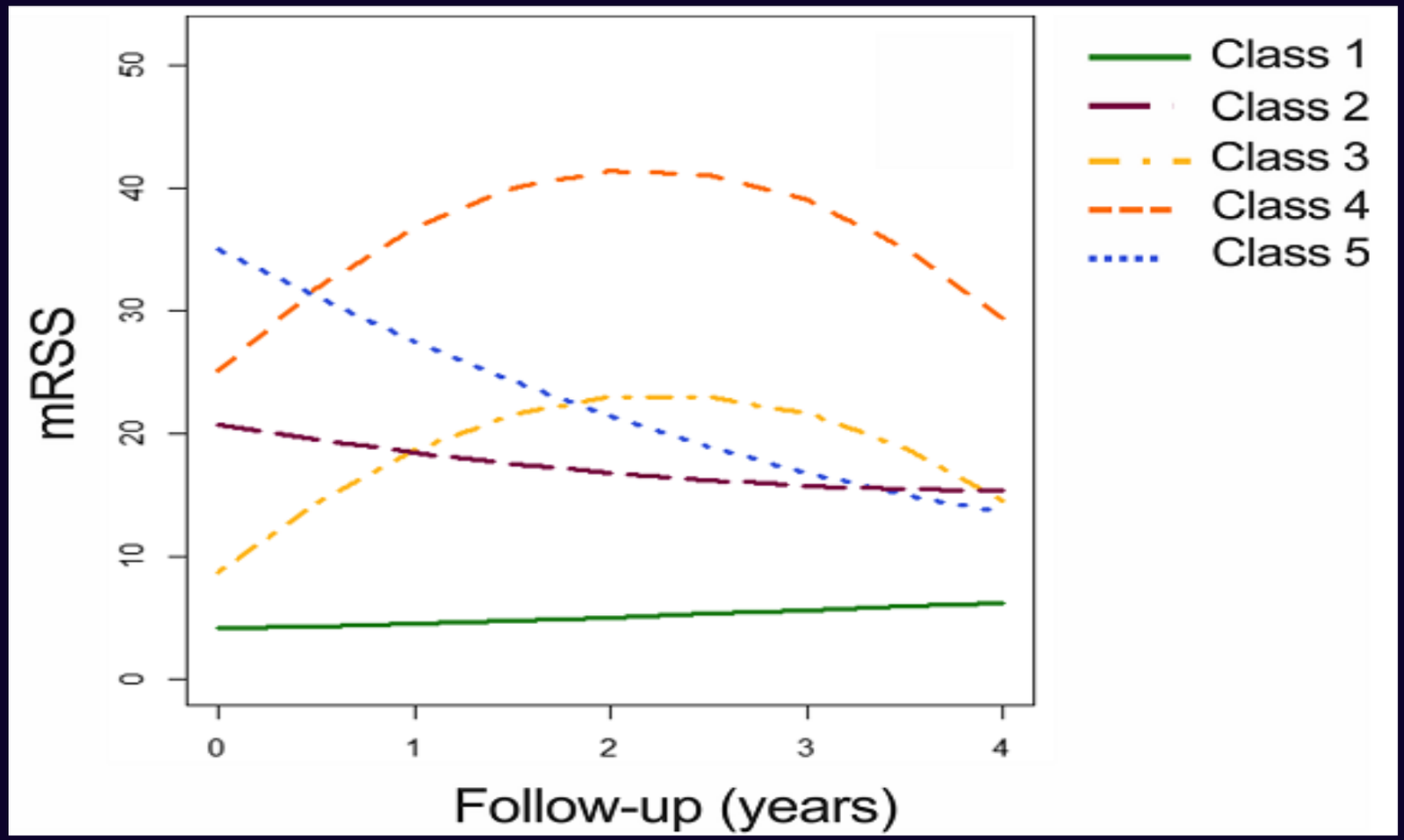
- Radiomics

Clinical trajectories over time

- French national SSc cohort (2020) :
- early identification of clinical phenotype based on **skin thickening trajectories** could predict morbimortality.



*Ledoult E, Launay D, Béhal H, Mouthon L, Pugnet G, Lega JC, Agard C, Allanore Y, Jego P, Fauchais AL, Harlé JR. Early trajectories of skin thickening are associated with severity and mortality in systemic sclerosis. Arthritis research & therapy. 2020 Dec;22(1):1-2.

RECENT PROPOSALS TO CLASSIFY SSc

- Considerations on skin, organ involvement and autoantibodies
- Systemic sclerosis-overlap syndromes
- Clinical trajectories over time
- **High-throughput omics technologies**
- Radiomics

High-throughput omics technologies

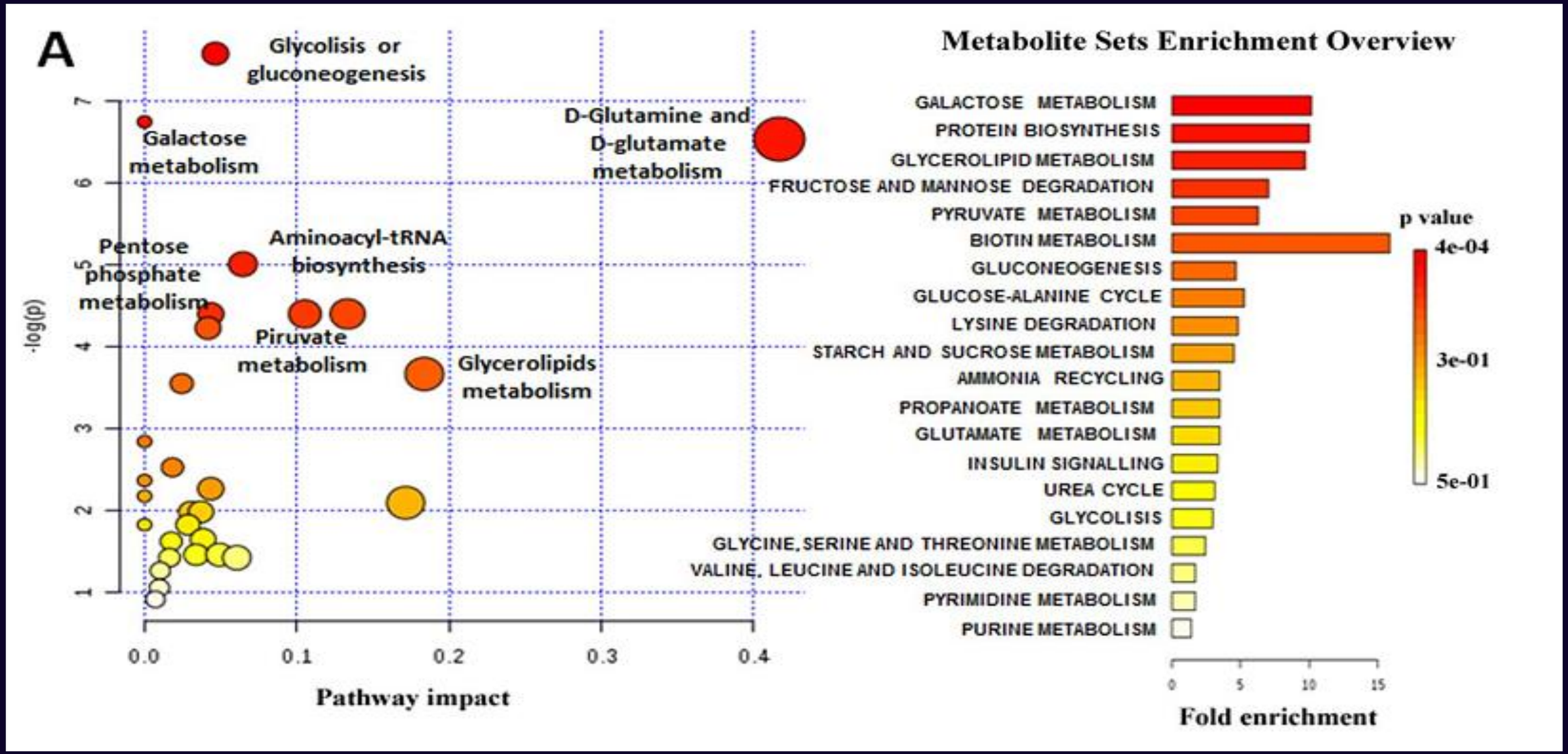
- Significant insights on **key pathogenic processes .**
- Serum **metabolomic** profiles could distinguish healthy controls from SSc patients, and the serum metabolomic signatures of dcSSc differed from those of lcSSc patients

High-throughput omics technologies

- Since recent evidence suggests that there is a link between metabolomics and immune mediated disease, serum metabolic profile of SSc patients and healthy controls was investigated by **H-NMRS** and **GC-MS** techniques.

*Murgia F, Svegliati S, Poddighe S, Lussu M, Manzin A, Spadoni T, Fischetti C, Gabrielli A, Atzori L. Metabolomic profile of systemic sclerosis patients. Scientific reports. 2018 May 16;8(1):1-1.

	Metabolites Model HC vs SSc	HC	SSc	Metabolites Model dcSSc vs lcSSc	dcSSc	lcSSc
^{1}H-NMR	Acetate	+	−	Acetate	+	−
	Glutamate	+	−	Fructose	+	−
	Dimethylurate	+	−	Glutamate	+	−
	Lysine	+	−	Glycerol	+	−
	3-OH-butyrate	−	+	Lysine	+	−
	Lactate	−	+	Valine	+	−
				Lactate	−	+
				Glutamine	−	+
GC-MS ^{1}H-NMR	Alanine	+	−	Sugars	−	+
	Aspartic acid	+	−			
	Citric Acid	+	−			
	Sugars	−	+			
GC-MS	2-pyrrolidone	−	+	Sorbitol	−	+
	D-threitol	−	+	Glycerate	+	−
	Butanoic Acid	−	+	Glutarate	+	−
	Glutaric Acid	+	−			
	L-threonic Acid	+	−			
	1–5-anhydrosorbitol	+	−			



Metabolic pathway analysis of (dcSSc) and (lcSSc) samples.

High-throughput omics technologies

- **In conclusion**, our metabolomic approach allowed the identification of significant biological molecules that are discriminant between SSc and HC and the resulted pathways involved.
- This may be useful to better clarify the **pathophysiology of SSc** and for the **classification of the patients** in the different subtypes of scleroderma.
- This study represents a preliminary step for future largest study

***Murgia F, Svegliati S, Poddighe S, Lussu M, Manzin A, Spadoni T, Fischetti C, Gabrielli A, Atzori L. Metabolomic profile of systemic sclerosis patients. Scientific reports. 2018 May 16;8(1):1-1.**

High-throughput omics technologies

- **Transcriptomic signatures** from skin biopsies also revealed different 'intrinsic' gene expression profiles especially within – but not limited to – dcSSc patients.

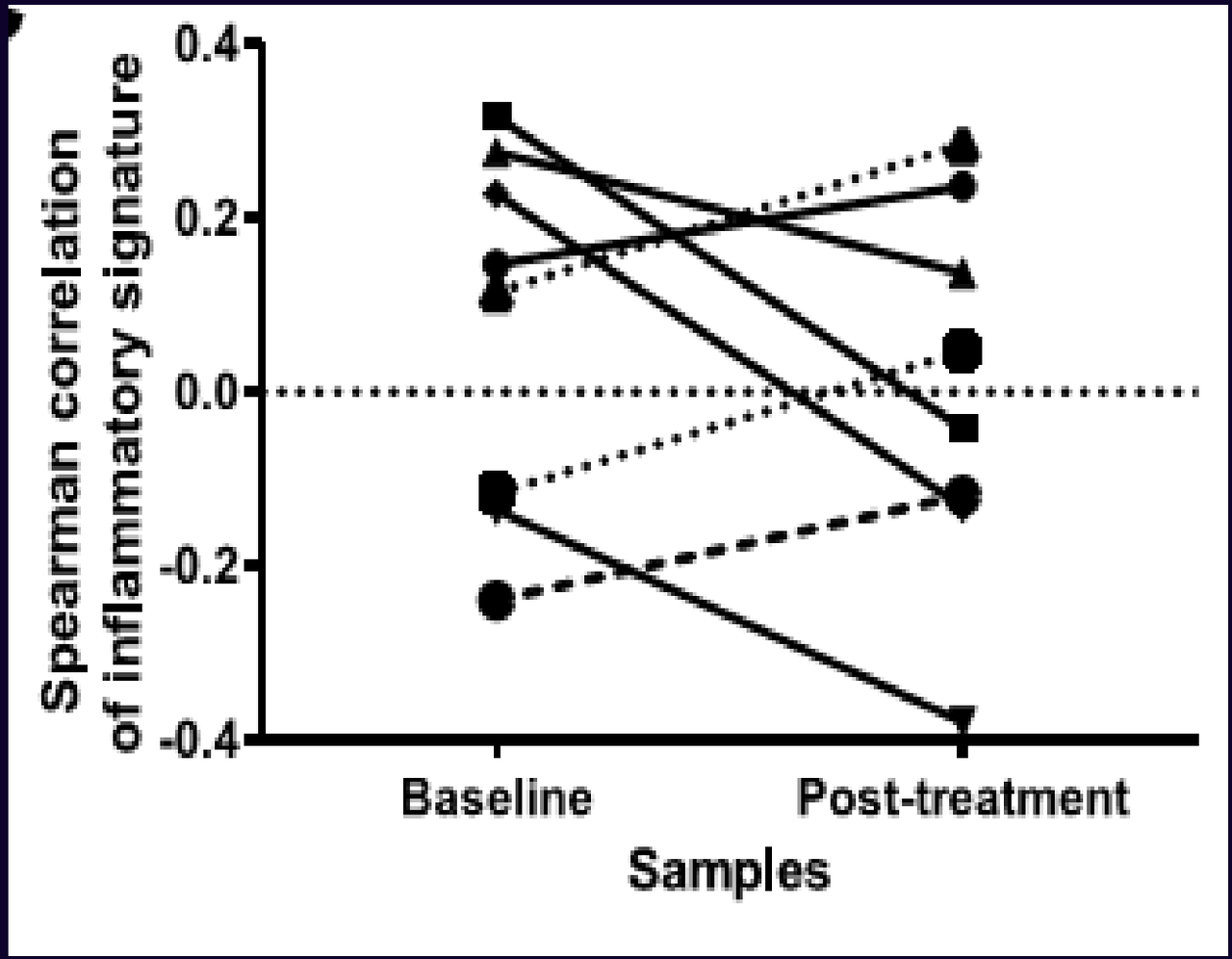
- **Four gene expression signatures** were the most consistently described : normal-like, inflammatory, fibroproliferative and limited patterns.

High-throughput omics technologies

- in the recent phase II trial evaluating **safety and efficacy of abatacept** in dcSSc, the analysis of **gene expression** in the skin at baseline showed that 39% patients were classified as inflammatory, 39% normal-like and 21% fibroproliferative
- it was a negative trial when considering the overall population.
- the decline in the mRSS over 12 months was clinically and significantly greater in the abatacept group versus the placebo group in the inflammatory and normal-like skin gene expression subsets

*Khanna D, Spino C, Johnson S, Chung L, Whitfield ML, Denton CP, Berrocal V, Franks J, Mehta B, Molitor J, Steen VD. Abatacept in early diffuse cutaneous systemic sclerosis: results of a Phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. Arthritis & Rheumatology. 2020 Jan;72(1):125-36.

- In a pilot study Adult dcss patients were randomized to receive abatacept or placebo over 24 weeks.
- Skin biopsies were obtained for differential gene expression
- abatacept therapy is associated with **distinct changes in gene expression** that are primarily seen in those with a positive clinical response.
- the improvers tend to be in the **inflammatory intrinsic subset** at baseline



- **Changes in inflammatory gene signature** between baseline and post-treatment. Improvers – solid lines, non-improver – dashed line, placebos – dotted lines

*Chakravarty EF, Martyanov V, Fiorentino D, Wood TA, Haddon DJ, Jarrell JA, Utz PJ, Genovese MC, Whitfield ML, Chung L. Gene expression changes reflect clinical response in a placebo-controlled randomized trial of abatacept in patients with diffuse cutaneous systemic sclerosis. Arthritis research & therapy. 2015 Dec;17(1):1-4.

High-throughput omics technologies

- Although the subclassification relying on **intrinsic gene signature** is only based on skin biopsy, SSc macrophages signature from blood and skin shared common pathways.

- Recent **single cell analysis** , especially in the lung could also participate to identify important cell sub-populations with molecular signature highly relevant for the definition of new SSc subgroups.

Radiomics

- Schniering et al. recently analyzed 1355 stable **'radiomic' features** extracted from computed tomography scans from 156 SSc-ILD patients, which allowed to describe different disease phenotypes and predict prognosis in two independent cohorts.

- a first **quantitative radiomic risk score (qRISSc)** : accurately predicted **progression-free survival** in SSc-ILD

- qRISSc could also be an accurate reflection of **pro-fibrotic remodeling processes**

*Schniering J, Maciukiewicz MA, Gabrys H, Brunner M, Bluethgen C, Meier C, Braga-Lagache S, Uldry AC, Heller M, Distler O, Guckenberger M. Resolving phenotypic and prognostic differences in interstitial lung disease related to systemic sclerosis by computed tomography-based radiomics. medRxiv. 2020 Jan 1.

A NOVEL CLASSIFICATION : FUTURE DIRECTIONS

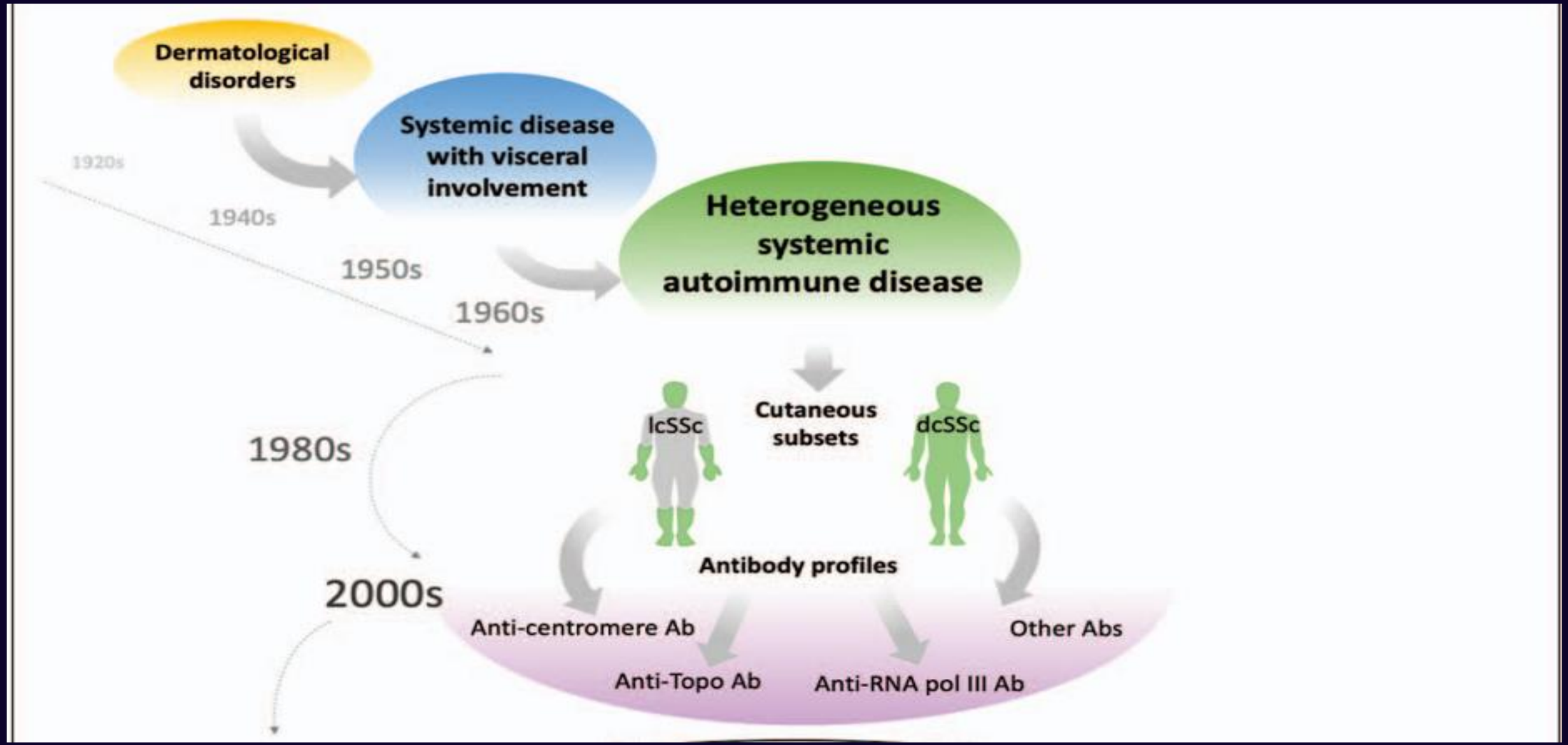
- It is anticipated that a more precise classification of SSc patients for the future will be based on an **integrated approach** that could synthesize :

- ✓ phenotypes
- ✓ clinical trajectories
- ✓ serological features
- ✓ ‘omic’ molecular signatures

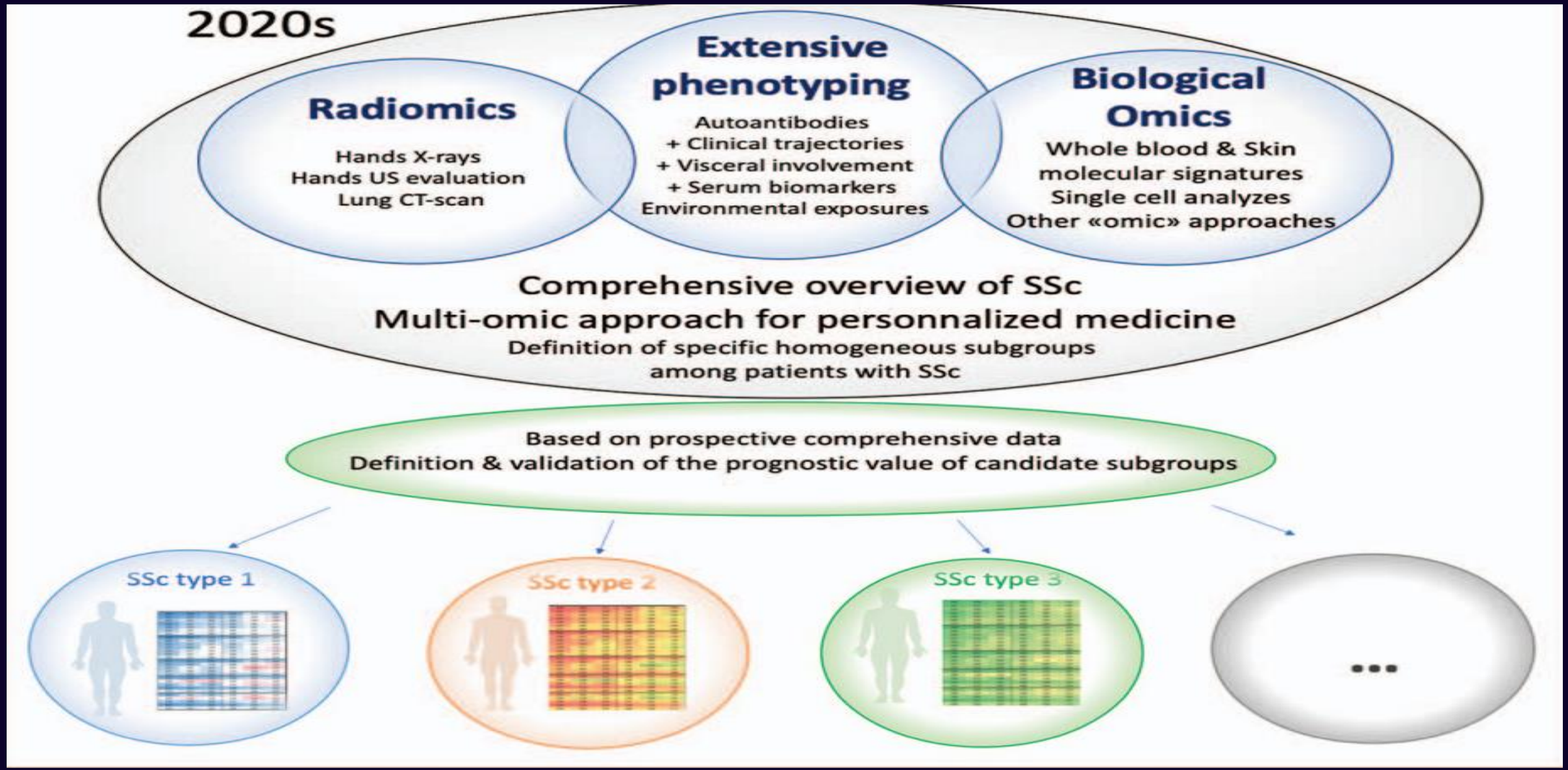
A NOVEL CLASSIFICATION : FUTURE DIRECTIONS

- exposome : a largely neglected field
- silica -associated SSc may be more severe
- Gender
- Skin microbiome dysbiosis : increased inflammatory gene expression

- Separating idiopathic SSc from SSc with known causes
- socioeconomic factors
- capillaroscopy and ultrasound examination



Historical perspectives towards a novel classification for SSc



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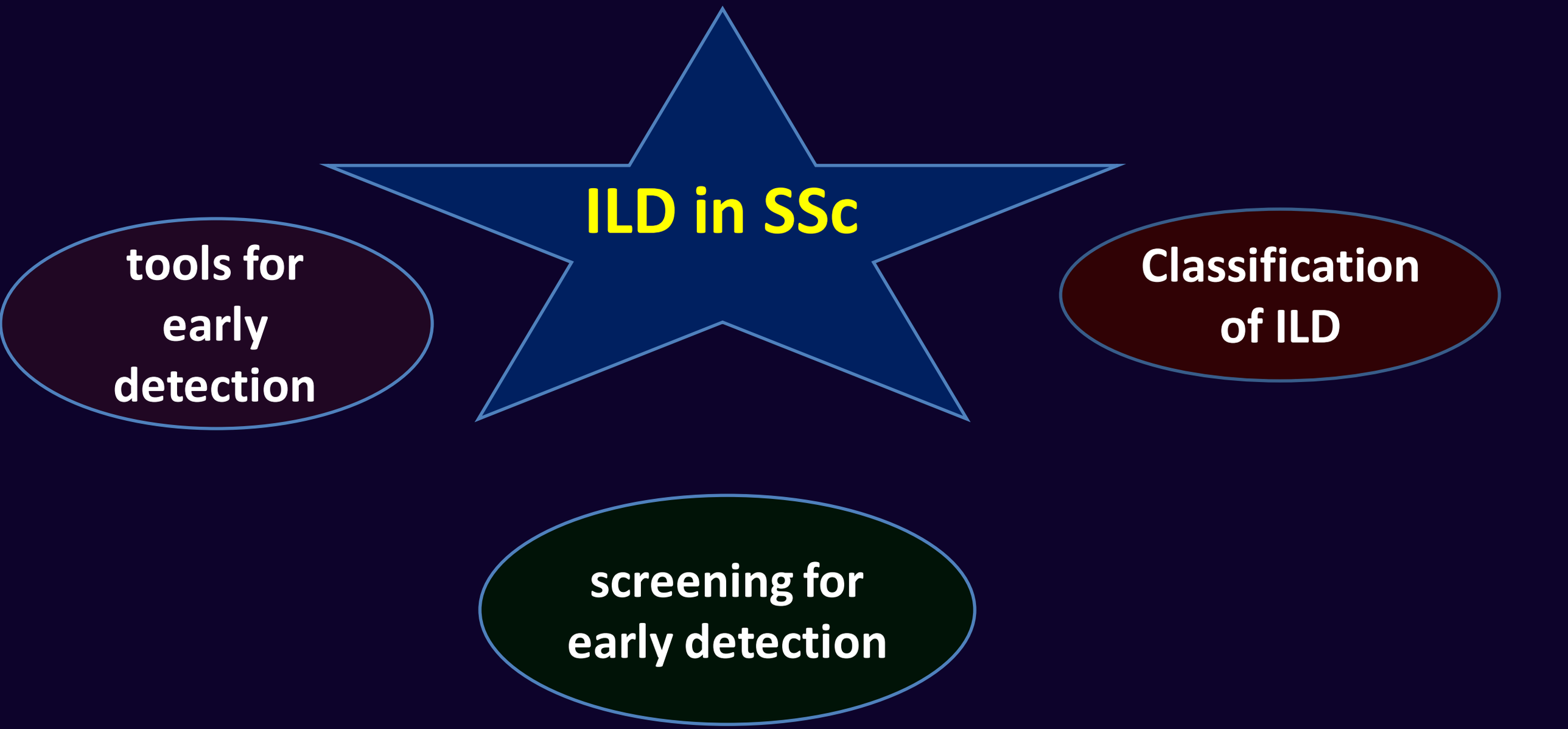

ILD in SSc
tools for early detection
Classification of ILD
screening for early detection

tools for early detection

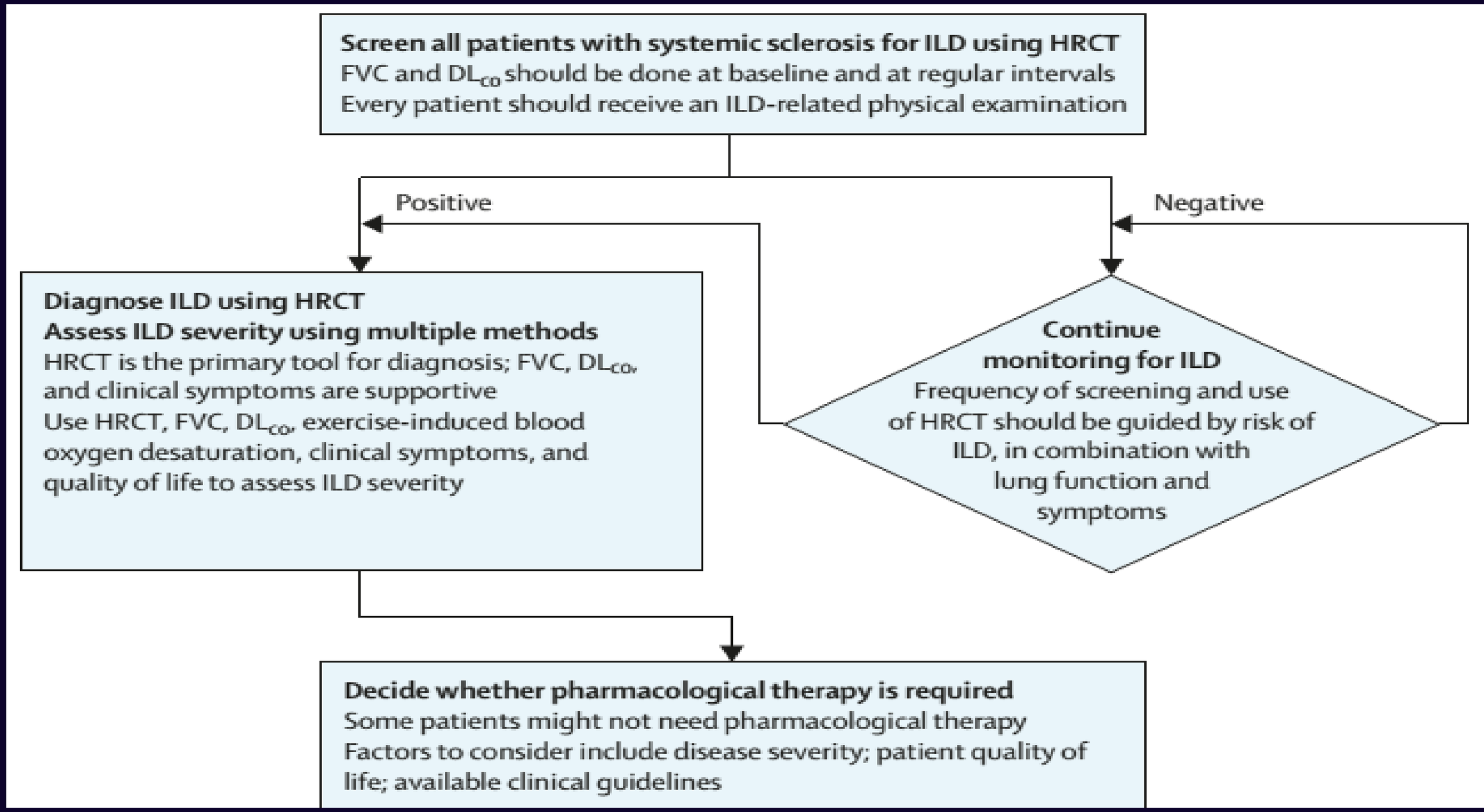
- In the 2013 classification criteria for SSc , the ILD criterion includes imaging abnormalities consistent with ILD or distinct clinical examination findings
- There are no official guidelines on how to diagnose SSc-ILD

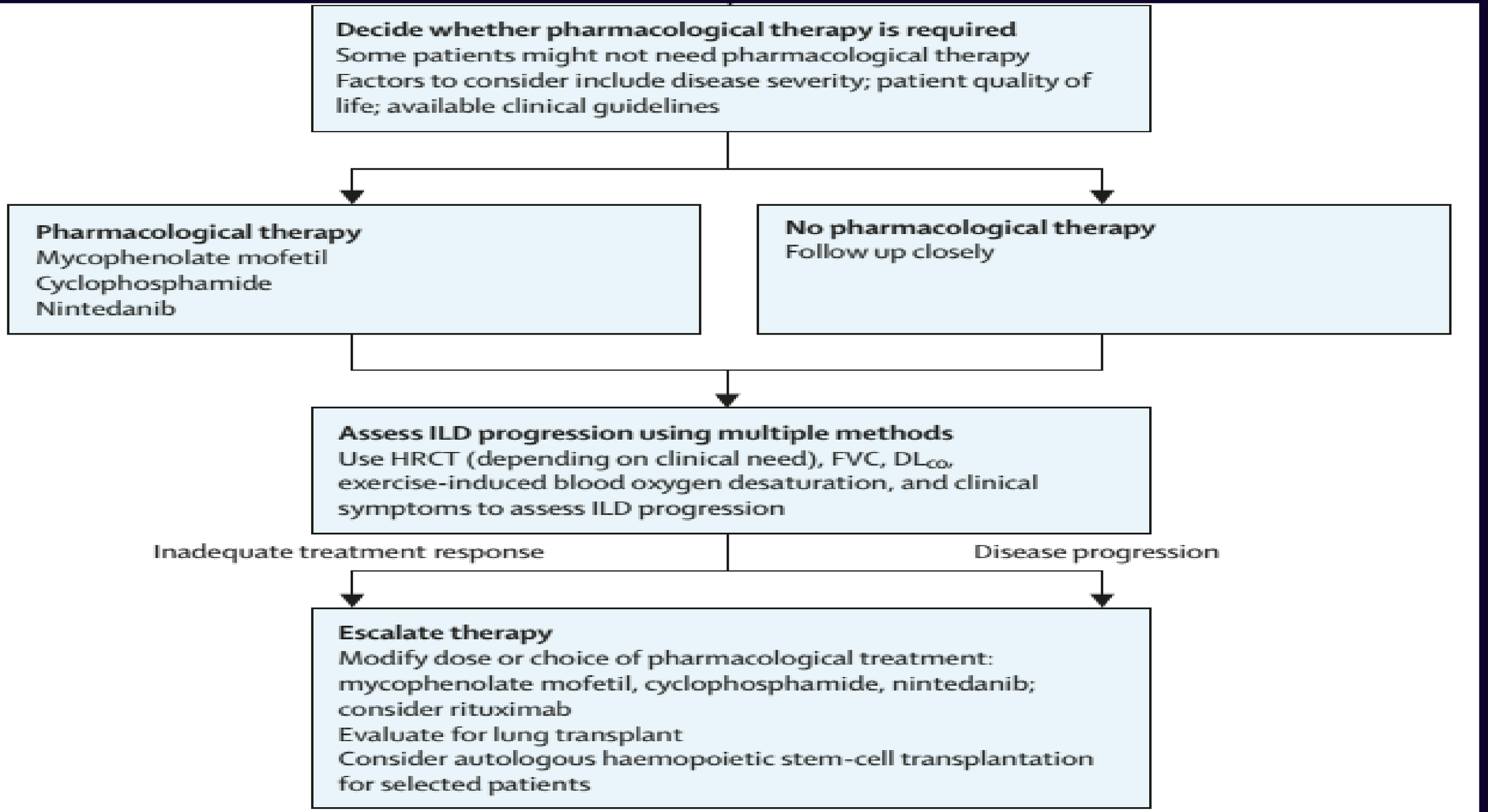
- the classification criteria suggestion to detect and diagnose ILD by imaging is in line with a very recent, **evidence-based European consensus statements (2019) :**

✓ the diagnosis of ILD in SSc is primarily by **HRCT**

✓ supporting tools for early ILD detection in the European consensus statement were **PFTs, patient-reported symptoms,** and the six-min walking distance **(6MWD)**

***Philpot EE, Ashrafzadeh A, Barake R, Bruni C, Carducci P, Carreira PE, Foeldvari I, Fraticelli P, Griffiths B, Hamid AM, Moazedi-Fuerst F. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements.**


Screen all patients with systemic sclerosis for ILD using HRCT
FVC and DLco should be done at baseline and at regular intervals
Every patient should receive an ILD-related physical examination
Positive
Negative
Diagnose ILD using HRCT
Assess ILD severity using multiple methods
HRCT is the primary tool for diagnosis; FVC, DLco, and clinical symptoms are supportive
Use HRCT, FVC, DLco, exercise-induced blood oxygen desaturation, clinical symptoms, and quality of life to assess ILD severity
Continue monitoring for ILD
Frequency of screening and use of HRCT should be guided by risk of ILD, in combination with lung function and symptoms
Decide whether pharmacological therapy is required
Some patients might not need pharmacological therapy
Factors to consider include disease severity; patient quality of life; available clinical guidelines


Decide whether pharmacological therapy is required
Some patients might not need pharmacological therapy
Factors to consider include disease severity; patient quality of life; available clinical guidelines
Pharmacological therapy
Mycophenolate mofetil
Cyclophosphamide
Nintedanib
No pharmacological therapy
Follow up closely
Assess ILD progression using multiple methods
Use HRCT (depending on clinical need), FVC, DL_{CO}, exercise-induced blood oxygen desaturation, and clinical symptoms to assess ILD progression
Inadequate treatment response
Disease progression
Escalate therapy
Modify dose or choice of pharmacological treatment: mycophenolate mofetil, cyclophosphamide, nintedanib; consider rituximab
Evaluate for lung transplant
Consider autologous haemopoietic stem-cell transplantation for selected patients

lung auscultation

not included in **ECS**

PFTs , patient-reported symptoms , 6MWD and other physical performance tests , circulating biomarkers

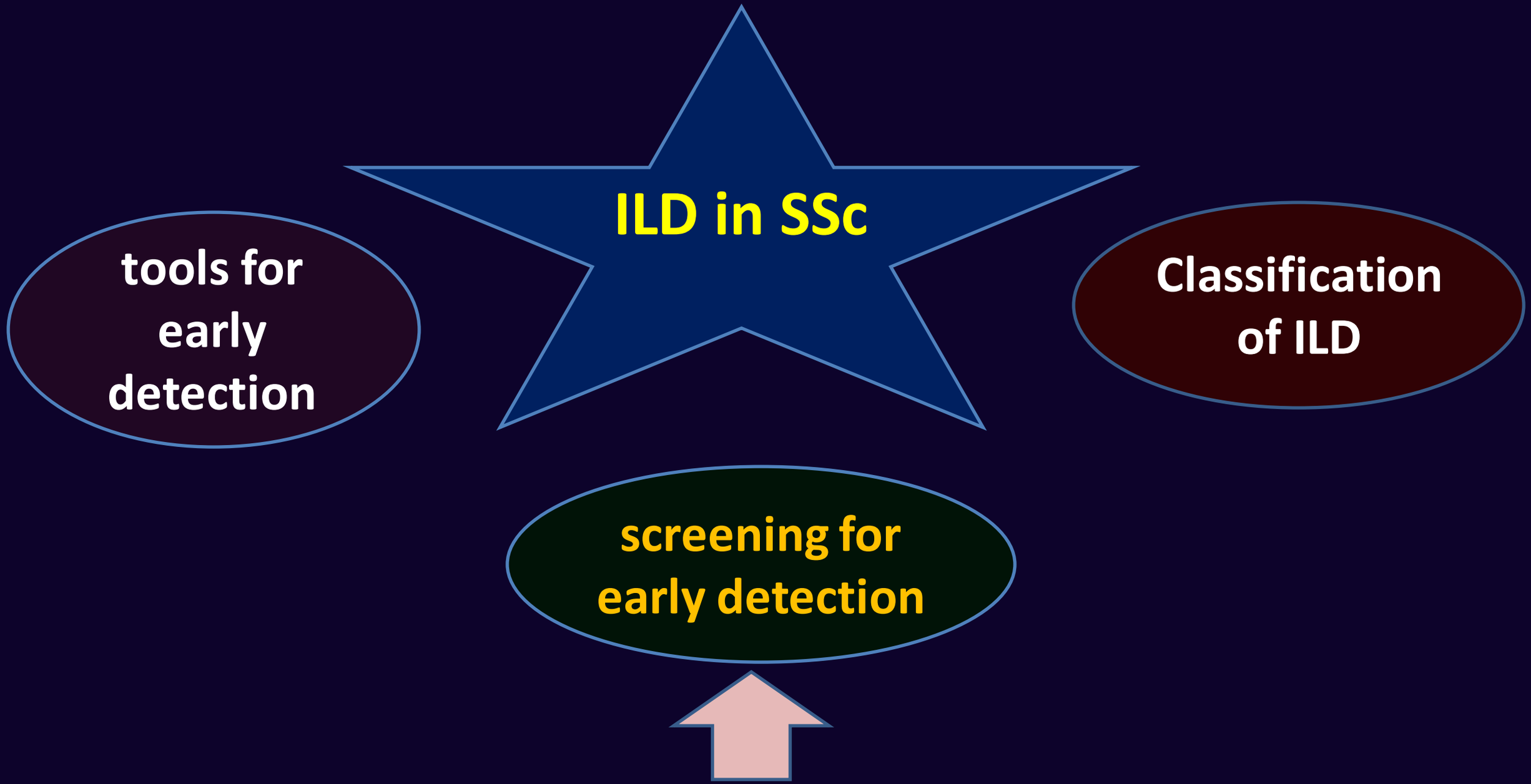
baseline ILD classification and risk management

tools for early detection

LUS

- A recent systematic literature review by the **(OMERACT) Ultrasound Group** about the use of LUS in SSc included 12 studies . there was insufficient evidence to support criterion validity, reliability, and sensitivity to change

- **Although LUS may currently not be appropriate for primary ILD detection in SSc , it may be useful for other purposes**


ILD in SSc
tools for early detection
Classification of ILD
screening for early detection

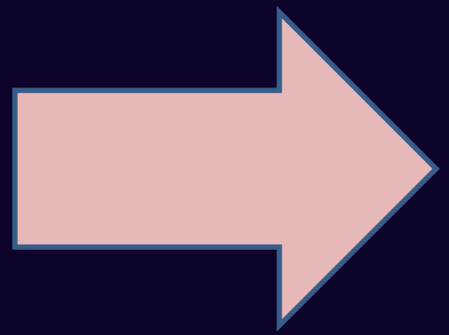
screening for early detection

IL D by HRCT : 50% of all SSc patients

gold standard for detection of ILD

a reasonable cost

an acceptable safety profile



HRCT : primary tool for ILD screening at time of SSc diagnosis

- how and when to repeat ILD screening in patients who do not have lung parenchymal involvement by HRCT at the primary screening?

- A recent review from the Michigan group stated that patients at presumed high risk for ILD development should be offered close follow-up with **PFTs every 4 – 6 months for 3 – 5 years .**

- If a patient develops clinically meaningful decline in FVC or DLCO or new-onset symptoms attributable to ILD, the authors recommend to conduct a new HRCT.

LUS

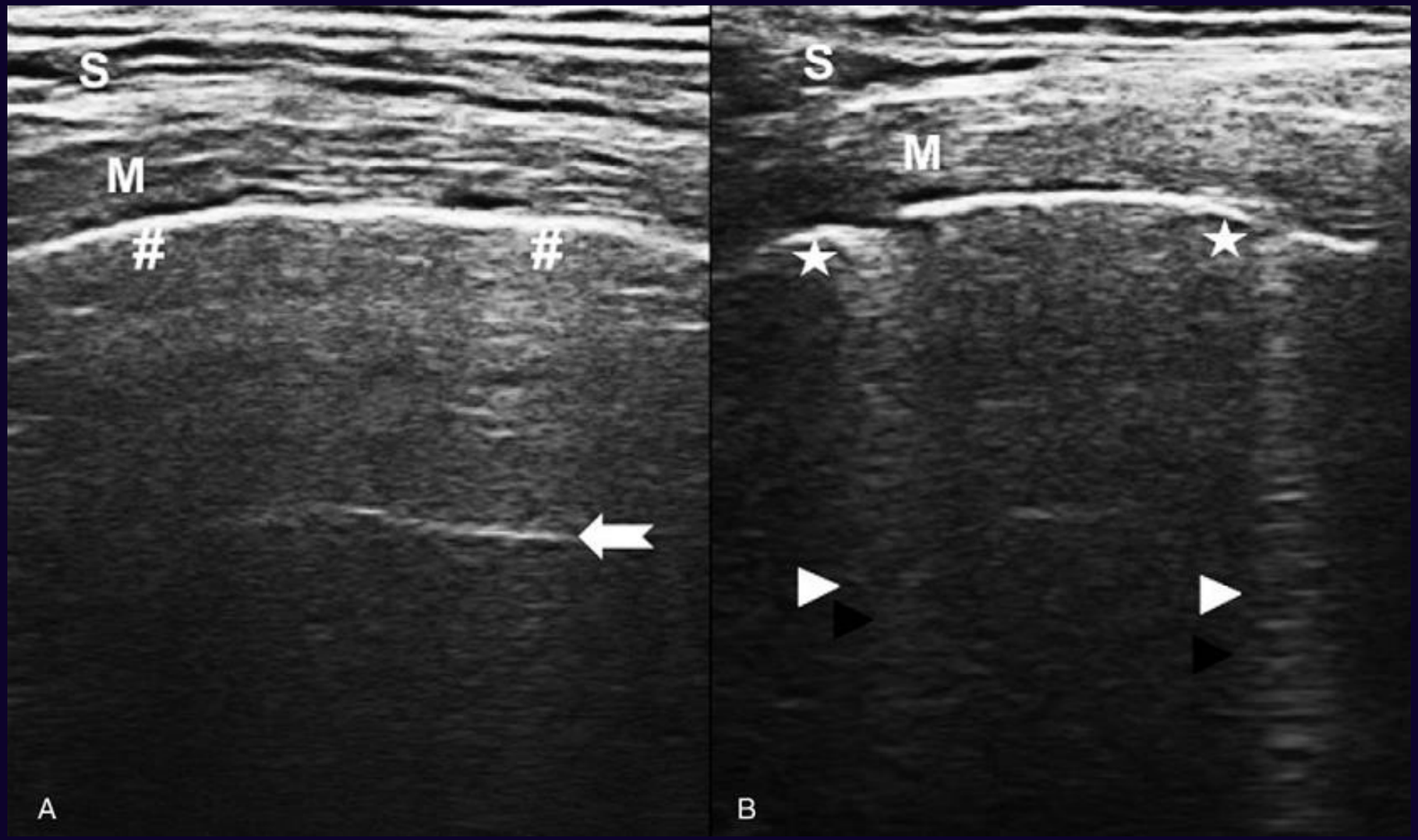
- **Another study (2018) :**

- The US B-lines number and the Warrick score confirmed excellent correlation.
- The detection of 10 B-lines is highly predictive for the HRCT presence of significant SSc-ILD.
- In SSc patients, the **LUS assessment as first imaging tool** may represent an effective model to improve the correct timing of chest HRCT

*Tardella M, Di Carlo M, Carotti M, Filippucci E, Grassi W, Salaffi F. Ultrasound B-lines in the evaluation of interstitial lung disease in patients with systemic sclerosis: cut-off point definition for the presence of significant pulmonary fibrosis. Medicine. 2018 May;97(18).

LUS

- (A) Normal lung with the typical reverberation artifact (line A, arrow); the normal pleural line (#) is regular.
- (B) Pathological lung with the presence of 2 ultrasound B-line (arrowheads), and the loss of A-line; the pathological pleural line shows irregularities (★).M = muscle of chest wall, S =subcutaneous tissues.



*Tardella M, Di Carlo M, Carotti M, Filippucci E, Grassi W, Salaffi F. Ultrasound B-lines in the evaluation of interstitial lung disease in patients with systemic sclerosis: cut-off point definition for the presence of significant pulmonary fibrosis. Medicine. 2018 May;97(18).

Screening for early detection

LUS

- **In on study (2019) :** B-lines were quantified and classified and severity and extent of lung involvement on the HRCT determined in 67 consecutive patients who met the 2013 classification criteria for SSc

➢ **Results :**

- LUS : a sensitivity of 100% and a specificity of 34%.
- analytic relation between the number of B-lines and the presence of ILD on the HRCT

➢ **Conclusions :**

- LUS may be a method to detect abnormal lung findings in a noninvasive manner in patients with SSc. Because of its **high sensitivity** , a low score almost rules out the need for an HRCT.

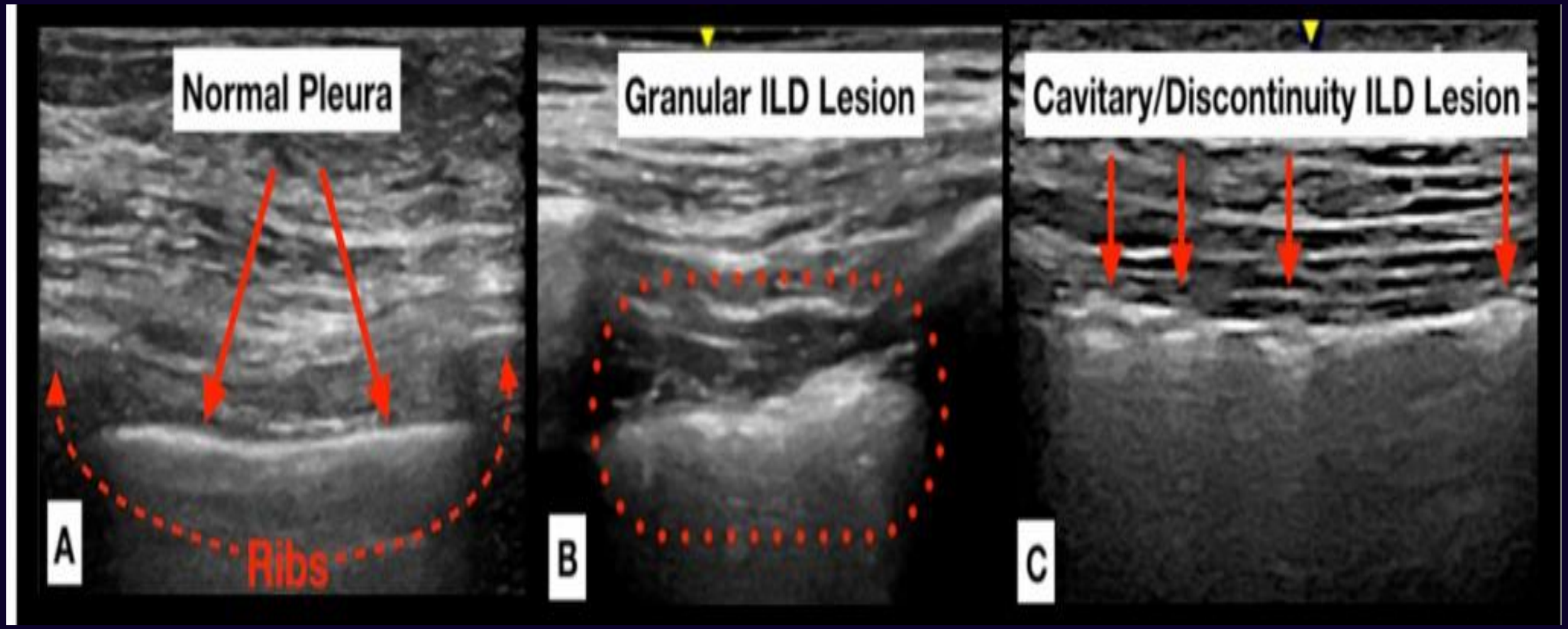
*Hassan RI, Lubertino LI, Barth MA, Quaglia MF, Montoya SF, Kerzberg E, del Carmen Binda M. Lung ultrasound as a screening method for interstitial lung disease in patients with systemic sclerosis. JCR: Journal of Clinical Rheumatology. 2019 Oct 1;25(7):304-7.

LUS

- another study (2019) Focusing on **pleural changes** rather than B lines reported highly promising findings in 20 patients.

- They found that LUS pleural changes identified ILD with 100% sensitivity and 82% specificity compared with HRCT

*Fairchild R, Yang D, Chung M, Sharpless L, Li S, Chung L. Development and Preliminary Validation of a Novel Lung Ultrasound Interpretation Criteria for the Detection of Interstitial Lung Disease in Patients with Systemic Sclerosis. InARTHRITIS & RHEUMATOLOGY 2019 Oct 1 (Vol. 71). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY.



*Fairchild R, Yang D, Chung M, Sharpless L, Li S, Chung L. Development and Preliminary Validation of a Novel Lung Ultrasound Interpretation Criteria for the Detection of Interstitial Lung Disease in Patients with Systemic Sclerosis. InARTHRITIS & RHEUMATOLOGY 2019 Oct 1 (Vol. 71). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY.

screening for early detection

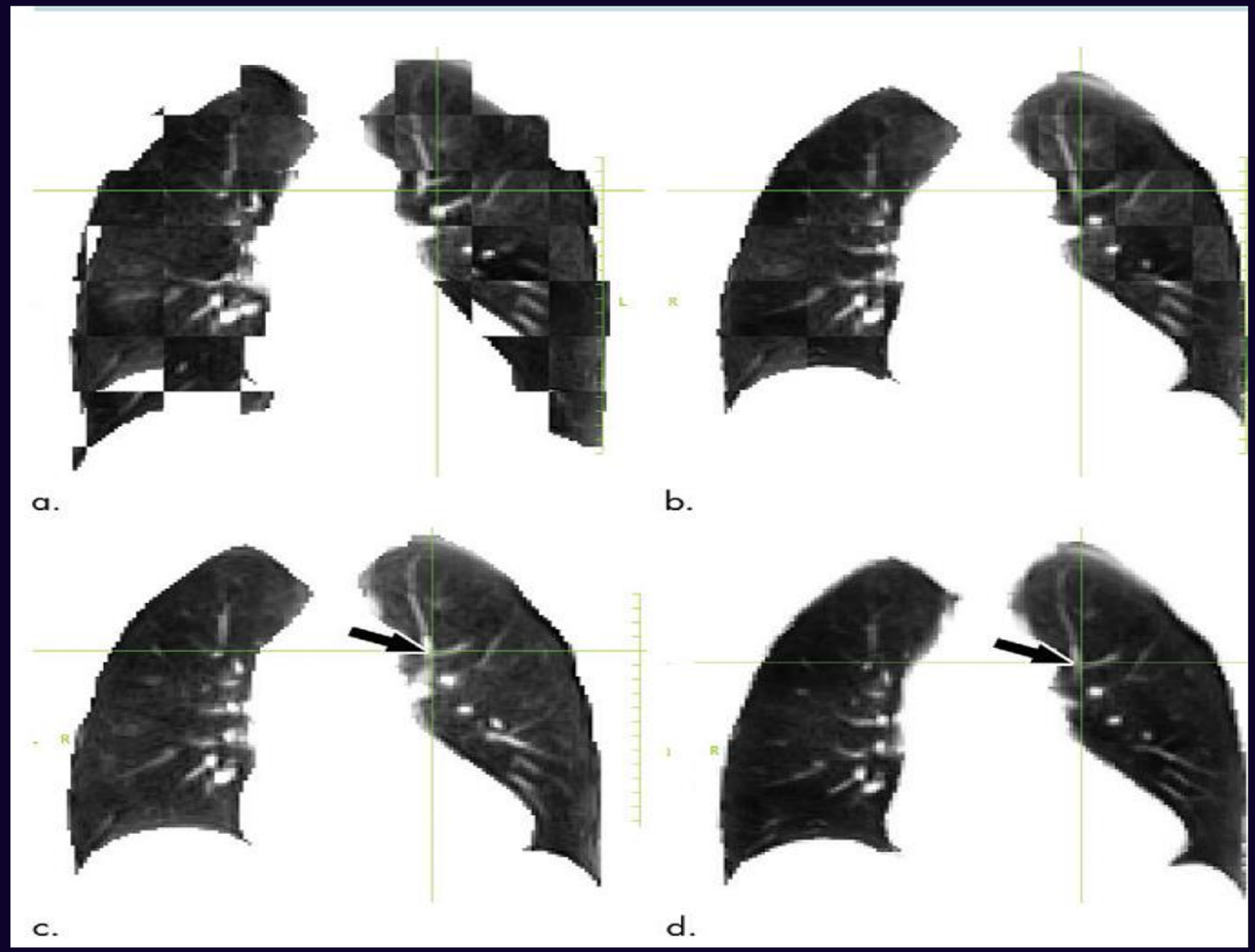
- LUS seems therefore to be a **promising tool for screening of ILD**, especially in patients who initially had no signs of ILD on the primary HRCT screening.

MRI

- a recent study (2019) assessed the role of MRI in the assessment of ILD in SSc

  (**inspiratory-to-expiratory elastic registration**)

- They found assessing 16 patients and 11 healthy controls that the **sensitivity and specificity of MRI for presence of lung fibrosis at HRCT were 86 and 75%**



- Images show example of inspiratory-to-expiratory elastic registration of coronal lung MRI in a healthy 24-year-old man using algorithm. **(a)** Checkboard image before elastic registration shows differences between source inspiratory image and target expiratory image. **(b)** Checkboard image after elastic registration. **(c)** Target expiratory image. **(d)** Inspiratory image after elastic registration. Arrows on vessel bifurcation in **c** and **d** show correct match between two images

*Chassagnon G, Martin C, Marini R, Vakalopolou M, Régent A, Mouthon L, Paragios N, Revel MP. Use of elastic registration in pulmonary MRI for the assessment of pulmonary fibrosis in patients with systemic sclerosis. Radiology. 2019 May;291(2):487-92.

tools for early detection

Classification of ILD

screening for early detection

Classification of ILD

- For ILD ,the most widely used system is the American Thoracic Society classification, which groups SSc-ILD among the **CTD-associated ILDs**
- Other generic ILD systems classify ILD by lung tissue histology or HRCT-imaging patterns
- By HRCT, the most prevalent ILD pattern in SSc : NSIP
- ILD pattern by HRCT : is not very frequently used for classification of SSc-ILD
- there is a tradition of using disease -specific markers to help classify ILD, but there is also interest in classification by **imaging characteristics** other than ILD patterns, and by **circulating biomarkers**

Classification of ILD

- ✓ Stratification of ILD in patients with systemic sclerosis severity grading
- ✓ Stratification of ILD in patients with systemic sclerosis by general systemic sclerosis markers
- ✓ Stratification of ILD in patients with systemic sclerosis by time dependent observations

Stratification of ILD : severity grading

- previous studies have applied **composite grading systems** based on various combinations of **PFT** impairment, extent of lung fibrosis by **HRCT** and presence or absence of respiratory **symptoms.**

- With regard to imaging alone, there are several studies indicating that the **extent of fibrosis on HRCT** is an important outcome measure

- **In a Norwegian SSc cohort (2019) :** At baseline, 50% of the subjects with SSc had ILD by HRCT and 46% displayed pulmonary function declines consistent with ILD progression.

- Mortality correlated with extent of lung fibrosis
- SMR (standardized mortality ratios) was inversely related to baseline FVC% and increased at all FVC levels below 100%.

- In patients with **normal-range baseline FVC ,** the 5- and 10-year survival rates correlated with presence or absence of lung fibrosis.

- **Conclusions:** The mere presence of ILD at baseline appears to affect outcome in SSc, suggesting that all patients with SSc should undergo a **baseline PFT** and **lung HRCT screening** to diagnose ILD early and tailor further management.

*Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, Garen T, Salberg A, Brunborg C, Midtvedt Ø, Lund MB. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. American journal of respiratory and critical care medicine. 2019 Nov 15;200(10):1258-66.

Stratification of ILD : severity grading

- At the time of ILD diagnosis, **respiratory symptoms** vary widely between patients
- The **presence of cough and dyspnea** aids severity assessment but should never be considered in isolation.
- Importantly, **absence of symptoms** should not automatically lead to consider a patient as having no or mild ILD or refrain from initiating treatment

Stratification of ILD : general SSc markers

- **Skin involvement :** dcSSc and the dcSSc-associated antibody anti-Scl70 associate with severe ILD

- there are severe ILD cases among the lcSSc patients

- lacking data on whether skin and lung progression occur in parallel

- **Assessment of mRSS** at time of SSc diagnosis and on a regular basis at follow-up visits

Stratification of ILD : time dependent observations

- The **disease course** of ILD in SSc : varies widely from stable disease to severe and rapidly progressing
- necessity to classify SSc-ILD patients for future ILD progression at time of diagnosis

Stratification of ILD : predicted risk for ILD progression

- Ideally , we should be able to provide **targeted therapies** already from time of diagnosis in SSc patients at high risk for progressive ILD.
- To reach this goal , we will need robust **prediction algorithms** allowing for early identification of SSc patients at high risk of ILD progress ion.

Stratification of ILD : predicted risk for ILD progression

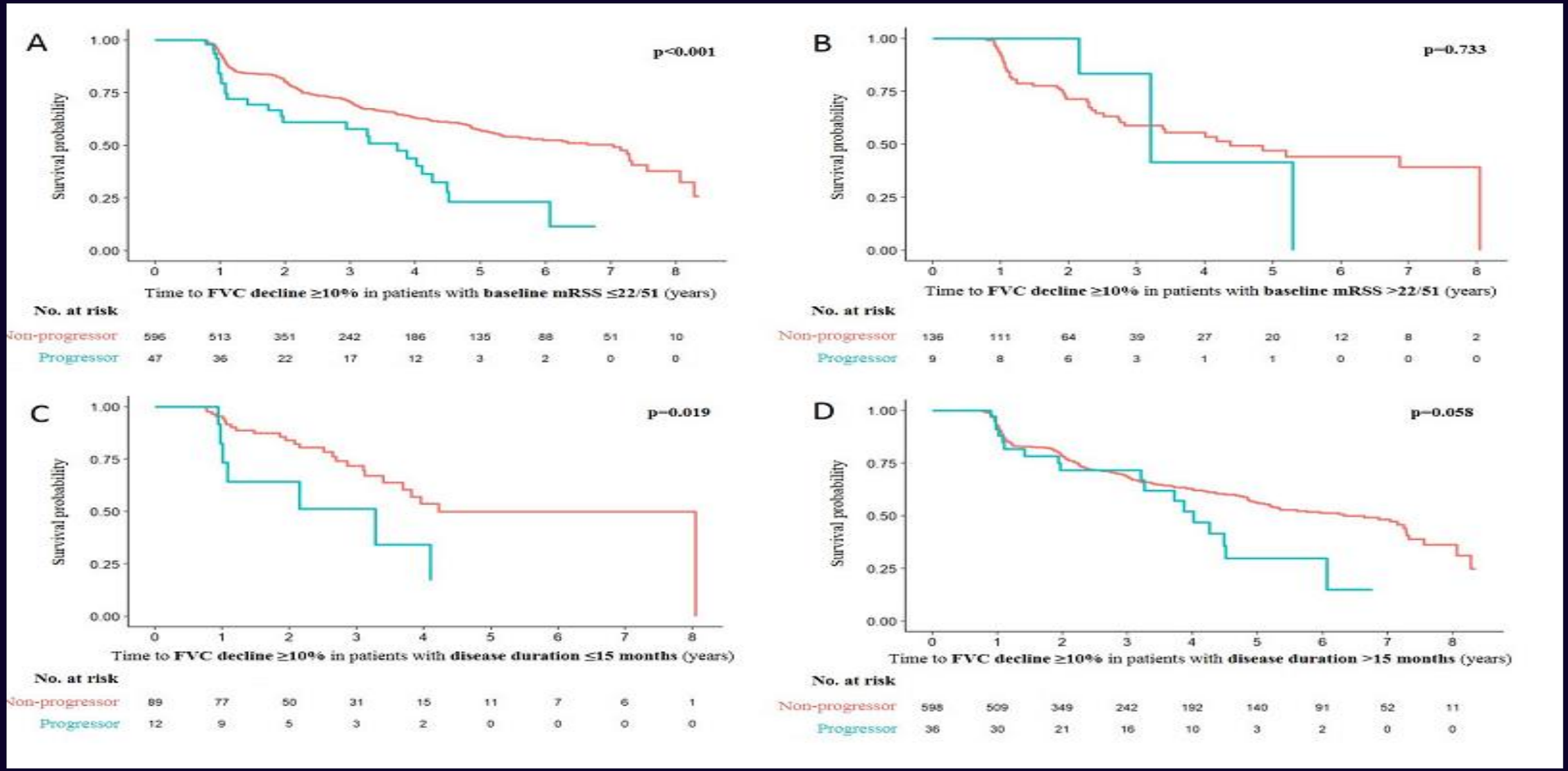
- The extent of skin involvement measure d by the **mRSS** has recently been shown to be a strong prognostic marker for progressive ILD in dcSSc
- Additionally , **progressive skin fibrosis within one year** was associated with decline in lung function and worse survival in dcSSc during follow-up

- **EUSTAR cohort (2019) :** To determine whether progressive skin fibrosis is associated with visceral organ progression and mortality during follow-up in patients with (dcssc).

- **results** Of 1021 included patients, 78 (7.6%) had progressive skin fibrosis (skin progressors). Median follow-up was 3.4 years. survival analyses indicated that **skin progressors had a significantly higher probability of FVC decline ≥10% and all-cause death** than non-progressors . These significant associations were also found in subgroup analyses of patients with either low baseline mRss (≤22/51) or short disease duration (≤15 months).

- **Conclusions :** Progressive skin fibrosis within 1 year is associated with decline in lung function and worse survival in dcssc during follow-up . These results confirm mRss as a surrogate marker in dcss.

*Wu W, Jordan S, Graf N, de Oliveira Pena J, Curram J, Allanore Y, Matucci-Cerinic M, Pope JE, Denton CP, Khanna D, Distler O. Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European Scleroderma Trials and Research (EUSTAR) cohort. Annals of the rheumatic diseases. 2019 May 1;78(5):648-56.



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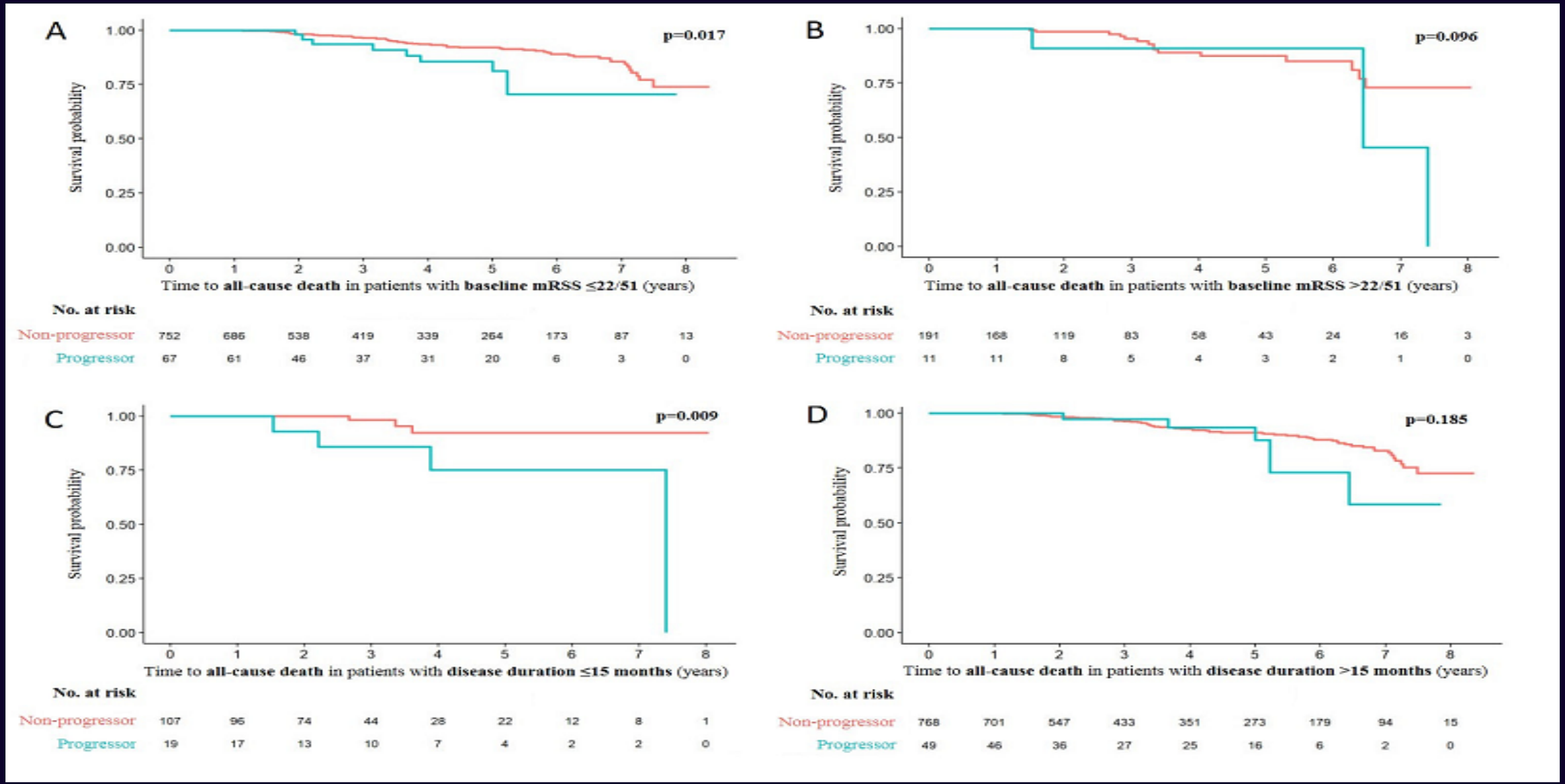

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Mrss

a helpful tool to classify ILD
early for treatment initiation
and choices

Stratification of ILD : predicted risk for ILD progression

- Previous studies have shown that **baseline PFTs** predict further lung function decline.

- SLS study : decline of FVC in the placebo group was greater during follow-up in patients with a **more severe ILD on baseline HRCT** .

- However ,In a very recent study assessing 58 SSc-ILD patients , less severe ILD at baseline were associated with a faster progression of IL D over time

- **Conclusion :** Male sex, dcSSc , anti-topoisomerase 1 antibodies and a less severe ILD at baseline were associated with a faster progression of ILD over time. Evolution of DLCO significantly correlated with change in ILD extent on HRCT scan.

***Forestier A, Le Gouellec N, Béhal H, Kramer G, Perez T, Sobanski V, Dubois SM, Lambert M, Hatron PY, Hachulla E, Duhamel A. nEvolution of high-resolution CT-scan in systemic sclerosis-associated interstitial lung disease: description and prognosis factors. InSeminars in Arthritis and Rheumatism 2020 Feb 29. WB Saunders.**

Stratification of ILD : predicted risk for ILD progression

- there is some progress on potential prediction by imaging parameters, with new data emerging on SSc ILD assessment by **quantitative computed tomography algorithms** .

- **2020 Study :** aim is to characterize and quantify SSc-ILD by using Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER)

- this study classified ILD at baseline by (**CALIPER**) in 66 SSc patients and found **correlation between ground glass by CALIPER and DLCO**, but not FVC.

- The results of this study show that CALIPER is useful not only for **quantifying lung damage** but also for **assessing worsening PFTs**, but larger studies are needed to confirm these preliminary data

*Ferrazza AM, Gigante A, Gasperini ML, Ammendola RM, Paone G, Carbone I, Rosato E. Assessment of interstitial lung disease in systemic sclerosis using the quantitative CT algorithm CALIPER. Clinical Rheumatology. 2020 Jan 15:1-6.

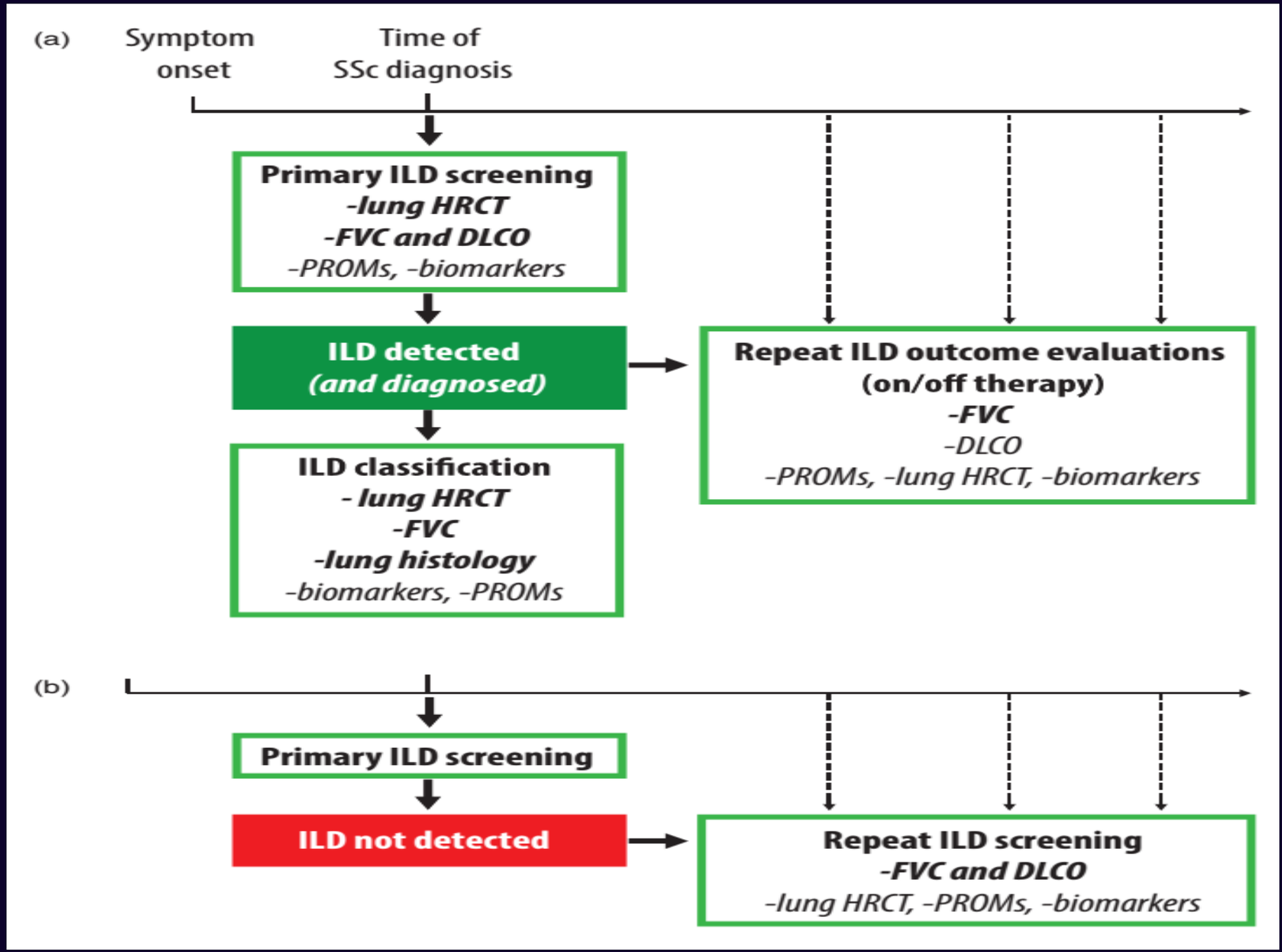
Stratification of ILD : predicted risk for ILD progression

- **6MWD :** to identify progressive patients early
- One study (2018), which included patients with mild ILD on HRCT, showed that arterial O2 desaturation to less than 94% after 6MWD and a history of arthritis was prognostic for ILD progression after one year.
- Therefore, **desaturation on 6MWD** can help to classify progressive ILD already at time of diagnosis

Stratification of ILD : predicted risk for ILD progression

➢ **circulating biomarkers :**

- Although of potential in the future, they are to date not validated for use in daily clinical practice for the management of SSc-ILD
- CCL-2 , CCL-18, Surfactant protein D,
- Interleukin 31 and squamous cell carcinoma antigen-Immunglobulin M


(a)
Symptom onset
Time of SSc diagnosis
Primary ILD screening
-lung HRCT
-FVC and DLCO
-PROMs, -biomarkers
ILD detected
(and diagnosed)
ILD classification
- lung HRCT
-FVC
-lung histology
-biomarkers, -PROMs
Repeat ILD outcome evaluations
(on/off therapy)
-FVC
-DLCO
-PROMs, -lung HRCT, -biomarkers
(b)
Primary ILD screening
ILD not detected
Repeat ILD screening
-FVC and DLCO
-lung HRCT, -PROMs, -biomarkers

right treatment to the right patient as early as possible