Screening Strategies for Pulmonary Hypertension in Patients with Interstitial Lung Disease: A Multidisciplinary Delphi Study

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Running head: Delphi study of screening for PH in ILD

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Abstract

Background: Pulmonary hypertension (PH) is a common complication of interstitial lung disease (ILD), and is associated with worse outcomes and increased mortality. Evaluation of PH is recommended in lung transplant candidates but there are currently no standardized screening approaches. Recent trials have identified therapies that are effective in this setting, providing another rationale to routinely screen ILD patients for PH.

Research Question: What screening strategies for identifying PH in patients with ILD are supported by expert consensus?

Study Design and Methods: The study convened a panel of 16 pulmonologists with expertise in PH and ILD, and utilized a modified Delphi consensus process with 3 surveys to identify PH screening strategies. Survey 1 consisted primarily of open-ended questions. Surveys 2 and 3 were developed from responses to Survey 1 and contained statements about PH screening that panelists rated from −5 (strongly disagree) to +5 (strongly agree).

Results: Panelists reached consensus on several triggers for suspicion of PH including: symptoms, clinical signs, findings on chest computed tomography or other imaging, abnormalities in pulse oximetry, elevations in brain natriuretic peptide (BNP) or N-terminal propeptide (NT-proBNP), and unexplained worsening in pulmonary function tests or 6-minute walk distance. Echocardiography and BNP/NT-proBNP were identified as screening tools for PH. Right heart catheterization was deemed essential for confirming PH.

Interpretation: Many patients with ILD may benefit from early evaluation of PH now that an approved therapy is available. Protocols to evaluate patients with ILD often overlap with evaluations for PH-ILD.
and can be used to assess the risk of PH. Since standardized approaches are lacking, this consensus statement is intended to aid clinicians in the identification of patients with ILD and possible PH, and provide guidance for timely right heart catheterization.

Key words: echocardiography; idiopathic pulmonary fibrosis; interstitial lung disease; pulmonary hypertension; right heart catheterization; screening.

Abbreviations:
- BNP, brain natriuretic peptide
- CT, computed tomography
- DLco, diffusing capacity of the lung for carbon monoxide
- FDA, Food and Drug Administration
- FVC, forced vital capacity
- ICJME, International Committee of Medical Journal Editors
- ILD, interstitial lung disease
- iNO, inhaled nitric oxide
- IPF, idiopathic pulmonary fibrosis
- mPAP, mean pulmonary artery pressure
- MRI, magnetic resonance imaging
- NT-proBNP, N-terminal propeptide brain natriuretic peptide
- PAH, pulmonary arterial hypertension
- PFT, pulmonary function tests
- PH, pulmonary hypertension
- PH-ILD, pulmonary hypertension-interstitial lung disease
- RHC, right heart catheterization
- RV, right ventricle
- RVSP, right ventricular systolic pressure
- SD, standard deviation
- \( \text{SpO}_2 \), oxygen saturation
TLC, total lung capacity
V/Q, ventilation/perfusion
WSPH, World Symposium for Pulmonary Hypertension
6MWD, six-minute walk distance
Pulmonary vascular involvement by numerous etiologies can result in pulmonary hypertension (PH), which is defined by a mean pulmonary artery pressure (mPAP) of >20 mmHg (1). The interstitial lung diseases (ILDs) are a broad, heterogeneous group of conditions with over 200 etiologies, which are always accompanied by variable amounts of inflammation and/or fibrosis. PH is a common complication of ILD and is classified as Group 3 in the World Symposium for Pulmonary Hypertension (WSPH) classification (1). PH associated with ILD is associated with worse outcomes, including an approximately threefold increased risk of mortality, a heightened propensity for acute exacerbations, impaired quality of life, decreased exercise capability, and increased need for supplemental oxygen (2-10).

The reported prevalence of PH in ILD varies based on the underlying population studied, the disease severity, and the method used for diagnosing PH. This has resulted in a wide range of reported prevalence rates, anywhere from 3% to 86% in different studies (11,12). In idiopathic pulmonary fibrosis (IPF), for example, the reported prevalence of PH ranges from 8% to 15% at diagnosis, 29% to 46% at evaluation for lung transplant, and 86% at the time of lung transplant (9,12-21). While echocardiography is an excellent noninvasive screening tool for PH, it has limited accuracy in estimating the right ventricular systolic pressure in the setting of ILD and is typically used for assessing the risk of PH rather than for diagnosis (21,22). Definitive diagnosis of PH requires right heart catheterization (RHC) to measure hemodynamics. In addition to confirming the diagnosis, RHC differentiates between pre- and post-capillary PH while providing other prognostic hemodynamic factors such as the right atrial pressure and cardiac index (1).

Historically, evaluation of PH in patients with ILD was performed primarily as part of the assessment for lung transplantation listing and to evaluate the patient’s prognosis (23). In the absence of an effective therapy for PH-ILD, the costs and risks of screening and confirmatory RHC have been thought to outweigh the potential benefits, except in the context of lung transplant evaluations (24). Consensus recommendations from the sixth WSPH suggested individualized care by expert PH centers
for patients with severe PH and lung disease, with acknowledgment that agents approved for the
treatment of pulmonary arterial hypertension (PAH) (Group 1 PH) were sometimes used off-label to
treat selected patients (25). There is no standard approach to assessing patients’ risk of PH. Based on
these factors, variations in practice patterns mean that patients with ILD may not routinely be screened
for PH and strategies for PH risk assessment may vary across different practices.

Recently, two randomized trials in PH associated with ILD reported positive outcomes: a Phase II
trial of inhaled nitric oxide (INO), and a Phase III trial of inhaled treprostinil. The latter led to US Food and
Drug Administration (FDA) approval of inhaled treprostinil for PH associated with ILD. With the advent of
effective therapy for PH associated with ILD, the paradigm has shifted, making assessment of PH
important for more than transplant evaluation and prognostication. Rather, diagnosis of PH in patients
with ILD may lead to improved functional capacity through targeted therapy.

Since there is currently no generally accepted standard approach for PH screening in patients with
ILD, the recent results and the availability of a specific therapy for PH-ILD raise questions of when and
how to screen for PH in this population. We therefore conducted a modified Delphi study to identify
current practices used by experts in the field to screen for PH in patients with ILD.

Study Design and Methods

Panel Selection

This modified Delphi study was conceived by members of a PH-ILD working group convened by the study
sponsor (United Therapeutics Corporation). The working group consisted of recognized experts in ILD
and/or ILD-associated PH. Members of the working group constituted the majority of the Delphi panel.
The working group members each nominated one or two colleagues as additional panelists, based on the
colleague’s experience treating patients with PH-ILD as well as their clinical and research interest in PH-
ILD. The candidates were reviewed, and the nominated experts were invited based on the number of
nominations and diversity. The nominees were invited to participate by an independent project organizer and were also invited to further participate as coauthors. Coauthors were required to complete at least two of three Delphi surveys, including the final survey; and to contribute to, review, and approve the manuscript, thereby meeting ICIME criteria for authorship. The sponsor reviewed the article at each draft and made minor editorial comments.

The Delphi panel consisted of 16 panelists, all of whom are pulmonologists who practice in the United States. The panel had a median of 15–19 years’ experience treating patients with ILD (range, 7–30 years), and had treated a median of 1,000–1,999 patients (range, 150–15,000) in their careers. Their practice settings include ILD centers (12 panelists), PH centers (8 panelists), general pulmonology practice (1 panelist), and other settings (2 panelists) (some panelists practice in multiple settings).

Modified Delphi Methodology

The Delphi methodology describes a structured method for group decision making in situations where evidence is lacking. It was developed by Delbecq et al. in 1975 (26) and is now widely used in medical settings including pulmonology (27-35). This study’s modified Delphi method used three rounds of surveys, all moderated by FFR, NAK, and SDN. Each survey was developed by the moderators. Surveys were elicited by electronic means. Panelists were asked to respond independently.

The initial survey consisted of open-ended questions intended to elicit panelist’s views on screening for PH in ILD. Question topics included: patients likely to benefit from early diagnosis and treatment of PH, routine test and imaging results that might suggest the need to screen for PH (computed tomography [CT], oxygen saturation [SpO₂], brain natriuretic peptide [BNP] or N-terminal proBNP [NT-proBNP], diffusing capacity of the lung for carbon monoxide [DLCO]), other pulmonary function tests (PFTs), physical signs, and symptoms that might raise suspicion for PH, the role of comorbidities, and the participants’ overall approach to screening.
Survey 2 consisted of statements related to screening for PH in ILD. The moderators derived the statements by combining panelists’ responses to Survey 1, while eliminating outlier responses and editing the responses for clarity and consistent language. Panelists were asked to rate their agreement with each statement on a Likert scale ranging from −5 (strongly disagree) to +5 (strongly agree). The statements were grouped into topics, and panelists were invited to expand on their responses with an open-response question for each topic.

Survey 3 contained the same statements as Survey 2, along with each panelist’s own answer to Survey 2 as well as the mean and standard deviation of all panelists’ responses. This allowed panelists to re-evaluate their answers in light of the group’s average responses and was intended to build consensus. The study began in July 2020 with distribution of Survey 1 and concluded in March 2021 with collection of all responses to Survey 3. Surveys were aggregated by Parexel under the direction of the moderators. Only descriptive statistics were used.

Consensus was predefined as a Likert scale mean score of 2.5 or greater with a standard deviation in the scores not crossing zero. These criteria have been used in previous Delphi studies, though there are no generally accepted criteria for defining consensus in Delphi studies (27-30,33-35). The Likert scale criteria we employed have been used in several other studies in pulmonology as well as other specialties (31,32,36-38).

As no patient contact or patient information was used in this study, institutional review board approval was not required.

**Results**

At the conclusion of Survey 3, panelists reached consensus on 80/135 items (59%). The full questionnaire and scores are presented in the Online Supplement (e-Table 1).
Patients With ILD Who Are Likely to Benefit from Early Diagnosis and Screening for PH

Panelists reached consensus that, if an FDA-approved therapy for PH in patients with ILD became available, earlier evaluations for PH than are done in current practice are likely to benefit patients, with a consensus score of 4.56 ± 0.70 (mean ± SD). Early diagnosis and treatment for PH-ILD would be beneficial for a wide array of ILDs (Figure 1). Early diagnosis and treatment would also be beneficial for patients with progressive ILD, patients who require supplemental oxygen, and patients with symptoms or signs disproportionate to the severity of their ILD, especially when changes in symptoms are not explained by progression of ILD (Figure 1).

Triggers for Suspicion of PH

In the initial Delphi survey, panelists suggested 19 signs and symptoms as possible triggers for suspicion of PH in patients with ILD. In Survey 3, panelists reached consensus on nine of these signs and symptoms: syncope, jugular venous distension, peripheral edema, ascites, altered heart sounds (especially loud P2 or S2), hepatomegaly, history of pulmonary embolism, dizziness, and palpitations (Figure 2). Development or worsening of these symptoms should prompt further evaluation. No consensus was reached for the signs and symptoms of weight gain, dyspnea on exertion, shortness of breath, cough, chest pain, arrhythmias, abnormal arterial blood gases, fatigue, signs of left heart failure, hemoptysis, Raynaud’s, or increased heart rate response to exercise (see e-Figure 1 in the Online Supplement).

Panelists reached consensus that several standard tests and procedures are triggers for suspicion of PH, including abnormalities on chest CT, poor oxygen saturation, elevated BNP or NT-proBNP, PFTs, and a reduced 6-minute Walk Distance test (6MWD; Figure 3). CT-related triggers that reached consensus included right ventricular enlargement; several measures related to pulmonary artery enlargement (eg, pulmonary artery/aorta ratio >1), and flattening of the interventricular septum. Worsening or “disproportionate” oxygen desaturation are triggers, but no specific SpO2 threshold
reached consensus. Panelists arrived at a consensus that an elevated BNP or NT-proBNP are triggers for suspicion, at BNP levels >200 pg/mL or NT-proBNP >395 pg/mL (cutoff based on a study of patients with systemic sclerosis with or without PAH) (39). The PFT-related triggers that reached consensus were DL\textsubscript{CO} % predicted <40%, rapid decline in DL\textsubscript{CO} (≥15%), and DL\textsubscript{CO} disproportionate to lung volumes (forced vital capacity [FVC]/DL\textsubscript{CO} ratio >1.6), but no consensus was reached on the use of FVC or total lung capacity (TLC) or any thresholds for these parameters. A worsening 6MWD despite stable PFTs also reached consensus as a trigger for suspicion. No consensus was reached on specific 6MWD thresholds or other exercise tests (see e-Figures 2 and 3 in the Online Supplement).

**Approach to Screening and Confirmation When PH is Suspected**

The panelists reached consensus that when PH is suspected, echocardiography and BNP or NT-proBNP are useful as subsequent screening tests. In addition to these two tests, panelists reached consensus that CT of the chest, PFTs, and 6MWD are useful to evaluate ILD stability or progression when symptoms are disproportionate to the severity of the underlying ILD (Figure 4).

There was no consensus for initial screening with RHC, electrocardiogram, CT angiogram, V/Q scan, or cardiac magnetic resonance imaging (MRI) (Table E1). Settings in which use of RHC to confirm a diagnosis of PH reached consensus include: potential lung transplant candidates, echocardiography findings suggestive of PH (in particular, elevated right ventricular systolic pressure (RVSP), right ventricle (RV) abnormalities including dilation or enlargement, and a low tricuspid annular plane systolic excursion), high clinical suspicion of PH (eg, based on the signs and symptoms described in Figure 1), and autoimmune ILD. A low threshold for RHC was considered appropriate to confirm a PH diagnosis, particularly with suggestive clinical or echocardiography findings (Figure 5).
Discussion

This modified Delphi study convened a panel of experts in ILD and PH to gain information on their practices regarding screening for and diagnosing PH in patients with ILD now that a therapy for PH in this setting has been approved. Panelists came to a consensus to perform early screening for PH, with a low threshold of suspicion. Early screening to identify patients with PH-ILD may benefit patients by prompting early treatment and transplant referral in this high-risk population. However, at this writing, the long-term impact of the available medical therapies for PH-ILD is not known. Patients who develop PH-ILD should still be referred for lung transplantation because medical therapy may provide only transient improvement.

Routine clinical evaluations and tests assessed for suspicion of PH included signs and symptoms suggestive of PH, CT imaging suggestive of pulmonary artery or RV enlargement, desaturation or changes in oxygen supplementation, PFT results (particularly DL CO and the FVC/DL CO ratio), decreases in the 6MWD, and abnormal BNP or NT-proBNP levels. If suspicious findings are present, screening echocardiography and a BNP or NT-proBNP test should be considered, possibly along with other tests based on clinical judgment and the patient’s specific situation. Confirmatory RHC is necessary if any combination of findings raises suspicion of PH. Figure 6 summarizes a consensus approach to screening and diagnosis of PH in patients with ILD.

Until recently, the primary benefit of assessing patients with ILD for PH was an improved estimate of the patient’s prognosis. There was no evidence for treating PH associated with ILD. On the contrary, several trials found no benefit from the PH therapies evaluated (24). The BPHIT study of bosentan for fibrotic idiopathic interstitial pneumonias (IIP) showed no benefit in the primary and many of the secondary endpoints (39). The RISE-IIP study demonstrated a harmful signal in patients with PH due to IIP who received riociguat (25). The ARTEMIS-IPF trial of ambrisentan in patients with IPF found that...
ambrisentan was ineffective and possibly increased the risk of disease progression and hospitalization regardless of the presence of PH (41).

The STEP-IPF trial found no benefit for 6MWD from sildenafil in patients with advanced IPF (42). Although RHC confirmation of PH was not available for these patients, a subgroup analysis of patients with RV dysfunction on echocardiography demonstrated significant improvements in 6MWT and health-related quality of life for sildenafil versus placebo (43).

Recently, two studies have found promising results in treating PH associated with ILD. A Phase II randomized, placebo-controlled study of inhaled nitric oxide (iNO) in 41 patients with fibrotic ILD who were at risk of PH by echocardiography found that iNO was associated with maintenance of physical activity as measured by actigraphy compared with placebo patients who had serial declines in activity (44). This modality of therapy is now being tested in a Phase III clinical trial (REBUILD, NCT03267108) (45). The Phase III randomized, placebo-control INCREASE trial demonstrated that inhaled treprostinil improved 6MWD, reduced NT-proBNP, and slowed rates of clinical worsening in patients with PH due to ILD, in comparison to placebo (46). The results of this study led to FDA approval of inhaled treprostinil for PH associated with ILD. The approval of an effective therapy for PH-ILD lowers the bar for making a diagnosis, and our study provides an outline for which patients should be screened.

Several earlier studies have evaluated approaches to screening or prediction of PH in patients with various subtypes of ILD (24). Zisman et al validated an equation using FVC/DLco (% predicted) and oxygen saturation on room air to estimate the mean pulmonary artery pressure (mPAP) in patients with IPF (47). Alkukhun et al found that impaired RV function and an elevated PA/aorta ratio predict PH in idiopathic pulmonary fibrosis (IPF), but have a limited ability to discriminate between patients with and without PH (48). Sonti et al reported that RVSP measured by echocardiography, the FVC/DLco ratio, and the PA/aorta ratio predicts PH more reliably than RVSP alone (49). Despite multiple studies assessing noninvasive screening techniques for PH in patients with ILD, there is no substitute for the gold-standard RHC.
We have taken a somewhat different, ILD-focused, approach to PH risk assessment and screening in that many of the screening techniques found useful in our surveys are already part of routine care in patients with ILD. Specifically, PFTs, chest CT, oxygen saturation, oximetry with ambulation and perhaps 6MWD are routinely obtained at the time of diagnosis, during serial follow-up, and as part of the assessment for lung transplant. Since many of these patients are older and other causes for their shortness of breath are frequently sought, it is not uncommon for these patients to have one or more echocardiograms during the course of their disease management. While these tests are not intended for PH screening in routine ILD practice, we have tried to highlight that these test results can provide useful information on risk stratification for underlying PH, and can be used in concert to identify patients who should be referred for RHC. It is our hope and goal that this report will increase awareness and spotlight these existing tests that can serve to prompt further investigation that might ultimately culminate in the performance of a RHC. Clinical judgment will of course need to be exercised by clinicians on a case-by-case basis in terms of obtaining further testing.

This study has several limitations. There is potential for bias in the selection of panelists and the development of the Delphi surveys. All our Delphi participants practice in the United States, mostly in specialty PH and/or ILD centers. Although the practice patterns reported here may not be reflective of other settings, we regard this as a strength since all our participants had expertise in PH, ILD, or both. By considering ILD as a whole, we may have reduced emphasis on specific ILD subtypes for which increased suspicion of PH is more appropriate. We also might not have highlighted all available screening options; for example, with regards to the 6MWD, we focused on distance and oxygen desaturation, but there are other parameters within this study that might further increase the suspicion for underlying PH, such as the Borg Dyspnea Scale and heart rate recovery (50). Similarly, our survey did not list all non-invasive parameters but only included NT-proBNP/BNP given that this biomarker is most routinely used in the care of ILD patients and has the most literature supporting its significance. As in all Delphi studies, this
study’s conclusions are based on expert opinion rather than clinical evidence. Our survey and recommendations included patients with ILD related to connective tissue disorders (CTD-ILD). Arguably, screening for PH is generally recommended for these patients already. However, screening recommendations in CTD are mostly geared towards patients with scleroderma and we therefore feel that our guidance reinforces the need for screening in not only scleroderma patients, but in all CTD-ILD patients (51). Lastly, the survey did not include every echocardiographic parameter that could be used in assessing for PH and a comprehensive review of echo results is warranted in risk stratifying patients for underlying PH.

A notable strength of this manuscript is that it helps fills a void highlighted by the recent approval of an agent to treat PH-ILD. Specifically, the consensus of seasoned clinicians in the field may aid clinicians at a time when definitive guidance is lacking and may further serve as a useful starting point for studies to better define screening parameters for this high-risk population. This is the first time the question of screening for PH in patients with ILD has been considered by a large panel of experts in the field. In addition, the panel took an ILD-specific approach that focused primarily upon tests routinely obtained in the management of ILD, with a focus on how these tests can be used to risk stratify for PH complicating ILD.

**Interpretation**

In conclusion, the development and availability of novel therapies specifically for PH in ILD, as well as rapid gains in scientific knowledge of the condition, have brought attention to the unmet need for guidelines on screening for PH in this setting. Our study highlights parameters that are important for screening for PH in patients with ILD. We further contextualize these through our methodical three-phase Delphi process and Likert weighting, which may provide a foundation and impetus for further guideline development. We hope that this work will encourage further research to identify appropriate
screening parameters and thresholds, and to develop and validate a strategy for screening, such as a screening algorithm and/or a scoring system that more accurately quantifies the risk of PH in ILD.

Take-Home Points

**Study question:** What screening strategies for identifying PH in patients with ILD are supported by expert consensus?

**Results:** Panelists reached consensus on several triggers for suspicion of pulmonary hypertension based on certain signs, symptoms, and other findings in usual tests performed in the care of patients’ with ILD such as Pulmonary Function Tests and CT scans.

**Interpretation:** Many patients with ILD may benefit from early evaluation of PH now that an approved therapy is available and this consensus statement may help clinicians to identify PH in patients with ILD.

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**Figure Legends**

**Figure 1.** Delphi consensus scores for ILD types and disease characteristics that could benefit from earlier diagnosis and treatment of PH if an FDA-approved treatment is available.

Items that reached consensus. Circles indicate the mean consensus score for each item. Horizontal error bars depict the standard deviation. Consensus was defined as a mean score ≥2.5 with a standard deviation that does not cross zero.

*Definition of abbreviations:* FDA = [US] Food and Drug Administration; ILD = interstitial lung disease; PH = pulmonary hypertension; SD = standard deviation.
Figure 2. Delphi consensus scores for signs and symptoms in the patient history that are possible triggers for PH screening in patients with ILD. Items that reached consensus.

Circles indicate the mean consensus score for each item. Horizontal error bars depict the standard deviation. Consensus was defined as a mean score ≥2.5 with a standard deviation that does not cross zero.

Definition of abbreviations: HRR = heart rate recovery; ILD = interstitial lung disease; PH = pulmonary hypertension; SD = standard deviation.
Figure 3. Delphi consensus scores for tests and procedure results that are possible triggers for PH screening in patients with ILD.

Items that reached consensus. Circles indicate the mean consensus score for each item. Items that reached consensus. Horizontal error bars depict the standard deviation. Consensus was defined as a mean score ≥2.5 with a standard deviation that does not cross zero.

Definition of abbreviations: 6MWD = 6-minute Walk Distance; BNP = brain-type natriuretic peptide; CT = computed tomography; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; PFT = pulmonary function test; PH = pulmonary hypertension; Scl-ILD = scleroderma associated ILD; SD = standard deviation.
Figure 4. Delphi consensus scores for initial screening tests and tools to evaluate symptoms.

Items that reached consensus. Circles indicate the mean consensus score for each item. Horizontal error bars depict the standard deviation. Consensus was defined as a mean score ≥2.5 with a standard deviation that does not cross zero.

Definition of abbreviations: 6MWD = 6-minute Walk Distance; BNP = brain-type natriuretic peptide; CT = computed tomography; DL\textsubscript{CO} = diffusing capacity of the lung for carbon monoxide; ILD = interstitial lung disease; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; PFT = pulmonary function test; PH = pulmonary hypertension; SD = standard deviation.
Figure 5. Delphi consensus scores for triggers for RHC.

Items that reached consensus. Circles indicate the mean consensus score for each item. Horizontal error bars depict the standard deviation. Consensus was defined as a mean score ≥2.5 with a standard deviation that does not cross zero.

Definition of abbreviations: ECHO = echocardiogram; ILD = interstitial lung disease; RHC = right heart catheterization; RV = right ventricle; RVSP = right ventricular systolic pressure; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion.

* In patients for whom RHC can be performed safely.
**Figure 6.** Consensus approach to screening for PH in patients with ILD

*Definition of abbreviations:* 6MWD = 6-minute Walk Distance; BNP = brain-type natriuretic peptide; CT = computed tomography; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; PA = pulmonary artery; PFT = pulmonary function test; PH = pulmonary hypertension; RHC = right heart catheterization; RV = right ventricle.

* Individual laboratories may have different thresholds.
<table>
<thead>
<tr>
<th>Statement</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ILD Types that could benefit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease—associated ILD</td>
<td>4.44</td>
<td>0.79</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>4.38</td>
<td>0.70</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>4.06</td>
<td>0.90</td>
</tr>
<tr>
<td>Idiopathic non-specific interstitial pneumonia</td>
<td>3.81</td>
<td>0.81</td>
</tr>
<tr>
<td>All types of idiopathic interstitial pneumonia</td>
<td>3.75</td>
<td>1.39</td>
</tr>
<tr>
<td>Fibrotic idiopathic interstitial pneumonia</td>
<td>3.75</td>
<td>1.20</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis (ILD)</td>
<td>3.50</td>
<td>1.00</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>3.06</td>
<td>1.56</td>
</tr>
<tr>
<td>Fibrotic ILD</td>
<td>2.50</td>
<td>1.15</td>
</tr>
<tr>
<td><strong>Disease characteristics that could benefit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms and/or signs disproportionate to ILD severity</td>
<td>4.56</td>
<td>0.61</td>
</tr>
<tr>
<td>Changes in symptoms/signs not explained by ILD progression</td>
<td>4.56</td>
<td>0.70</td>
</tr>
<tr>
<td>ILD requiring oxygen</td>
<td>3.94</td>
<td>0.90</td>
</tr>
<tr>
<td>Active, rapidly progressive disease</td>
<td>3.81</td>
<td>0.95</td>
</tr>
</tbody>
</table>

ILD, interstitial lung disease; FDA, United States Food and Drug Administration; PH, pulmonary hypertension; SD, standard deviation.
<table>
<thead>
<tr>
<th>Sign/symptom</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>3.56</td>
<td>0.93</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>3.50</td>
<td>1.17</td>
</tr>
<tr>
<td>Ankle swelling/peripheral edema</td>
<td>3.38</td>
<td>1.27</td>
</tr>
<tr>
<td>Ascites</td>
<td>3.31</td>
<td>1.16</td>
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<tr>
<td>Altered heart sounds, especially loud P2 or S2</td>
<td>3.25</td>
<td>1.30</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>3.06</td>
<td>1.14</td>
</tr>
<tr>
<td>History of pulmonary embolism</td>
<td>2.88</td>
<td>1.11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.75</td>
<td>1.44</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2.69</td>
<td>1.31</td>
</tr>
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</table>

HRR, heart rate recovery; SD, standard deviation.
<table>
<thead>
<tr>
<th>Statement</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle enlargement</td>
<td>4.31</td>
<td>0.58</td>
</tr>
<tr>
<td>Increased pulmonary artery/aorta ratio (&gt;1)</td>
<td>4.25</td>
<td>1.20</td>
</tr>
<tr>
<td>Pulmonary artery enlargement</td>
<td>4.00</td>
<td>1.22</td>
</tr>
<tr>
<td>Flattening of the septum</td>
<td>3.81</td>
<td>0.81</td>
</tr>
<tr>
<td>Enlarged pulmonary arteries in the lung periphery</td>
<td>3.31</td>
<td>1.31</td>
</tr>
<tr>
<td><strong>Desaturation/hypoxemia/supplemental O</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trends should be monitored over time</td>
<td>4.69</td>
<td>0.46</td>
</tr>
<tr>
<td>Desaturation/hypoxemia disproportionate to ILD burden</td>
<td>4.19</td>
<td>0.63</td>
</tr>
<tr>
<td>Worsening desaturation/increase in supplemental O</td>
<td>3.75</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>BNP/NT-proBNP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated BNP and/or NT-proBNP levels</td>
<td>3.75</td>
<td>0.43</td>
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<tr>
<td>Trends in BNP/NT-proBNP should be monitored</td>
<td>2.63</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>What is the threshold for suspicion?</strong></td>
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<td></td>
</tr>
<tr>
<td>BNP &gt;200 pg/mL</td>
<td>2.75</td>
<td>1.35</td>
</tr>
<tr>
<td>BNP &gt;280 to 320 pg/mL</td>
<td>3.19</td>
<td>1.38</td>
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<tr>
<td>NT-proBNP &gt;395 pg/mL (based on Scl-ILD)</td>
<td>3.88</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>PFTs</strong></td>
<td></td>
<td></td>
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<tr>
<td>DLco</td>
<td>3.81</td>
<td>0.73</td>
</tr>
<tr>
<td>Worsening DLco should trigger suspicion</td>
<td>3.75</td>
<td>0.83</td>
</tr>
<tr>
<td>FVC%/DLco%</td>
<td>3.5</td>
<td>1.37</td>
</tr>
<tr>
<td>There is no clear threshold for suspicion</td>
<td>3.00</td>
<td>1.58</td>
</tr>
<tr>
<td><strong>Thresholds for DLco changes and level</strong></td>
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<tr>
<td>Changes in DLco</td>
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<td></td>
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<tr>
<td>DLco is worsening with stable FVC</td>
<td>4.19</td>
<td>0.63</td>
</tr>
<tr>
<td>DLco has declined by 15% or more</td>
<td>3.06</td>
<td>1.25</td>
</tr>
<tr>
<td>DLco has declined rapidly</td>
<td>3.63</td>
<td>1.11</td>
</tr>
<tr>
<td>DLco level</td>
<td></td>
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<tr>
<td>DLco is less than 40%</td>
<td>3.31</td>
<td>1.26</td>
</tr>
<tr>
<td>Decrease threshold if other concerning features</td>
<td>3.44</td>
<td>1.12</td>
</tr>
<tr>
<td><strong>FVC/DLco ratio</strong></td>
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<tr>
<td>Worsening FVC/DLco ratio</td>
<td>2.94</td>
<td>0.75</td>
</tr>
<tr>
<td>Consider trends in FVC/DLco over time</td>
<td>2.88</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Thresholds</strong></td>
<td></td>
<td></td>
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<tr>
<td>DLco disproportionate to lung volumes</td>
<td>3.81</td>
<td>0.95</td>
</tr>
<tr>
<td>FVC/DLco ratio &gt;1.6</td>
<td>2.56</td>
<td>1.12</td>
</tr>
<tr>
<td><strong>6MWD and exercise testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening 6MWD triggers suspicion</td>
<td>2.94</td>
<td>1.03</td>
</tr>
<tr>
<td>Worsening 6MWD despite stable PFTs triggers suspicion</td>
<td>2.81</td>
<td>1.29</td>
</tr>
</tbody>
</table>

- CT, computed tomography; DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PFT, pulmonary function test; pg/mL, picograms per milliliter; SD, standard deviation.
Components of the initial set of screening tests

<table>
<thead>
<tr>
<th>Statement</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram</td>
<td>4.75</td>
<td>0.43</td>
</tr>
<tr>
<td>BNP or NT-proBNP</td>
<td>4.00</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Useful to evaluate ILD stability and progression when symptoms are disproportionate to ILD

<table>
<thead>
<tr>
<th>Statement</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram</td>
<td>4.56</td>
<td>0.61</td>
</tr>
<tr>
<td>PFTs, including spirometry and DLCO</td>
<td>4.44</td>
<td>0.61</td>
</tr>
<tr>
<td>CT</td>
<td>4.38</td>
<td>0.60</td>
</tr>
<tr>
<td>6MWD: oxygen saturation with exertion</td>
<td>4.25</td>
<td>0.75</td>
</tr>
</tbody>
</table>

6MWD, 6 minute walk distance; BNP, brain-type natriuretic peptide; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; ILD, interstitial lung disease; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PFT, pulmonary function test; PH, pulmonary hypertension.
<table>
<thead>
<tr>
<th>Statement</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Confirmatory RHC should be ordered</em> In potential lung transplant candidates</em>*</td>
<td>4.75</td>
<td>0.56</td>
</tr>
<tr>
<td>Suggestive ECHO with other suggestive signs/ symptoms</td>
<td>4.44</td>
<td>0.61</td>
</tr>
<tr>
<td>Suggestive ECHO</td>
<td>4.31</td>
<td>0.85</td>
</tr>
<tr>
<td>Clinical suspicion of PH is high</td>
<td>4.13</td>
<td>0.93</td>
</tr>
<tr>
<td>Echo and/or other noninvasive tests suggest PH</td>
<td>4.06</td>
<td>1.09</td>
</tr>
<tr>
<td>In autoimmune ILD</td>
<td>3.69</td>
<td>1.10</td>
</tr>
<tr>
<td>Low threshold for RHC in suggestive clinical settings</td>
<td>4.00</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>These parameters on ECHO should prompt RHC</strong></td>
<td></td>
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</tr>
<tr>
<td>Elevated RVSP</td>
<td>3.75</td>
<td>1.03</td>
</tr>
<tr>
<td>RV dilation/enlargement</td>
<td>4.19</td>
<td>0.63</td>
</tr>
<tr>
<td>Other RV abnormalities</td>
<td>3.75</td>
<td>0.83</td>
</tr>
<tr>
<td>Low TAPSE</td>
<td>3.44</td>
<td>1.12</td>
</tr>
</tbody>
</table>

ECHO, echocardiogram; ILD, interstitial lung disease; RHC, right heart catheterization; RV, right ventricle; RVSP, right ventricular systolic pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.
Risk Factors/Symptoms
- History of pulmonary embolism or heart failure
- Dizziness, palpitations, syncope

Signs
- Altered heart sounds (loud P2 or S2)
- Signs of right heart failure:
  - Jugular venous distension
  - Ankle swelling/peripheral edema
  - Hepatomegaly/Ascites

Tests (used in concert to risk stratify for PH)
- BNP/NT-proBNP*
  - Elevated BNP (>200 pg/mL)
  - Elevated NT-proBNP (>395 pg/mL)
- Oxygen saturation and 6MWT
  - Any supplemental oxygen needs
  - Desaturation disproportionate to ILD severity
  - Worsening desaturation
  - Lower distance on 6MWT
- PFTs
  - DLCO Decline 15% or more
  - DLCO <40%
  - Worsening FVC/DLCO
  - FVC%/DLCO%>1.6
- CT
  - RV enlargement
  - PA enlargement
  - PA/Aorta ratio >1.0

Echocardiographic Probability of PH

<table>
<thead>
<tr>
<th>Clinical Suspicion of PH</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>RHC</td>
<td>RHC</td>
<td>Consider RHC</td>
</tr>
<tr>
<td>Low</td>
<td>RHC</td>
<td>Consider RHC</td>
<td>No RHC</td>
</tr>
</tbody>
</table>

Echocardiography

High suspicion

Low suspicion

No suspicion

No further work up

6MWD, 6 minute walk distance; BNP, brain-type natriuretic peptide; DLCO, diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; ILD, interstitial lung disease; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PFT, pulmonary function test; RHC, right heart catheterization;

* individual laboratories may have different thresholds