Systemic Sclerosis Associated Interstitial Lung Disease: A Conceptual Framework for Subclinical, Clinical, and Progressive Disease

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Abstract

Objectives:
Establish a framework by which experts define disease subsets in systemic sclerosis associated interstitial lung disease (SSc-ILD).

Methods:
A conceptual framework for subclinical, clinical, and progressive ILD was provided to eighty-three experts, asking them to use the framework and classify actual SSc-ILD patients. Each patient profile was designed to be classified by at least 4 experts in terms of severity and risk of progression at baseline; progression was based on 1-year follow-up data. A consensus was reached if >75% of experts agreed. Experts provided information on which items were important in determining classification.

Results:
Forty-four experts (53%) completed the survey. Consensus was achieved on the dimensions of severity (75%, 60 of 80 profiles), risk of progression (71%, 57 of 80 profiles) and progressive ILD (60%, 24 of 40 profiles). For profiles achieving consensus, most were classified as clinical ILD (92%), low risk (54%), and stable (71%). Severity and disease progression overlapped in terms of framework items that were most influential in classifying patients (forced vital capacity, extent of lung involvement on high resolution chest CT (HRCT)); risk of progression was influenced primarily by disease duration.

Conclusions:
Using our proposed conceptual framework, international experts were able to achieve a consensus on classifying SSc-ILD patients along the dimensions of disease severity, risk of progression, and progression over time. Experts rely on similar items when classifying disease severity and progression: a combination of spirometry and gas exchange and quantitative HRCT.
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Key words:
Systemic Sclerosis Interstitial Lung Disease, Connective Tissue Disease Interstitial Lung Disease, Systemic Sclerosis Associated Interstitial Lung Disease subsets

Abbreviations:

ANA Antinuclear Antibody
BDI/TDI Mahler Dyspnea and Transition Index
CTD-ILD Connective tissue disease associated interstitial lung disease
DLco Diffusion Capacity of Carbon Monoxide
FVC Forced Vital Capacity
HRCT High resolution computed tomography
LCQ Leicester Cough Questionnaire
mRSS Modified Rodnan Skin Score
PRO Patient-reported outcome
PtGa Patient Global Assessment
SGRQ St. George’s Respiratory Questionnaire
SSc Systemic sclerosis
SSc-ILD Systemic sclerosis associated interstitial lung disease
TCZ Tocilizumab

Key Messages:

- We created a rubric characterizing systemic sclerosis associated interstitial lung disease (SSc-ILD) along disease severity, risk of progression, and progression.
- Experts used this framework to classify real patients in terms of these dimensions.
- This framework is a foundation for future classification criteria of SSc-ILD subsets.
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INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease characterized by the presence of serological autoantibodies, vascular dysfunction, and progressive fibrosis of skin and internal organs\(^1\). Systemic sclerosis-associated interstitial lung disease (SSc-ILD) has a significant impact on quality of life and healthcare costs\(^2\)–\(^5\), and portends the highest risk for mortality of all potential organ involvement\(^6\)–\(^7\). More than 50% of SSc patients in North America have SSc-ILD\(^8\), however the disease impact is heterogeneous, varying in terms of severity and progression\(^9\). This heterogeneity of ILD has been well-described, with identified SSc-ILD subsets, or subpopulations that share a similar clinical trajectory\(^10\)–\(^11\). With the advent of two FDA-approved medications for the treatment of SSc-ILD\(^12\)–\(^13\), there is an increasing need to develop consensus definitions of the varying SSc-ILD subsets for appropriate patient stratification\(^14\)–\(^16\).

A conceptual framework is a cognitive schema that may be used to characterize SSc-ILD subsets along the dimensions of severity, risk of progression, and progression, and highlight the important variables used to delineate these subsets. A shared conceptual framework forms the basis for classification criteria, which are used for cohort enrollment in clinical studies, and serve to identify those patients most likely to benefit from treatment in clinical trials. In terms of treatment and the development of therapy algorithms, decisions to initiate or advance treatment are often based on a shared understanding of severity, likelihood of progression, and progressive disease. Thus, the objectives of this research effort were two-fold: 1) to build a conceptual framework that allows experts to classify severity, risk of progression, and progressive disease in SSc-ILD, and 2) observe how well the international experts agree with one another when using that framework and to identify those items most important in determining their classification.

METHODS:

Proposed Conceptual Framework and Iterative Revisions:
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Thirty-nine experts (disciplines including pulmonology medicine (n=19), rheumatology (n=13), and thoracic radiology (n=7)) evaluated a proposed conceptual framework delineating subclinical, clinical, and progressive ILD. Experts were invited to propose modifications and revisions; details on this process are available in the Supplementary Material, available at Rheumatology online. An updated framework was disseminated back to the working group for final feedback and subsequently presented at a national meeting17.

Development of Patient Profiles:

Eighty patient profiles were developed from participants in the Scleroderma Lung Study-II18 (n=53) and ILD patients seen at the University of Michigan Scleroderma Program (n=27). All patients included in this study met 2013 American College of Rheumatology/European League Against Rheumatism Criteria for Systemic Sclerosis (N=80). Experts in rheumatology, pulmonary medicine, radiology, and selected members of the Outcomes Measures in Rheumatology (OMERACT) CTD-ILD Working Group14 provided key domains to be included in profiles.

Profiles were formatted to create baseline patient profiles and baseline with follow-up information over the course of 1 year (Supplementary Figure S1, available at Rheumatology online). Information on cardiopulmonary exercise testing (e.g., 6-minute walking distance [6MWD]) and presence or absence of pulmonary hypertension was not included in the patient profiles due to a lack of available data (these data were not included uniformly in the 2 cohorts). Disease progression, as it is defined here, refers to progression of SSc-ILD, not other manifestations of the disease.

Expert Classification:
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We identified 83 international experts (pulmonologists, rheumatologists, and thoracic radiologists). Surveys were sent to the experts via Qualtrics Online Survey tool (www.qualtrics.com); each survey took an estimate of 30 minutes to complete.

The data generated from this study came from experts who volunteered to participate, after providing electronic consent on the survey provided to them. Each participant was informed and aware of his/her options to participate or decline participation. None of the data generated in the study came from patient participation.

The survey contained an introduction with a rationale for their participation, the conceptual framework for SSc-ILD subsets, and a collection of five baseline patient profiles and five baseline with follow-up profiles. Each baseline profile was classified by the expert on two dimensions: disease severity and risk of progression; each profile with follow-up was classified on one dimension: progression. For baseline profiles, the expert faced a forced choice for each profile with three options for severity (subclinical ILD, clinical ILD, and unable to determine) and risk of progression (low risk, high risk, and unable to determine). For follow-up profiles, the expert chose between four options for progression (stable ILD, progressive ILD, improved ILD, or unable to determine). After classification, experts were required to identify factors influential in her/his classification decision, with a rank order preference with the top rank being the most influential, as previously done for SSc response criteria\textsuperscript{19}.

Experts were randomly selected to one of eight groups, where a minimum of four experts and up to ten experts received a set of ten profiles (five baseline and five baseline with follow-up surveys). The survey distribution discontinued when 80 profiles were fully adjudicated. A set was considered fully adjudicated when a minimum of four experts assessed the same set of profiles, with at least one expert being a rheumatologist and one being a pulmonologist. Consensus was defined as a concordance of $\geq 75\%$ on a classification (e.g., 3 of 4 experts classified the profile the same way).
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Agreement within and between disciplines (e.g., pulmonologists and rheumatologists) was determined by calculating the kappa coefficient for inter-rater reliability. Patient profiles were sent out in groups and rated by different sets of pulmonologists and rheumatologists. To calculate the kappa statistics among pulmonologists and the corresponding confidence intervals we used the following method. We first calculated the mean of pair-wise Cohen’s kappa statistics between all possible pairs of pulmonologists in each group. For example, for a group of profiles that was rated by three pulmonologists, we can derive the mean kappa statistics based on three pair-wise kappa statistics. We then calculated agreement among pulmonologists as the average of mean kappa among all groups. We used a bootstrap method to calculate the 95% confidence interval for the above kappa statistics. Kappa results being interpreted as follows: 0.01–0.20 as none, 0.21–0.39 minimal, 0.40–0.59 as weak, 0.60–0.79 as moderate, and 0.80–0.90 as strong, and above 0.91 as almost perfect agreement.

Chi-square statistic was used for comparing distribution of categorical variables. P-values < 0.05 were considered to be significant for all tests.

RESULTS:

Proposed Conceptual Framework:

A preliminary proposed conceptual framework (Supplementary Table S1, available at Rheumatology online) was created after careful review of the existing literature. Our working definitions were based on literature focusing on disease severity, items that prognosticate outcome, assessment of disease impact, and treatment recommendations.

Iteratively Revised Conceptual Framework:

Table 1 is an update of Supplementary Table S1 and incorporates the proposed set of working definitions based on experts’ feedback. Four key concepts are illustrated in this revised conceptual framework. First, subclinical ILD was revised to include only asymptomatic patients...
Subsets of Systemic Sclerosis Associated Interstitial Lung Disease regarding ILD; several experts clarified that subclinical ILD should be defined by the absence of symptoms attributable to ILD and that absence of symptoms is not synonymous with absence of disease. All experts agreed that detecting respiratory symptoms in patients with ILD is challenging for several reasons (e.g., diminished exercise capacity due to advancing cutaneous, musculoskeletal, or pulmonary disease precluding effort that elicits dyspnea), as is differentiating dyspnea (e.g., secondary to ILD vs. pulmonary hypertension, or both). Second, in the context of a defined connective tissue disease, such as SSc, the radiographic changes seen in SSc patients, even if asymptomatic, are not included in the definition of interstitial lung abnormalities (ILAs), as agreed by a recently published expert statement. Third, experts commented that management of the disease should not be yoked to the SSc-ILD subset. In our original conception, subclinical ILD did not require treatment, clinical ILD generally did require treatment, and progressive ILD required change, escalation, or addition of new therapies. The rationale for removing language about treatment was that this is a matter for empiric discovery; the classification of patients should not be determined by the behavior of the treating physician. As an example, the recently completed phase III trial of tocilizumab (TCZ) shows a beneficial effect in a subset of patients who may have been characterized as subclinical ILD; in our original conception, this population would have fallen outside the scope of clinical ILD, not treated, and would not have benefited from treatment. Finally, progression should not be seen as a subset separate from subclinical or clinical ILD, but rather a property of either subset. In the original conception, progressive ILD was described as a state of advancing fibrotic disease on HRCT with escalation of respiratory symptoms and/or decline on serial lung physiology, gas exchange, or both. In the revised version advancing symptoms, declining lung physiology, and increased extent of ILD on HRCT marks the state of progression in either subclinical or clinical ILD. The critical revision here centers on recognizing that progressive SSc-ILD should be contextualized: a subclinical ILD patient with progression may not have the same disease mechanism or expected response to treatment as a clinical ILD patient with progression.
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Expert Classification:

Forty-four of 83 (53%) of invited experts from 12 countries completed the survey, representing the following disciplines: rheumatology n=26, pulmonary medicine n=16, and thoracic radiology n=2 (Supplementary Table S2, available at Rheumatology online).

A majority of profiles achieved consensus along the three dimensions. The highest degrees of concordance were seen in severity (75%, or 60 of 80 baseline profiles) and risk of progression (71%, or 57 of 80 baseline profiles). Fewer profiles reached consensus for progression (60%, or 24 of 40 follow-up profiles) (Table 2). For each dimension, the majority subsets achieving consensus were as follows: Severity-clinical ILD (92%, or 55 of 60), Risk of progression-low risk of progression (54%, or 31 of 57), and Progression-stable (71%, or 17 of 24 follow-up profiles).

Classification agreement between the two most common disciplines (e.g., pulmonology-rheumatology) did not differ in terms of the kappa statistic assessing inter-rater assessment for each of the three dimensions (Table 3). Agreement between pulmonologists and rheumatologists were not found to be different from the agreement within each discipline either. Kappa reported for severity was none whereas for the risk of progression and progression were generally weak or moderate.

For those profiles achieving consensus and only assessing the relationship between two disciplines (e.g., radiology was excluded due to the low representation in participation), a chi-squared analysis assessed the proportion of each domain’s outcomes (e.g., clinical ILD vs. subclinical ILD) by the discipline (e.g., pulmonologist and rheumatologist), and did not show statistically disproportionate disagreement for each dimension (Table 3).

Table 4 reports the most frequently cited single item that experts used to influence their classification, as determined by the first item selected by the expert, representing their top
choice in diagnostic importance. These data show that the items reported by experts were most influential in their classification for severity of ILD (in order of top ranked items) were FVC, HRCT quantitative total lung involvement (sum percentage of ground glass opacities, fibrotic reticulations, and honeycombing), dyspnea index (BDI/TDI), and DLCO. For progression, the top ranked items included FVC, HRCT total lung involvement, total lung fibrosis on HRCT, dyspnea index, and DLCO. The highest ranked item used to assess risk of progression classification was a disease factor, specifically disease duration followed by FVC, HRCT total lung involvement, and scleroderma-specific autoantibodies.

**DISCUSSION and INTERPRETATION:**

To our knowledge, this is the first collaborative effort to establish a conceptual framework for SSc-ILD subsets. We created a literature-based, expert-informed rubric that characterizes SSc-ILD along three dimensions: disease severity, risk of progression, and progression over time. This framework 1) was tested by having experts classify real-world patient profiles, 2) reached agreement for all three dimensions, having a majority of patient profiles achieving consensus (>75% concordance with other experts), and 3) helped identify which items are most important in adjudicating between SSc-ILD subsets. Importantly, the framework does not include any specific values or cut-points in the definition of each subset. The goal of this work was to provide an inventory of clinical information necessary and general guidelines for implementation, to lead to a classification scheme along different dimensions. The result of this body of work is fundamental to the future development of classification criteria of SSc-ILD subsets and may provide a platform to expand to other fibrotic ILDs.

A majority of experts reached consensus on severity (75% of experts) and risk of progressive disease (71% of experts); this may reflect experts’ familiarity with the basis of the framework, the extensive literature focusing on disease severity (e.g., epidemiologic data, expert opinion on
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determining which patients should receive treatment, inclusion criteria for SSc-ILD clinical trials) and risk of progression (e.g., identifying prognostic items that identify those with a concerning clinical trajectory). Kappa statistics was poor for the severity classification (Table 3). Kappa statistics is known to be a chance-corrected statistic which is dependent on prevalence and in our case affected by the low prevalence of subclinical ILD classifications; for rare outcomes; very low kappa values do not necessarily reflect low rates of overall agreement. Progressive SSc-ILD is perhaps a less well-defined concept in the literature, with few clinical trials providing clear operational definitions of progression in the form of inclusion/exclusion criteria. At the time the survey was conducted (January 2019-June 2019), the INBUILD trial, which focused on a population of patients with progressive fibrosing lung disease, had not yet been published (9/2019); this may provide insight as to why a smaller percent of experts achieved consensus (60%). The exercise may also reflect the heterogeneous progressive nature of SSc-ILD, compared to severity or risk of progression.

Experts reported the FVC and extent of lung involvement on HRCT as the most important features used in classifying along severity and progression. The top priority on FVC and quantitative HRCT (Whole Lung Involvement %) in this study likely reflects the impact of Goh et al.’s work and the subsequent data supporting the prognostic value in terms of disease severity and progression. SSc-specific disease factors (e.g., factors describing SSc, without specific respiratory symptoms/lung function/imaging of the chest) were the most influential features in terms of determining risk of progression (accounting for 51% of all the items selected as the most important in classification), with disease duration as the most influential. This likely stems from the well-documented relationships to risk of progression, with shorter disease duration and presence of anti-SCL-70 (anti-topoisomerase I) increasing the risk for developing clinically significant SSc-ILD.
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Classification agreement did not differ significantly between disciplines (e.g., pulmonology and rheumatology). The moderate degree of reliability between disciplines suggests that the invited authors all shared the same conceptual framework when completing the classification task for each dimension. One statistical consideration, given the relatively small number of evaluations per group, is the possibility that some profiles achieving or not achieving consensus could have been the result of chance alone and not a shared consensus.

Four limiting factors contextualize these results. First, the data in this initiative are generated from experts responsive to an invitation to participate; to avoid a selection bias, we invited a network broader than those with phone or email contact. Social media is playing a larger role in collaborative efforts in science\textsuperscript{33,34}. We broadcasted this initiative using social media platforms and received interest from participants in several countries and from several disciplines. We selected only those respondents who have demonstrated considerable contribution to the field of ILD. Importantly, there were no expert participants from East Asian countries, although there was representation from South Asia. Pulmonologists who participated in this exercise (data shared by 13 of the 16) spend about half of their time dedicated to clinical practice (54%); of that clinical time, more than half (58%) is spent dedicated to fibrotic ILDs and about 40% is spent on general pulmonary medicine/critical care medicine. Input from general pulmonologists should also be considered in the future to evaluate the conceptual framework’s ease-of-use. Second, patients recruited from clinical trials tend to have more severe manifestations of lung disease than those not enrolled in trials. Knowledge that patient profiles were created from SLS-II patients may have biased experts to classify patients as ‘clinical’ rather than ‘subclinical’. We sought to offset that bias with patients from our institution who did not participate in clinical trials, to provide experts with a cache of SSC patients with minimal-mild ILD. Third, a major limitation of the presented conceptual framework supposes that patient reported outcomes are measuring symptoms (e.g., dyspnea, exercise limitation) attributed to SSC-ILD not confounded by other
causes (e.g., pulmonary hypertension, anemia, musculoskeletal disease, diaphragmatic weakness, smoking, deconditioning). Future work will require classification exercises to be based on more granular detail of the cardiorespiratory status of patients with SSc-ILD; this may allow for more generalizable interpretations of symptom assessment in the setting of real-world, co-occurring and potentially confounding features. Finally, the framework is the product of expert discussion that reflects an understanding of SSc-ILD in a particular time-dependent context and will require revisions as our understanding of the disease progresses. This project was launched in 2019 when phase III focuSSced data were being analyzed. Notably absent from the framework are acute phase reactants, which may now be considered a marker of a progressive phenotype demonstrated in the focuSSced population. The framework in its current form will be updated with acute phase reactants in subsequent iterations. Future efforts working towards developing formal classification criteria of SSc-ILD will dovetail with the American College of Rheumatology’s ongoing initiative to develop guidelines for screening and management of CTD-ILDs. Additionally, there will need to be consideration for patient-input in the classification to capture an element of lived experience with this disease not captured by patient reported outcome measures. There is an ongoing effort to get patients’ input as part of the OMERACT CTD-ILD working group.

Johnson et al., 2018 has identified a need for new SSc subset criteria, with the advent of an improved understanding of the disease (e.g., biomarkers, autoantibody profiles, genetic markers), and early disease identification, in the era of personalized medicine. The impetus for developing working definitions of SSc-ILD subsets is based on the same principles; this effort is timely in light of two treatments approved for the indication of SSc-ILD by Food and Drug Administration. These data form the basis for a multi-dimensional assessment of SSc-ILD (severity, risk of progression, and progression over time) and is a step towards building
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classification criteria for these subsets. Future work will include validation of the conceptual framework in a separate cohort of patients.
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Subsets of Systemic Sclerosis Associated Interstitial Lung Disease

from DevPro, from Gala, personal fees from Integritas, personal fees from IQVIA, personal fees from Projects in Knowledge, personal fees and non-financial support from Sanofi/Regeneron, from twoXAR, personal fees from Vindico, other from AbbVie, personal fees from Academy for Continuing Healthcare Learning, outside the submitted work; Dr. Oddis reports personal fees from Kezar and Pfizer, outside the submitted work); Dr. Pauling received speakers honoraria and/or personal support from Janssen, Astra Zeneca, Permeatus Inc, Boehringer-Ingelheim and Sojournix Pharma; Dr. Seibold reports personal fees from Atlantic (UK), Blade, Boehringer Ingelheim, Camurus, Corbus, Indalo, Prometheus, Sojournix, and Xenikos; Dr. Steen reports grants and other from Boehringer Ingelheim, grants from Genentech, outside the submitted work; Dr. Strand is a member of the executive of OMERACT [1992 – present], an organization that develops and validates outcome measures in rheumatology randomized controlled trials and longitudinal observational studies and receives arms-length funding from 36 sponsors; Dr. Walsh reports personal fees from Sanofi-Aventis, personal fees from Roche, grants and personal fees from Boehringer Ingelheim, personal fees from Galapagos, personal fees from OSIC, personal fees from Bracco, grants from NIHR, personal fees from Vercyte, outside the submitted work; Drs. White and Zoz are employed by Boehringer Ingelheim; Dr. Volkmann reports personal fees from Boehringer Ingelheim, grants from Corbus, grants from Forbius, outside the submitted work; Dr. Khanna reports personal fees from Abbvie, Actelion, Boehringer Ingelheim, Galapagos, CSL Behring, Genentech/ Roche, Prometheus, Horizon, Merck, Mistubishi Tanabe, and grants from Boehringer Ingelheim, Horizon, and Pfizer. He has stock options in Eicos Sciences, Inc.

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Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author
BIBLIOGRAPHY


15. Roofeh D, Jaafar S, Vummidi D, Khanna D. Management of systemic sclerosis-.
Subsets of Systemic Sclerosis Associated Interstitial Lung Disease


<table>
<thead>
<tr>
<th><strong>Table 1</strong>: Revised Conceptual Framework</th>
<th><strong>SUBCLINICAL SSC-ILD</strong></th>
<th><strong>CLINICAL SSC-ILD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td><em>All variables should be met but there may be exceptions</em></td>
<td><em>Must have ≥1 feature</em></td>
</tr>
<tr>
<td>Demographics</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Age, Sex, Race</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>SSc Disease Factors</strong></td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SSc cutaneous classification</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Disease duration</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>ANA status</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SSc specific autoantibody</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Modified Rodnan Skin Score</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Respiratory Symptoms</strong></td>
<td>All features should be met</td>
<td>Must have ≥1 feature</td>
</tr>
<tr>
<td>Mahler Dyspnea Index and Transitional Index</td>
<td>Normal-to-near normal</td>
<td>Deficits present</td>
</tr>
<tr>
<td>Leicester Cough Questionnaire</td>
<td>Normal-to-near normal</td>
<td>Deficits present</td>
</tr>
<tr>
<td>Patient Global Assessment</td>
<td>Normal-to-near normal</td>
<td>Deficits present</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire</td>
<td>Normal-to-near normal</td>
<td>Deficits present</td>
</tr>
<tr>
<td><strong>Spirometry with gas exchange</strong></td>
<td>Forced vital capacity (%predicted)</td>
<td>Deficits present</td>
</tr>
<tr>
<td>Diffusion capacity of carbon monoxide (%predicted)</td>
<td></td>
<td>Deficits present</td>
</tr>
<tr>
<td><strong>Desaturation on exercise</strong></td>
<td>Normal-to-near normal</td>
<td>Deficits present</td>
</tr>
<tr>
<td>Oxygen desaturation during 6-minute walk test</td>
<td>Normal-to-near normal</td>
<td>Deficits present</td>
</tr>
<tr>
<td><strong>Quantitative HRCT</strong></td>
<td>Whole Lung Involvement</td>
<td>Mild-to-severe disease</td>
</tr>
<tr>
<td>(% of ground glass opacities, fibrotic reticulations, and honeycombing)</td>
<td></td>
<td>Mild-to-severe disease</td>
</tr>
<tr>
<td>Whole Lung Fibrosis</td>
<td>Minimal-to-mild</td>
<td>Mild-to-severe disease</td>
</tr>
<tr>
<td>(% of only the fibrotic reticulations)</td>
<td></td>
<td>Mild-to-severe disease</td>
</tr>
<tr>
<td><strong>DISEASE IMPACT</strong></td>
<td>All features should be met</td>
<td>Must have ≥1 feature</td>
</tr>
<tr>
<td>Feel</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Function</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Survive</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>DISEASE PROGRESSION</strong></td>
<td>Must have ≥1 feature for either category (attributable to ILD)</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>New onset dyspnea or cough</td>
<td>Advancing dyspnea or cough</td>
</tr>
<tr>
<td>Spirometry with gas exchange</td>
<td>New decline</td>
<td>Advancing decline</td>
</tr>
<tr>
<td>Desaturation on exercise or exercise limitation</td>
<td>New desaturation and/or limitation</td>
<td>Advancing desaturation and/or limitation</td>
</tr>
<tr>
<td>Quantitative HRCT</td>
<td>New, larger extent of disease burden</td>
<td>Advancing extent of disease burden</td>
</tr>
</tbody>
</table>
Abbreviations:
1 CTD-ILD  Connective Tissue Disease-Interstitial lung disease
2 HRCT    High resolution computed tomography
3 SSc     Systemic sclerosis
4 SSc-ILD Systemic sclerosis associated Interstitial lung disease
### Table 2: Profiles Assessed by Dimension

<table>
<thead>
<tr>
<th></th>
<th>Severity</th>
<th>Risk of Progression</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Profiles Assessed</td>
<td>80</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>Profiles Achieving Consensus (%)*</td>
<td>60 (75%)</td>
<td>57 (71%)</td>
<td>24 (60%)</td>
</tr>
<tr>
<td>Subset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclinical</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannot Classify</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(Based on the Given Information)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profiles Not Achieving Consensus (%)</td>
<td>20 (25%)</td>
<td>23 (29%)</td>
<td>16 (40%)</td>
</tr>
</tbody>
</table>

* A consensus was reached if >75% of experts in each group agreed.
Table 3 Agreement of Classification by Discipline, Along Dimensions of Severity, Risk of Progression, and Progression

a) Determined by Kappa Statistic

<table>
<thead>
<tr>
<th>Kappa Calculation</th>
<th>N (pair) [1]</th>
<th>Average N (profile) [2]</th>
<th>Mean</th>
<th>Bootstrapped mean (95% CI) [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between rheumatologists and pulmonologists</td>
<td>66</td>
<td>7.6</td>
<td>0.13</td>
<td>0.13 (0.00, 0.25)</td>
</tr>
<tr>
<td>Among rheumatologists</td>
<td>44</td>
<td>8.7</td>
<td>0.17</td>
<td>0.17 (-0.01, 0.45)</td>
</tr>
<tr>
<td>Among pulmonologists</td>
<td>17</td>
<td>6.6</td>
<td>0.20</td>
<td>0.18 (0, 0.25)</td>
</tr>
<tr>
<td><strong>Risk of progression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between rheumatologists and pulmonologists</td>
<td>66</td>
<td>6.6</td>
<td>0.61</td>
<td>0.59 (0.49, 0.69)</td>
</tr>
<tr>
<td>Among rheumatologists</td>
<td>44</td>
<td>8.3</td>
<td>0.70</td>
<td>0.66 (0.51, 0.86)</td>
</tr>
<tr>
<td>Among pulmonologists</td>
<td>17</td>
<td>5.9</td>
<td>0.48</td>
<td>0.4618 (0.26, 0.66)</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between rheumatologists and pulmonologists</td>
<td>66</td>
<td>3.1</td>
<td>0.56</td>
<td>0.51 (0.18, 0.70)</td>
</tr>
<tr>
<td>Among rheumatologists</td>
<td>44</td>
<td>3.5</td>
<td>0.78</td>
<td>0.70 (0.36, 0.95)</td>
</tr>
<tr>
<td>Among pulmonologists</td>
<td>17</td>
<td>3.1</td>
<td>0.29</td>
<td>0.24 (-0.00, 0.50)</td>
</tr>
</tbody>
</table>

b) Determined by Chi Square Analysis

<table>
<thead>
<tr>
<th>Chi Square Calculation</th>
<th>Rheumatology</th>
<th>Pulmonology</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical ILD</td>
<td>205 (93.2%)</td>
<td>114 (89.8%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Subclinical ILD</td>
<td>15 (6.8%)</td>
<td>13 (10.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk of progression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>97 (45.3%)</td>
<td>55 (46.2%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Low risk</td>
<td>117 (54.7%)</td>
<td>64 (53.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive</td>
<td>17 (18.9%)</td>
<td>11 (20.0%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Stable</td>
<td>57 (63.3%)</td>
<td>40 (72.7%)</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>16 (17.8%)</td>
<td>4 (7.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*Cannot Tell was removed from this calculation.

[1] Number of paired used to calculate kappa statistics.
[2] Average number of profile in each pair.
[3] 100 bootstrap datasets, randomly selecting based on profile with replacement.
Fitted generalized linear mixed model, with severity/risk of progression/progression as the outcome, discipline as the predictor (ref=Pulmonology), expert and profile as the random effect.

**Table 4**: Importance Based on Percent of Items Used in the Classification of Profiles Along Dimensions of Severity, Risk of Progression, and Progression

<table>
<thead>
<tr>
<th>Domain with Items Used in Classification</th>
<th>Severity</th>
<th>Risk of Progression</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain with Items Used in Classification</td>
<td>Rank Between Domains</td>
<td>Importance Based on Percent Selected</td>
<td>Rank Between Domains</td>
</tr>
<tr>
<td>Demographics</td>
<td>5</td>
<td>Least Influential</td>
<td>4</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Disease Factors</td>
<td>4</td>
<td>Less Influential</td>
<td>1</td>
</tr>
<tr>
<td>Systemic Sclerosis Subtype</td>
<td></td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Disease Duration</td>
<td></td>
<td>2%</td>
<td>31%</td>
</tr>
<tr>
<td>ANA Status</td>
<td></td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Systemic Sclerosis Autoantibody Status</td>
<td></td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>Modified Rodnan Skin Score</td>
<td></td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Patient Reported Outcome Measures</td>
<td>3</td>
<td>Influential</td>
<td>5</td>
</tr>
<tr>
<td>Baseline Dyspnea Index/Transition Index</td>
<td></td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Leicester Cough Questionnaire</td>
<td></td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Patient Global Assessment</td>
<td></td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire</td>
<td></td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Spirometry and Gas Exchange</td>
<td>1</td>
<td>Most Influential</td>
<td>2</td>
</tr>
<tr>
<td>Forced Vital Capacity</td>
<td></td>
<td>29%</td>
<td>17%</td>
</tr>
<tr>
<td>Diffusion Capacity of Carbon Monoxide</td>
<td></td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Quantitative High Resolution Chest CT</td>
<td>2</td>
<td>Very Influential</td>
<td>3</td>
</tr>
<tr>
<td>Total Lung Involvement</td>
<td></td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Total Lung Fibrosis</td>
<td></td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Abbreviations:
SSc  Systemic sclerosis
ANA  Antinuclear Antibody
mRSS Modified Rodnan Skin Score
BDI/TDI Mahler Dyspnea and Transition Index
LCQ  Leicester Cough Questionnaire
PtGa Patient Global Assessment
SGRQ St. George’s Respiratory Questionnaire
FVC  Forced Vital Capacity
DLco  Diffusion Capacity of Carbon Monoxide
HRCT High resolution computed tomography
Indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate.

Refer to Summary of Product Characteristics (SmPC) before prescribing, and for full prescribing information.

JYSELECA® filgotinib 100 mg or 200 mg film-coated tablets.

JYSELECA is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs).

Jyseleca may be used as monotherapy or in combination with methotrexate.

Decay: Adults: 200 mg once daily. Taken orally with/without food. It is recommended that tablets are swallowed whole. Laboratory Monitoring: Refer to the SmPC for information regarding laboratory monitoring and dose initiation or interruption. Elderly: A starting dose of 100 mg once daily is recommended for patients aged ≥ 75 years and older as clinical experience is limited. Renal Impairment: No dose adjustment required in patients with estimated creatinine clearance (CrCl) ≥ 60 mL/min. A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to ≤ 60 mL/min). Not recommended in patients with CrCl < 15 mL/min. Hepatic Impairment: Mild to moderate hepatic impairment: no dose adjustment required. Severe hepatic impairment: not recommended. Children (<18 years): Safety and efficacy not yet established.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis (TB) or active serious infections. Pregnancy. Warnings/Precautions: See SmPC for full information. Immunosuppression: Combination use with immunosuppressants e.g. ciclosporin, tacrolimus, biologics or other Janus kinase (JAK) inhibitors is not recommended as it is a risk of additive immunosuppression or cannot be excluded. Infections: including serious infections such as pneumococcal and opportunistic infections e.g. tuberculosis (TB), varicella zoster, Reye’s syndrome, feline leukaemia virus (FeLV) and blood transfusions. Infections such as pneumonia, histopathological effects on male reproductive organs and fertility: In clinical studies (see SmPC). Fertility: In males, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed (see SmPC). The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown.

Immunological abnormalities: Do not start therapy, or temporarily stop it, if neutrophil count (ANC) <1 × 10^9 cells/L, ALC <0.5 × 10^9 cells/L or haemoglobin <8 g/dL. Temporarily stop therapy if these values are observed during routine patient management. Vaccinations: Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. Newly treated with filgotinib was associated with dose dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased (see SmPC). Cardiovascular risk: Rheumatoid arthritis patients have an increased risk of cardiovascular disorders. Patients should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care. Venous thromboembolic events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib. Caution should be used in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery, and prolonged immobilisation. Lactose contents: Contains lactose patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take filgotinib. Pregnancy: Lactation: Filgotinib is contraindicated in pregnancy. Filgotinib should not be used during breast-feeding. Women of childbearing potential must use effective contraception during and for at least 1 week after cessation of treatment. Driving/Using machinery: No or negligible influence. However, dizziness has been reported.

Side effects: See SmPC for full information. Common (≥1/100 to <1/10): nausea, upper respiratory tract infection, urinary tract infection and dizziness. Uncommon (≥1/1000 to <1/100): herpes zoster, pneumonia, mononeuropathy, hypereosinophilia, anaemia and blood creatine phosphokinase increase. Serious side effects: See SmPC for full information. Legal category: POM Pack: 30 film-coated tablets/Box Price UK Net cost: £93.10 Marketing authorisation numbers: Great Britain Jystyce 100mg film-coated tablets PL 2017/000047/00 200mg film-coated tablets PL 2017/000048/00 Further information: Galapagos UK, Belmont House, 148 Belmont Road, Uxbridge UB8 10S, United Kingdom 00800 7878 1345 medicinalinfo@glpg.com Jyseleca is a trademark. Date of Preparation: January 13/06/2022

Additional monitoring required.

Adverse events should be reported. For Great Britain and Northern Ireland, reporting forms and information can be found at: https://www.mhra.gov.uk or via the Yellow Card app (download from the Apple App Store or Google Play Store). Adverse events should also be reported to Galapagos via email to DrugSafety.UK.Ireland@jyseleca.com or 08000 7878 1345.