ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Review

Home monitoring of physiology and symptoms to detect Interstitial Lung Disease exacerbations and progression: a systematic review

Malik A Althobiani, Rebecca A. Evans, Jaber S. Alqahtani, Abdulelah M. Aldhahir, AM Russell, John R. Hurst, Joanna C. Porter

Please cite this article as: Althobiani MA, Evans RA, Alqahtani JS, *et al*. Home monitoring of physiology and symptoms to detect Interstitial Lung Disease exacerbations and progression: a systematic review. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00441-2021).

Home monitoring of physiology and symptoms to detect Interstitial Lung Disease exacerbations and progression: a systematic review

*Malik A Althobiani[1], Rebecca A. Evans[2], Jaber S. Alqahtani[1], Abdulelah M. Aldhahir[1], AM Russell[*3] John R. Hurst [*1], Joanna C. Porter [*1]*

Affiliation

1. UCL Respiratory, University College London
2. University College London Hospitals NHS Foundation Trust
3. University of Exeter College of Medicine and Health.

*Joint senior authors

Take home message: First systematic review that provides supportive evidence for the feasibility and utility of home monitoring in ILD, further studies are necessary to evaluate approaches to detect exacerbation and/or progression.

Key words: Interstitial lung disease, home monitoring, idiopathic pulmonary fibrosis, spirometry

Background: Acute exacerbations and disease progression in interstitial lung disease (AE-ILD) pose important challenges to clinicians and patients. AE-ILD are variable in presentation but may result in rapid progression of ILD, respiratory failure and death. However, in many cases AE-ILD may go unrecognised so that their true impact and response to therapy is unknown. The potential for home monitoring to facilitate early, and accurate, identification of AE and/or ILD progression has gained interest. With increasing evidence available, there is a need for a systematic review on home monitoring of patients with ILD to summarise the existing data.

AIM: To systematically evaluate the evidence for use of home monitoring for early detection of exacerbations and/or progression of ILD.

METHOD: We searched Ovid-EMBASE, MEDLINE, and CINAHL using MeSH terms in accordance with the PRISMA guidelines. PROSPERO registration number (CRD42020215166).

RESULTS: Thirteen studies comprising 968 patients have demonstrated that home monitoring is feasible and of potential benefit in patients with ILD. Nine studies reported that mean adherence to home monitoring was greater than 75%, and where spirometry was performed there was a significant correlation ($r = 0.72\text{-}0.98$, $P<0.001$) between home and hospital-based readings. Two studies suggested that home monitoring of Forced Vital Capacity (FVC) might facilitate detection of progression in idiopathic pulmonary fibrosis (IPF).

CONCLUSION: Despite the fact that individual studies in this systematic review provide supportive evidence suggesting the feasibility and utility of home monitoring in ILD, further studies are necessary to quantify the potential of home monitoring to detect disease progression and/or acute exacerbations.

Introduction

Interstitial lung disease (ILD) is a general term for approximately 200 different diseases that may result in inflammation and scarring of the lung [2]. ILD is characterised by progressive dyspnoea, inflammation, fibrosis, and reduced quality-of-life (QOL) [2]. Most cases of ILD result from an aetiological factor, such as exposure to allergens, toxins, or drugs or from an underlying autoimmune disease, with a modifying influence of genetics and exogenous factors such as air pollution [3-5]. In many cases the aetiology is unclear[1]. The most severe form of ILD is idiopathic pulmonary fibrosis (IPF) [2, 6], for which there is no cure [2]. The median survival time after diagnosis of untreated IPF is 2 to 5 years [2, 7, 8].The considerable variability seen between patients makes individual outcome prediction difficult. In addition, there is a lack of validated biomarkers of disease progression [9, 10]. FVC is one possible biomarker of disease progression and is usually measured intermittently. There are currently two anti-fibrotic drugs approved for use in IPF, nintedanib and pirfenidone, which have been demonstrated to slow the rate of FVC decline [11-14] and may increase median survival [13, 15, 16]. There is an urgent unmet need for better treatments. Currently all clinical trials of novel therapies for IPF have used the established end-point of rate of decline in FVC and have required large patient cohorts followed for a significant length of time (years) to identify meaningful treatment responses [17, 18]. More frequent measures, such as the use of home spirometry, may reduce the size, length of time, and cost of clinical trials [19-22]. Ineffective drug treatments could also be identified at an earlier stage. More regular monitoring of physiological parameters in ILD might be of benefit in clinical practice and in research.

Patients with ILD may experience acute deteriorations ('exacerbations' or AE) of their condition, and there is a growing body of research into the detection of exacerbation in ILD [23, 24]. AEs of ILD are highly variable but may result in rapid respiratory deterioration, alveolar abnormalities, and in severe cases death [23-25]. This rapid progression can cause severe distress to patients and burden healthcare systems. The potential for home monitoring to identify progression, including AE, at an early stage is of significant interest. Supporting evidence exists in other respiratory diseases. It has been demonstrated that early detection of exacerbations in Chronic Obstructive Pulmonary Disease (COPD) speeds recovery time [26, 27]. Home monitoring has thus been recommended in lung diseases such as COPD to support earlier detection of exacerbation [28, 29]. It is suggested that similar technology may benefit patients with ILD [22, 30-34].

Another challenge in ILD is the marked inter-patient heterogeneity which makes it very difficult to accurately predict life expectancy and so to provide a reliable prognosis to individual patients and their families [24]. A benefit of home monitoring may be that more frequent monitoring of individual patients may allow prediction of a patient's personal trajectory that can inform prognostication and decisions of future care[33, 34].

The potential role for home monitoring in ILD has been amplified by the COVID-19 pandemic. The guidance from the British Lung Foundation and NHS for patients with ILD has been to 'shield', to reduce the risk of contracting COVID-19 [35]. Home monitoring could arguably decrease the inherent risk in physical attendance at outpatient clinics [28, 32]. This may also prove useful beyond the COVID-19 pandemic, given that ILD can limit patient mobility and care is often centralised at tertiary centres [36, 37].

There is no existing systematic synthesis of the literature to examine the role of home monitoring to detect ILD exacerbation and/or disease progression. Thus, we aimed to systematically gather, summarize, and evaluate the evidence not just of feasibility and reliability, but also on detection of AE-ILD and/ or disease progression in this systematic review.

Search Methods:

Protocol and registration

We undertook a systematic review of the literature using a protocol in accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2015) [38, 39]. We prospectively registered this systematic review at PROSPERO (protocol registration number: CRD42020215166).

Eligibility criteria

We utilized the PICO framework (participants/population, intervention(s)/exposure(s), comparator(s)/ control, main outcome(s)) as a search strategy. We systematically searched for studies on home monitoring and interstitial lung disease published worldwide with no restriction on date of publication. Home monitoring was defined as the regular use of any home-based technology and spirometry to monitor symptoms and/or physiological parameters (such as vital signs and spirometry) over a period of at least 3 weeks. The selected papers met the following inclusion criteria:(1) patients with confirmed diagnoses of ILD determined by the authors local criteria; (2) written in English; (3) focus on home monitoring to detect exacerbations and/or progression in patients with ILD; (4) to detect ILD exacerbations and progression (5) randomised controlled trials (RCTs); prospective and retrospective cohort observational studies; and case control studies.

Studies were excluded if the following criteria were met:

(1) Studies that were conference abstracts, theses, and book chapters; (2) systematic reviews and meta-analysis (we screened the bibliography), literature reviews, or qualitative studies.

Search strategy

Between October and November 2020, we searched electronic databases for published articles at any date prior to this, and then updated the search in February 2021 to identify further relevant publications on ILD and home monitoring. We developed a search strategy with medical library staff and extensively searched the following databases: Ovid-EMBASE, Ovid-MEDLINE, Cumulative Index to Nursing and Allied Health Literature (Supplemental Material Tables S1 to S5). We also searched the references of studies thoroughly for any eligible articles. We searched the above electronic databases for Medical Subject Headings (MeSH) terms, and the main terms classified into three groups that describe ILD, home monitoring, and progression. Further detailed related terms to this systematic review are included in the Supplemental Material Tables (S1 to S5).

Data collection

All studies found to be potentially eligible were retrieved from the electronic databases and stored for de-duplicating in the reference management software package EndNote. We exported the results, after removing duplicates, to the online software Rayyan, where the title and abstract of potential studies were screened by two independent reviewers (MA and RE). The software allows the two reviewers to include and exclude studies blindly, and when completed disagreements were

resolved by reading the full text and discussion. We exported the included studies to a new EndNote library, where the articles were read in full.

Quality assessment

Two authors (MA and JA) conducted detailed quality assessment using the Cochrane risk of bias tool for the assessment of the included RCT studies, and the Newcastle-Ottawa tool was used in regard to the observational studies. The Cochrane risk of bias tool comprises seven domains. The Newcastle-Ottawa tool consists of three broad perspectives used to assess the quality of non-randomised studies included in this systematic review. The quality of the cohort studies is based upon a "star" system with a total possible score of nine stars. Study ratings are indicated with the following: 7–9 stars = GOOD, 4–6 stars = FAIR, 1–3 stars = POOR (Table 1-2).

Table 1. Use of Cochrane Risk of Bias tool to assess quality of Randomised Controlled trials.

First author	Random Sequence generation	Allocation concealment	Selective reporting	Blinding subject+ personnel	Blinding outcome assessment	Incomplete outcome data	Other source of bias
Maher et al. (2020)	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Unclear**
Moor Mostard et al. (2020)	**Low**	**Low**	**Low**	**High**	**High**	**Low**	**Unclear**

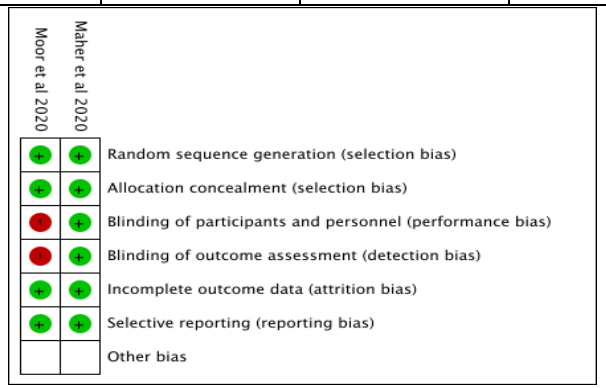


Table 2. Use of Newcastle-Ottawa Tool to assess the quality of cohort studies.

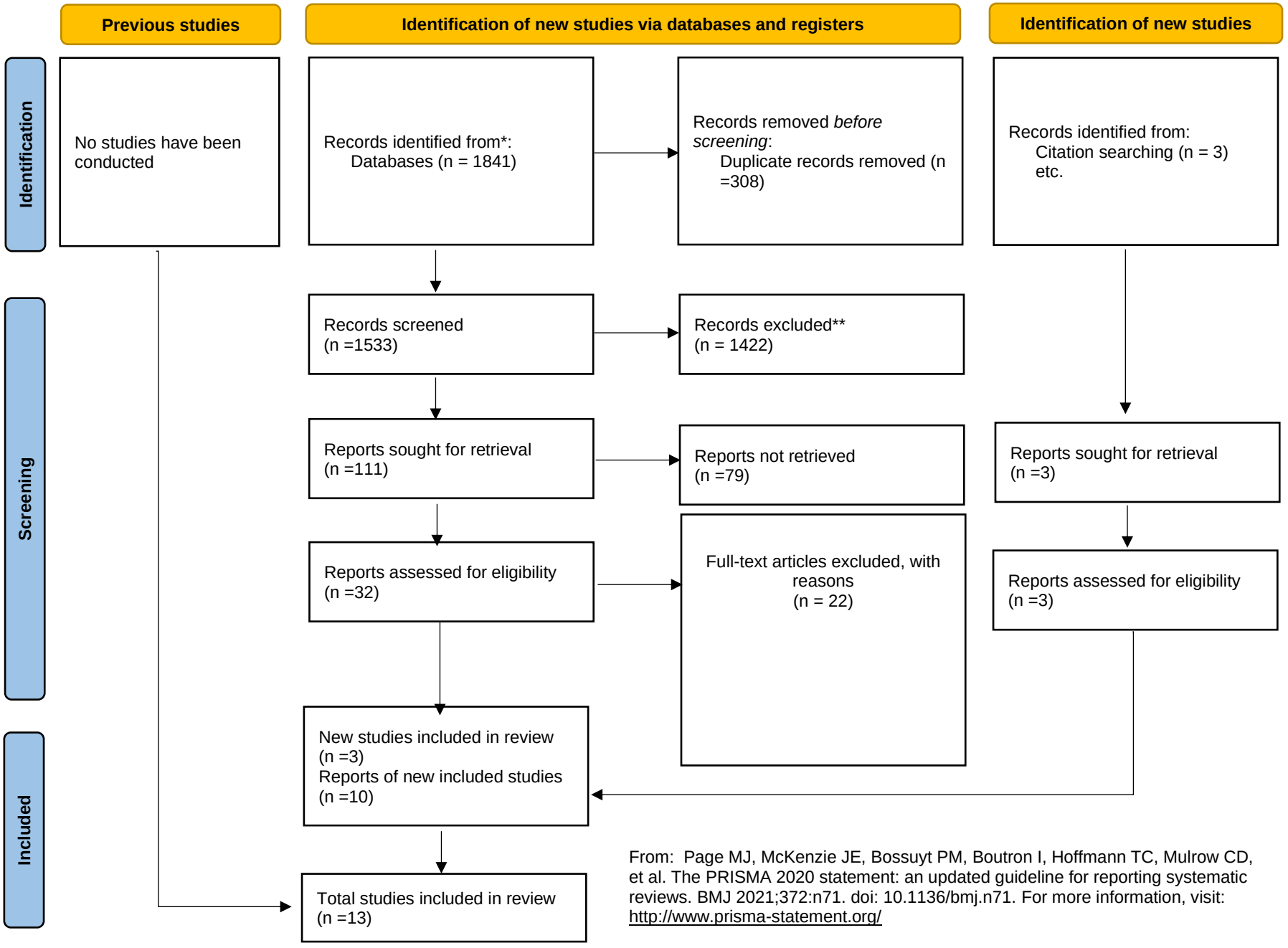
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of all-cause	Outcome not present at the start of study	Comparability of cohort	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Score	Quality
Russell et al. (2016)	**1**	**0**	**1**	**1**	**2**	**0**	**1**	**1**	**7**	**Good**
Johannson et al. (2017)	**1**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**7**	**Good**
Veit et al. (2020)	**1**	**0**	**1**	**1**	**2**	**1**	**1**	**1**	**8**	**Good**
Edwards et al. (2020)	**0**	**0**	**1**	**1**	**2**	**1**	**1**	**1**	**7**	**Good**
Moor, Gür-Demirel et al. (2019)	**1**	**0**	**1**	**1**	**0**	**1**	**1**	**1**	**6**	**Fair**
Moor, Wapenaar et al. (2018)	**1**	**0**	**1**	**1**	**2**	**1**	**1**	**1**	**8**	**Good**
Moor CC, van Leuven, et al. (2020)	**1**	**0**	**1**	**1**	**0**	**1**	**1**	**1**	**6**	**Fair**
Broos et al. (2017)	**1**	**0**	**1**	**1**	**2**	**1**	**1**	**1**	**8**	**Good**
Marcoux et al. (2019)	**1**	**0**	**1**	**1**	**2**	**1**	**1**	**1**	**8**	**Good**
Noth et al. (2021)	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**9**	**Good**
Moor CC, Visser L, et al. (2020)	**1**	**0**	**1**	**1**	**2**	**1**	**1**	**1**	**8**	**Good**

Synthesis of results

Narrative synthesis was undertaken according to outcomes that were reported in the included studies with more emphasis given to studies of higher quality. We considered how differences in design, outcomes, intervention, population and setting may have contributed to any differences in observed results.

Results

The original search across five databases identified 1,841 publications; 1,533 articles remained after duplicates were manually reviewed and removed. A total of 1,422 articles were excluded using title-only screening, followed by 79 exclusions after title and abstract screening. A total of 32 articles remained for full-text screening, 22 articles were excluded. Three articles were included as relevant from searching the references. Thus, thirteen studies were considered for inclusion in this systematic review as depicted in the PRISMA flow diagram (Figure 1 PRISMA flow diagram)



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Description of the included studies

Eleven prospective cohort studies and two randomised controlled trials were identified and included by the systematic search. The RCTs were conducted in the Netherlands, and in multiple centres internationally. Seven cohort studies were conducted in the Netherlands, one in the UK, one in the USA, one in Germany, and one across the USA and Ireland.

General description

Characteristics for the included studies are summarized in Table 3. The studies were published between 2016 and 2021 and involved a total of 968 recruited patients with ILD. The sample size for these studies ranged from 10-346 patients, with age ranging from 31 to 73 years. The majority of the patients were male. The RCT duration were 24 weeks and the prospective cohort studies ranged from 2 to 70 weeks.

TABLE 3. Characteristics of included studies on home monitoring in ILD patients.

Author (Year)	Setting / Design	Sample size and characteristics	Disease group	Clinic measures/ Frequency	Home measures/ Frequency	Study length	Outcome	Quality	Results
Moor, Mostard et al. (2020) [32]	NL /RCT	n=90 Age mean: 71±6.9 yrs. Intervention (n=46) Male:39, (85%) Age mean: 70 yrs. Control (n=44) Male:43, (98%) Age mean: 72 yrs.	IPF	Spirometry , K-BILD, PESaM, EQ-5D-5L, HADS, VAS, GRC, EQ-VAS (Baseline, and at 12 and 24 weeks)	FVC (Once daily) K-BILD, PESaM, EQ-5D-5L, HADS, VAS, GRC, EQ-VAS (Weekly)	24 weeks	Investigate whether a Home monitoring program improves HRQOL and medication use for patients with IPF.	Moderate	(1) improved psychological well-being compared to standard care alone (mean difference 1.04 points; 95% CI, 0.09–2.00; P = 0.032). (2) Mean change in FVC was not significantly different between hospital-based group (-87.9ml; range,-209 to 33.2ml) and home monitoring group (-7.9ml; range, -96 to 69.4ml; p=0.25). Correlation between home and hospital spirometry was high at all time-points (r = 0.97, P<0.001 at baseline and 12 weeks; r = 0.96, P<0.001 at 24 weeks). (3) Correlation between slopes was moderately strong (r = 0.58; P<0.001).
Maher et al. (2020) [40]	RCT	n=253 Intervention (n=127) Age mean:70 yrs(61.0-76.0). Male:70 (55%) Placebo (n=126) Age mean:69 yrs(63.0-74.0) Male:69(55%)	Unclassifiable ILD	Spirometry 6MWD, UCSD-SOBQ, Leicester Cough Q, SGRQ. (Baseline, and at 24 weeks)	FVC (Once daily)	24 weeks	The mean change in FVC measured by daily home-based spirometry, change in FVC measured by site spirometry, change in 6MWD,change in UCSD-SOBQ	Good	(1) The primary endpoint was not adequately analysed due to technical issues result in variability home based spirometry measurements. (2) Mean FVC decline measured by clinic spirometry was less in pirfenidone than placebo group (treatment difference 95·3 mL [95% CI 35·9 to 154·6], p=0·002)
Russell et al. (2016)	UK /PCS	n=50 Male:45, (90%)	IPF	Spirometry baseline, and at ,3 6	FEV1, FVC (Once daily)	Median 279 days,	Feasibility and reliability	Good	(1) Daily FVC measurement was most predictive for disease progression and mortality when measured at 3 months

Author (Year)	Setting / Design	Sample size and characteristics	Disease group	Clinic measures/ Frequency	Home measures/ Frequency	Study length	Outcome	Quality	Results
[33]		Age mean: 66.7±7.9 yrs.		and 12 months		range 13–490 days	of measuring daily FVC.		(hazard ratio 1.04; 95% confidence interval, 1.02–1.06; P≤0.001), 6 months (HR 1.02; 95% CI, 1.01–1.03; P<0.001), and 12 months (HR 1.012; 95% CI, 1.007–1.01; P = 0.001); 28 days did not yield a positive correlation. (2) Regular home measurement of FVC is feasible and reliable. (3) Home spirometry showed high correlation with hospital-based spirometry.
Johannson et al. (2017) [22]	USA/ PCS	n=25 Male:21, (84%) Age mean: 73.6±7.5 yrs.	IPF	Spirometry baseline and at 24 weeks	FEV1, FVC, (three times per week) UCSD-SOBQ (weekly), Dyspnoea-VAS (weekly)	24 weeks	Feasibility and reliability of measuring FVC and dyspnoea.	Good	(1) Weekly home measurement of FVC and dyspnoea in patients with IPF is reliable and feasible over 24 weeks. (2) Mean adherence to weekly home spirometry > 90%.
Veit et al. (2020) [34]	DE/ PCS	n=47 Male:28, (59.6%) Age mean: 62.7 ±11.5 yrs.	ILD	Spirometry, 6MWD 6-min, DLCO, FVC, K-BILD, SGRQ,VAS Cough (baseline, at 3 and 6 months)	FVC (three times per day)	6 months	Determine feasibility in different types of fibrotic non-IPF ILD and investigate the clinical impact of daily home spirometry in patients with progressive ILD with respect to disease progression.	Good	(1) Adherence was higher within the first three months compared to the second three months (83.5 ± 19.6% vs. 78.4 ± 22.3% of the days; P = 0.0086). (2) Correlation between hospital FVC values and the mean of the home FVC measurements was similarly strong at three month (r = 0.95; P < 0.0001) and six-month visits (r = 0.93; P < 0.0001).

Author (Year)	Setting / Design	Sample size and characteristics	Disease group	Clinic measures/ Frequency	Home measures/ Frequency	Study length	Outcome	Quality	Results
Edwards , et al. (2020) [41]	IE / USA/ PCS	n=36 USA Age mean: 62 yrs. Ireland Age mean: 66 yrs.	PF		FVC (once daily) mMRC (once daily) IPF-PROM (weekly)	1 year	Acceptability and utility of patientMpower.	Fair	(1) 93% of respondents reported a positive impact on their well-being. (2) Good correlation between hospital-based and home-based spirometry.
Moor et Gür-Demirel al. (2019) [31]	NL /PCS	n=10 Male:45, (90%) Age mean: 53 yrs.	Sarcoidosis	Spirometry, activity, PROM (baseline and at 1 month), patients' KSQ, EQ5D-5L, HADS, FAS Satisfaction (interview)	PEF FEV1, FVC, (daily) VAS fatigue, dyspnoea, cough, wellbeing (weekly)	4 weeks	Evaluate feasibility of home monitoring program, and patient satisfaction program.	Fair	(1) Home spirometry measurements highly correlated with in-hospital measurements of FVC ($r = 0.97$, $p < 0.001$) and FEV1 ($r = 0.96$, $P < 0.001$). (2) Mean adherence to daily spirometry was 94.6%. It was measured by dividing the total number of measurements by the total numbers of days.
Moor, Wapenaar et al. (2018) [42]	NL /PCS	n=10 Male:9, (90%) Age mean: 71 yrs.	IPF	Spirometry, patient-reported outcome (baseline and at one month) patients' K-BILD, HADS, EuroQoL 5D-5 L	Home spirometry (daily) Patient reported outcome (Weekly)	4 weeks	Feasibility of a pre-developed home monitoring program in IPF (home spirometry).	Fair	(1) Home-based spirometry showed similar results to hospital-based spirometry. Measurements of home and hospital FVC were correlated ($r = 0.94$ ($P < 0.001$)) and FEV1 ($r = 0.97$ ($p < 0.001$)) were highly correlated. (2) Feasibility and potential barriers of home spirometry: 80% of patients reported easy to use and 90% said it was not burdensome. Mean adherence was 98.8% to home monitoring program.

Author (Year)	Setting / Design	Sample size and characteristics	Disease group	Clinic measures/ Frequency	Home measures/ Frequency	Study length	Outcome	Quality	Results
Moor Visser L et al. (2020) [43]	NL/PCS	n=50 (n=44 acceptable data) Age range: 43-79 yrs. Male: 68%	IPF	Questionnaire (baseline and at 6 weeks)	FVC (twice daily) Patient-reported K-BILD online	6 weeks	Measure diurnal variation in FVC in patients with f-ILD using home spirometry, evaluate the relationship between FVC and activity, home-based FVC, home and hospital based correlation.	Fair	(1) Morning FVC was significantly higher than afternoon FVC (mean difference 36 mL, P<0.001). The mean difference between morning and afternoon FVC was similar for patients with IPF compared with all f-ILDs. (2) Daily step correlated with FVC, (r=0.32, P=0.028, K-BILD total score (r=0.5, P<0.001)). (3) Home and hospital-based spirometry were correlated (r=0.98, P<0.0001).
Broos et al. (2017) [44]	NL/PCS	n=21 Male:13 Female:8 Age mean: 43±11 yrs. 76% diagnosed with Scadding stage II sarcoidosis	Sarcoidosis	Clinic spirometry, SGRQ,SF-36,KSQ,MRC,FAS at baseline, 1, and 3 months.	FVC (daily) MRC, FAS (weekly)	3 months	Detect early steroid treatment effects in newly treated pulmonary sarcoidosis.	Good	(1) Home spirometry in sarcoidosis is reliable. (2) Home and hospital spirometry were correlated r=0.98 (P<0.001).
Marcoux et al. (2019) [30]	NL/PCS	n=20 Male:16, (80%) Age mean: 73± 6.9 yrs.	IPF	Clinic spirometry at baseline, 4 and 23 weeks. 6MWD (baseline and at 12 weeks)	FVC (3 manoeuvres daily)	12 weeks	Test the 12-week feasibility of blinded daily handheld spirometry and physical activity monitoring in patients with IPF.	Good	(1) The correlation for office-based and handheld FVC measurements was 0.99 (95% confidence interval [CI], 0.97–0.99) and 0.95 (95% CI, 0.91–0.98), respectively. (2) Mean adherence to home spirometry was 84%.

Author (Year)	Setting / Design	Sample size and characteristics	Disease group	Clinic measures/ Frequency	Home measures/ Frequency	Study length	Outcome	Quality	Results
Noth et al. (2021) [45]	NL/PCS	n=346 diagnosed with IPF in the previous 3 years and had a forced vital capacity (FVC) ≥80% predicted. 116 randomized to nintedanib, 230 randomized to placebo for 12 weeks, followed by an open-label period in which all subjects received nintedanib 150 mg BD for 40 weeks.	IPF	Clinic spirometry at baseline and weeks 4, 8, 12, 16, 20, 24, 36 and 52.	FVC (weekly)	1 year	Investigate the feasibility and validity of home spirometry as a measure of lung function decline in patients with idiopathic pulmonary fibrosis (IPF).	Good	(1) Over 52 weeks, mean adherence was 86%. (2) Strong correlations were observed between home- and clinic-measured FVC at all time-points (r=0.72 to 0.84), but correlations between home- and clinic-measured rates of change in FVC were weak (r=0.26 for rate of decline in FVC over 52 weeks). The correlations were weaker in subjects who provided more FVC readings per week. This was due to variability in change in FVC measured at home (greater number of outliers), and errors in measurements.
Moor CC, van Leuven et al. 2020 [46]	NE/ PCS	n=10 Female: 60% Age mean: 60.3± 9.9 yrs.	Systemic sclerosis-associated ILD	spirometry at baseline, and 3 months. K-BILD, HADS, EQ-5D-5L (Baseline and at 6 weeks)	FVC (once daily)	3 months	Investigate the feasibility of an online home monitoring application, and spirometry.	Good	(1) Mean adherence was 98.8% (SD 1.5). (2) Strong adherence and acceptability. 90% found home monitoring pleasant and wanted to continue to use home monitoring application daily.

Definition of abbreviations: CAT, COPD Assessment Test; EQ-5D-3L, EuroQoL Five- Dimensions Questionnaire; FEV1, forced expiratory volume in one second; FVC, Forced Vital Capacity; GRC, Global Rating Change; HRQL, Health Related Quality of Life; HADS, Hospital Anxiety and Depression Scale; IE, Ireland; K-BILD The King's Brief Interstitial Lung Disease; NL, Netherlands; PESaM, Patient Experiences and Satisfaction with Medication questionnaire; PCS, Prospective Cohort Study; RCT, Randomised Controlled Trial; SGRQ, St. George's Respiratory Questionnaire UK, United Kingdom; US, United States; VAS, visual analog scale

A variety of types of home monitoring techniques including but not limited to spirometry, weekly symptom reporting through electronic means, wearable devices to track/monitor vitals and activity were used. Table 4 summarises the techniques and tools used in the included studies.

TABLE 4. The components and outcomes measured in the home monitoring intervention in this systematic review.

Study	**Measurement parameters**					**Data Transmission**			**Online platform/ app**
First author(Year)	Spirometer/ Quality check		Oximetry	Step count/6MWD	Symptom report	Downloaded by staff	Real time	Diary card	
Moor, Mostard et al. (2020)	✓	✓			✓		✓		✓
Russell et al. (2016)	✓							✓	
Johannson et al. (2017)	✓	✓			✓	✓			
Moor Gür-Demirel et al. (2019)	✓	✓		✓	✓		✓		✓
Veit, et al. (2020)	✓	✓		✓	✓	✓			
Moor, Wapenaar. et al. (2018)	✓	✓			✓		✓		✓
Edwards et al. (2020)	✓	✓	✓	✓	✓		✓		✓
Noth et al. (2020)	✓	✓							
Moor CC, Visser L, et al. (2020)	✓	✓		✓	✓		✓		✓
Broos et al. (2017)	✓				✓	✓			
Marcoux et al. (2019)	✓	✓		✓			✓		✓
Moor CC, van Leuven, et al. (2020)	✓			✓			✓		✓
Maher et al. (2020)	✓	✓		✓	✓	✓			

Feasibility

- **Feasibility**

A recent study by Maher et al.[40] raised some concerns related to the data integrity of home-based spirometry in patients with pulmonary fibrosis due to high variability and technical problems. However, thirteen studies support the feasibility and utility of home-based spirometry in patients with ILD [22, 30, 32-34, 41, 42, 44, 46-49]. Moor et al.[32] reported that the slopes of home- and clinic- based FVC over time were comparable. The rate of discontinuation was not dissimilar to the rates seen in other clinical trials. Most participants were able to provide daily readings, with at least four every five days, for up to 1 year [32, 33, 41, 46]. In contrast, Veit et al.[34] and Marcoux et al.[30] required patients to perform three spirometry manoeuvres every day and found it feasible. In summary, regular home measurement of FVC in the context of a clinical study was found to be feasible. Johannson et al.[22] and Noth et al.[47] showed feasibility and reliability of weekly spirometry in patients with ILD. Two studies in sarcoidosis [44, 49] and one in IPF [31] included 121 patients who performed daily home spirometry, and completed patient-reported outcomes at baseline, weekly, and at the end of the studies. The articles concluded that home monitoring program for IPF and sarcoidosis was indeed feasible, and was well tolerated by most of the patients [31, 32, 44].

In general, all the included studies presented positive experience in relation to acceptance of home monitoring programs by patients. Edwards et al.[41] demonstrated acceptability of home monitoring to patients at six weeks, and the majority of patients wished to continue with home monitoring beyond this time-point. Patients showed a positive attitude towards home monitoring techniques despite differences in age and the size of studies. Ease of use and friendliness of

technology contributed to good compliance among patients and their acceptance of the home monitoring systems [34].

- **Adherence**

Adherence was calculated by the number of home measurements divided by the number of weeks enrolled in the study for weekly measurements, and number of home measurements divided by the number of days enrolled in the study for daily measurements [22, 34]. In the study by Johannson et al. [22] mean adherence to three times weekly home FVC monitoring over 24 weeks was 90.5% (SD=18.3). The Veit et al. [34] study reported that adherence to three times daily home spirometry decreased over time. Median adherence dropped within the first 28 days and decreased from 90% to 81% over six months. Acceptance, however, was high; only four patients discontinued within the first week as dyspnoea made it too difficult to perform daily measurements. Noth et al. [47] demonstrated that adherence to weekly home spirometry decreased with time but remained over 75% throughout the entirety of the study. Studies by Moor et al. [31, 32, 42, 46, 49] demonstrated that mean adherence to once daily home FVC ranged from 90.5% to 98.8%. In summary, adherence to a home monitoring program varied depending on study duration, frequency of measurement, and transmission. However, nine studies [22, 30, 32, 34, 41, 42, 46, 47, 49] reported that mean adherence to home spirometry was greater than >75%. Veit et al. [34] reported that the decrease adherence with time might be due to lack of reminders to perform spirometry. Moor et al. found good adherence that did not decrease with time [32] and suggested that in other studies such challenges with home spirometry might have arisen because patients were blinded from their results and had no technical helpdesk [32].

Utility

- **Prediction of disease progression, and mortality**

Only Russell et al. [33] and Veit et al. [34] reported information describing whether home-based monitoring was able to detect disease progression. Russell et al.[33] reported 18 deaths out of 50 subjects during the 490-day study of patient-recorded daily spirometry. The study compared the rate of change in FVC between baseline to 28 days, 3 months, 6 months, and 12 months. It demonstrated that the rate of change in FVC was more predictive for disease progression and mortality when measured at 3 months (hazard ratio 1.04; 95% confidence interval, 1.02–1.06; $P \leq 0.001$), 6 months (HR, 1.02; 95% CI, 1.01–1.03; $P < 0.001$), and 12 months (HR 1.012; 95% CI, 1.007–1.01; $P = 0.001$); 28 days did not yield a significant correlation [33].

Veit et al. [34] included 47 patients and provided reliable daily measurements of spirometry for the cohort study. The study defined disease progression as death due to respiratory failure, lung transplantation, acute exacerbation, or hospital-based relative FVC decline > 10% at three or six months [34]. During the six months twelve of these 40 participants experienced disease progression [34]. A group of patients displayed high daily variability in FVC during the initial 28 days of the study; 60.0% showed a variation ≥5%. FVC variability over 28 days was independently associated with disease progression (HR 1.20; 95% CI: 1.05–1.3; $P = 0.007$). FVC variability over three months was also a significant predictor for disease progression (HR: 1.2; 95%-CI: 1.01–1.64; $P = 0.03$). It is possible that individual techniques for performing daily spirometry could cause the variation seen in FVC results early on. This study examined results prior to and post the 3-month hospital FVC check and saw no significant variations. This helps eliminate individual technique as a contributor to varied results and so the correlation between results of 28 days and 3 months being strong, significantly supports the relationship between change in FVC and disease

progression. The six minute walk distance (6MWD) (301 ± 140 m vs. 433 ± 89 m; P = 0.009) and the King's Brief Interstitial Lung Disease questionnaire (K-BILD) total score (46.3 ± 8.1 vs. 55.8 ± 12.7; P = 0.004) were lower in the progressive group, indicating more limitation of physical and subjective wellbeing [34].

- **Correlation between home-based spirometry and hospital-based monitoring**

Nine studies [30, 32-34, 41, 44, 46, 49, 50] confirmed strong correlation between home and hospital-based spirometry readings of FVC. Six studies [32, 34, 44, 46, 49, 50] showed a significant positive correlation with a P-value <0.001, and r=0.93-0.98. Noth et al. [47] reported strong correlations between home- and clinic-measured FVC at all time-points (r=0.72 to 0.84), but correlations between home- and clinic-measured rates of change in FVC were weak (r=0.26 for rate of decline in FVC over 52 weeks). The correlations were weaker in subjects who provided more FVC readings per week. This was due to variability in change in FVC measured at home (greater number of outliers), and errors in measurements[47]. Variability in change from baseline in FVC was greater when measured by home rather than clinic spirometry[47]. However, Johannson et al.[21] and Maher et al.[55] report studies that had problems with measurement variability and the quality assurance of home-based spirometry is a major consideration. Johannson et al.[21] showed that home-based monitoring of FVC value was variable and hence suggested hospital-based confirmation of FVC decline to prevent error, defeating the object of home monitoring. Similarly, Maher et al. [47, 55, 56] recommended further research before home measurements of FVC be used as a primary endpoint in clinical trials and in particular, a need for *a priori* consideration of how the planned statistical analysis will handle data from patients with missing or variable spirometry values, so as not to affect planned statistical analyses[47, 56]. Variability might also have been caused by limited adherence, training, technical problems, and

lack of reminders [21, 31, 56]. Marcoux et al. reported that correlation between home spirometer and office-based measurements decline at week 12.

- **Home vs hospital monitoring of medication use**

Two studies by Moor et al.[32, 49] used an online eHealth application developed for patients with sarcoidosis and IPF. Patients kept track of their own health-related data, such as lung function, symptoms, medication, and side effects, and were provided with a graphical overview of their data. It was found that patients reported better insights into the effects of medication by seeing a daily overview of their lung function and potential disease progression. This suggests that patients with ILD had better-tailored treatment decisions during home monitoring programs [32, 49]. Moreover, Broos et al.[44] suggest that home monitoring of physiological parameters could help physicians not only to detect disease progression but also to evaluate response to therapy.

- **Home vs hospital monitoring of well-being and health-related quality of life**

Moor et al.[32] assessed health-related quality of life in patients with IPF using the K-BILD questionnaire in a 24-week randomised controlled trial[32]. K-BILD is a validated, 15-item self-rated questionnaire, and an interstitial lung disease-specific, health-related quality of life questionnaire[32]. Home monitoring was not associated with a statistically significant improvement in K-BILD (mean difference 2.67 points; 95% CI, -1.85-7.17; $P = 0.24$). The RCT consisted of 90 patients; 46 out of 90 received home monitoring services. It was found that both the mean K-BILD score and the K-BILD psychological domain score was greater in the home monitoring group indicating improved general psychological well-being. The results of the RCT showed that the anxiety scores were low in both groups, improved psychological wellbeing and allowed for individually tailored treatment adjustments.

DISCUSSION

We have conducted the first systematic review examining home monitoring of lung function and symptoms to detect ILD exacerbations and progression. Thirteen studies utilized home monitoring to measure feasibility and utility with two studies including disease progression as an outcome. The included studies provide evidence to support the feasibility and utility of home-based monitoring in patients with ILD [22, 30, 32-34, 41, 42, 44, 46-49]. However, the included studies varied in their primary outcome, and were heterogeneous with respect to duration, measurements, and the type of technology and questionnaires used.

ILD relies on regular pulmonary function testing to guide management [10, 51-54]. Among the tools used for home-based monitoring, comparison of spirometry before and after an exacerbation and/or progression demonstrated that FVC decline reflects the severity of disease progression [2, 55, 56]. At present, spirometry is the primary test used to detect exacerbation and/or progression in ILD [57-59]. FVC variability was addressed in two of the included studies in patients with ILD. Veit, et al. [34] and Russell et al. [33] demonstrated a link between variability of FVC and ILD disease progression [33, 34]. Veit et al. [34] found that FVC variability was a statistically significant predictor for disease progression [58, 60, 61]. Moreover, Russell et al.[33] confirmed that the rate of change in FVC was most predictive for disease progression and mortality when measured over 3, 6 and 12 months. Risk of variation can be mitigated by providing training, a technical helpdesk, and real-time monitoring with reminders [32].

Early detection of disease progression and acute exacerbation has been a focus for several diseases, especially in COPD [62]. Home monitoring of heart rate and oxygen saturation has been shown to

result in early detection of exacerbation in COPD [28]. Similarly, previously studies reported exacerbation and/or progression in patients with ILD [10, 23, 24, 63]. Most studies until recently have only focused on the feasibility and reliability of home monitoring. However, the potential for home monitoring to facilitate early identification of AE-ILD has gained increasing interest during the past years. Recently, Moor et al.[42] reported that FVC decline could be detected 2 days before symptoms of infection began. Although it is possible to continuously monitor heart rate and oxygen saturation, the included studies in this review did not examine data for heart rate and oxygen saturation. Monitoring heart rate, 6MWD, activity and oxygen saturation remotely might contribute to a more precise prediction of disease exacerbation and/or progression [54, 58, 64-71].

Other factors to be considered are potential use of real-time monitoring and artificial intelligence to predict exacerbation and/or progression [66, 72-74]. Artificial intelligence is now adapted to interpret complex data in COPD to predict acute respiratory events [66, 75-79]. Artificial intelligence could allow monitoring of a large number of patients continuously and simultaneously. Utilizing machine learning via an online platform with real-time data transmission could allow real-time detection of exacerbation and/or progression [58, 64, 80]. Predictors of disease exacerbation and/or progression have already been published but not specifically for patients with ILD [75, 81-83]. The ability to accurately detect rare occurrences, such as AE-IPF, offers the potential for clinical trials to assess early treatments for these, often devastating, events. We believe that machine learning and the use of an online platform with direct data transmission, of proven value in other diseases [75, 78] , has promising potential in the field of ILD.

Encouraging findings were the high level of adherence and that patients were generally satisfied with home monitoring [31, 32, 41, 42]. Nevertheless, some studies showed that adherence to home-based monitoring decreased over time [22, 34, 84]. It is suggested that involving patients in monitoring their own condition would give some feeling of being in control and managing the condition [22, 85, 86]. This aligns with what has been suggested in respect to patients' increase in adherence to, and satisfaction with, home-based monitoring [22, 42, 87, 88]. Another reason for patients to remain adherent might be the ability of home monitoring to generate early alerts of deterioration with the potential for early interventions [32].

In a recent assessments of home monitoring for patients with ILD, healthcare providers were interested to use home monitoring for regular care and research purposes[89]. Although these findings are encouraging, further studies considering clinician perspectives are necessary. It is important to consider that the total number of participants was fewer than one thousand, and all were patients. This is not a complete representation of real-world clinical experience. Both patients and clinicians could benefit from effective home monitoring for patients with ILD to detect exacerbations and/or progression and to allow timelier intervention; for closer monitoring of therapeutic interventions; and to assess novel medications in clinical trials. The potential cost reduction on both patient and clinician sides could also be explored.

The potential of home monitoring of ILD patients was a consistent focus of the included studies, but the challenge of providing effective detection of exacerbation and/or progression has yet to be addressed. The published trials were mostly feasibility studies with a few ongoing studies [61, 90, 91] focusing on detection of AE-ILD using home spirometry. Researchers should conduct

longitudinal studies of physiological parameters and symptoms with real-time feedback from integrated spirometry, pulse oximetry and wearable devices and smartphone applications to assess their ability to detect exacerbation and/or progression in patients with ILD.

Conclusion:

Although there were no studies reporting conclusively on the ability of home-monitoring to detect deteriorations of ILD and AE-ILD, this systematic review suggests good adherence and feasibility of home monitoring. Home monitoring presents an opportunity for earlier detection of exacerbation and/or progression in ILD and examining this question should be the focus of future research.

Abbreviations

FVC: Forced vital capacity

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

K-BILD: King's Brief Interstitial Lung Disease Questionnaire

SD: Standard deviation

SGRQ: St. George's Respiratory Questionnaire

VAS: Visual analogue scale

CI: Confidence interval

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: Randomised controlled trial

6MWD: 6-minute walk distance

COPD: Chronic obstructive pulmonary disease

DLCO: Diffusing capacity of the Lung for Carbon Monoxide

FEV1: Forced expiratory volume in one second

PCS: Prospective cohort study

References:

1. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165(2):277-304.
2. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine. 2011;183(6):788-824.
3. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A Common MUC5B Promoter Polymorphism and Pulmonary Fibrosis. New England Journal of Medicine. 2011;364(16):1503-12.
4. Kropski JA, Pritchett JM, Zoz DF, Crossno PF, Markin C, Garnett ET, et al. Extensive phenotyping of individuals at risk for familial interstitial pneumonia reveals clues to the pathogenesis of interstitial lung disease. Am J Respir Crit Care Med. 2015;191(4):417-26.
5. Marshall RP, Puddicombe A, Cookson WO, Laurent GJ. Adult familial cryptogenic fibrosing alveolitis in the United Kingdom. Thorax. 2000;55(2):143-6.
6. Ley B, Collard HR, Talmadge E. King J. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. American Journal of Respiratory and Critical Care Medicine. 2011;183(4):431-40.
7. Foundation BL. Lung disease in the UK – big picture statistics. 2020.
8. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. New England Journal of Medicine. 2018;378(19):1811-23.
9. Lee SH, Kim SY, Kim DS, Kim YW, Chung MP, Uh ST, et al. Predicting survival of patients with idiopathic pulmonary fibrosis using GAP score: a nationwide cohort study. Respiratory Research. 2016;17(1):131.
10. Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183(4):431-40.
11. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. The Lancet. 2011;377(9779):1760-9.
12. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. New England Journal of Medicine. 2014;370(22):2083-92.
13. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. New England Journal of Medicine. 2014;370(22):2071-82.
14. Maher TM, Strek ME. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. Respiratory Research. 2019;20(1):205.
15. Raghu G, Chen SY, Yeh WS, Maroni B, Li Q, Lee YC, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. Lancet Respir Med. 2014;2(7):566-72.

16. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760-9.
17. Win T, Screaton NJ, Porter JC, Ganeshan B, Maher TM, Fraioli F, et al. Pulmonary (18)F-FDG uptake helps refine current risk stratification in idiopathic pulmonary fibrosis (IPF). European journal of nuclear medicine and molecular imaging. 2018;45(5):806-15.
18. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib. N Engl J Med. 2015;372(13):1189-91.
19. Spagnolo P, Maher TM. Clinical trial research in focus: why do so many clinical trials fail in IPF? Lancet Respir Med. 2017;5(5):372-4.
20. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. N Engl J Med. 2001;345(7):517-25.
21. Wells AU, Behr J, Costabel U, Cottin V, Poletti V, Richeldi L. Hot of the breath: mortality as a primary end-point in IPF treatment trials: the best is the enemy of the good. Thorax. 2012;67(11):938-40.
22. Johannson KA, Vittinghoff E, Morisset J, Lee JS, Balmes John R, Collard HR. Home monitoring improves endpoint efficiency in idiopathic pulmonary fibrosis. European Respiratory Journal. 2017;50(1):1602406.
23. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. American Journal of Respiratory and Critical Care Medicine. 2016;194(3):265-75.
24. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. European Respiratory Journal. 2011;37(2):356.
25. Leuschner G, Behr J. Acute Exacerbation in Interstitial Lung Disease. Front Med (Lausanne). 2017;4:176-.
26. Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Patel AR, Wedzicha JA. Domiciliary pulse-oximetry at exacerbation of chronic obstructive pulmonary disease: prospective pilot study. BMC Pulm Med. 2010;10:52.
27. Wilkinson TMA, Donaldson GC, Hurst JR, Seemungal TAR, Wedzicha JA. Early Therapy Improves Outcomes of Exacerbations of Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine. 2004;169(12):1298-303.
28. Al Rajeh AM, Aldabayan YS, Aldhahir A, Pickett E, Quaderi S, Alqahtani JS, et al. Once Daily Versus Overnight and Symptom Versus Physiological Monitoring to Detect Exacerbations of Chronic Obstructive Pulmonary Disease: Pilot Randomized Controlled Trial. JMIR Mhealth Uhealth. 2020;8(11):e17597.
29. Denis F, Basch E, Septans A-L, Bennouna J, Urban T, Dueck AC, et al. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. JAMA. 2019;321(3):306-7.
30. Marcoux V, Wang M, Burgoyne SJ, Fell CD, Ryerson CJ, Sajobi TT, et al. Mobile Health Monitoring in Patients with Idiopathic Pulmonary Fibrosis. Annals of the American Thoracic Society. 2019;16(10):1327-9.
31. Moor CC, Gür-Demirel Y, Wijsenbeek MS. Development and feasibility of an eHealth tool for idiopathic pulmonary fibrosis. Journal of Personalized Medicine. 2019;9(2).

32. Moor CC, Mostard RLM, Grutters JC, Bresser P, Aerts JGJV, Chavannes NH, et al. Home Monitoring in Patients with Idiopathic Pulmonary Fibrosis. A Randomized Controlled Trial. American Journal of Respiratory and Critical Care Medicine. 2020;202(3):393-401.
33. Russell AM, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016;194(8):989-97.
34. Veit T, Barnikel M, Crispin A, Kneidinger N, Ceelen F, Arnold P, et al. Variability of forced vital capacity in progressive interstitial lung disease: a prospective observational study. Respiratory Research. 2020;21(1):270.
35. Foundation BL. Coronavirus and COVID-19 2020 [Available from: https://www.blf.org.uk/support-for-you/coronavirus/what-is-social-shielding.
36. Nakshbandi G, Moor CC, Wijsenbeek MS. Home monitoring for patients with ILD and the COVID-19 pandemic. The Lancet Respiratory medicine. 2020;8(12):1172-4.
37. Antoniou KM, Raghu G, Tzilas V, Bouros D. Management of Patients with Interstitial Lung Disease in the Midst of the COVID-19 Pandemic. Respiration. 2020;99(8):625-7.
38. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
39. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLOS Medicine. 2021;18(3):e1003583.
40. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet Respiratory Medicine. 2020;8(2):147-57.
41. Edwards C, Costello E, Cassidy N, Vick B, Russell AM. Use of the patientMpower App With Home-Based Spirometry to Monitor the Symptoms and Impact of Fibrotic Lung Conditions: Longitudinal Observational Study. JMIR Mhealth Uhealth. 2020;8(11):e16158.
42. Moor CC, Wapenaar M, Miedema JR, Geelhoed JJM, Chandoesing PP, Wijsenbeek MS. A home monitoring program including real-time wireless home spirometry in idiopathic pulmonary fibrosis: a pilot study on experiences and barriers. Respir Res. 2018;19(1):105.
43. Moor CC, van den Berg CAL, Visser LS, Aerts JGJV, Cottin V, Wijsenbeek MS. Diurnal variation in forced vital capacity in patients with fibrotic interstitial lung disease using home spirometry. ERJ Open Res. 2020;6(1):00054-2020.
44. Broos CE, Wapenaar M, Looman CWN, in 't Veen JCCM, van den Toorn LM, Overbeek MJ, et al. Daily home spirometry to detect early steroid treatment effects in newly treated pulmonary sarcoidosis. European Respiratory Journal. 2018;51(1):1702089.
45. Noth I, Cottin V, Chaudhuri N, Corte TJ, Johannson KA, Wijsenbeek M, et al. Home spirometry in patients with idiopathic pulmonary fibrosis: data from the INMARK trial. Eur Respir J. 2021.
46. Moor CC, van Leuven SI, Wijsenbeek MS, Vonk MC. Feasibility of online home spirometry in systemic sclerosis-associated interstitial lung disease: a pilot study. Rheumatology (Oxford). 2020.
47. Noth I, Cottin V, Chaudhuri N, Corte TJ, Johannson KA, Wijsenbeek M, et al. Home spirometry in patients with idiopathic pulmonary fibrosis: data from the INMARK trial. European Respiratory Journal. 2021:2001518.

48. Moor K, Visser L, Aerts J, Cottin V, Wijsenbeek M. Diurnal variation in forced vital capacity in patients with fibrotic interstitial lung disease using home spirometry: the DIVA study. European Respiratory Journal. 2019;54(suppl 63):PA2246.
49. Moor CC, Gür-Demirel Y, Wijsenbeek MS. Feasibility of a Comprehensive Home Monitoring Program for Sarcoidosis. J Pers Med. 2019;9(2).
50. Moor CC, van den Berg CAL, Visser LS, Aerts J, Cottin V, Wijsenbeek MS. Diurnal variation in forced vital capacity in patients with fibrotic interstitial lung disease using home spirometry. ERJ Open Res. 2020;6(1):00054-2020.
51. Martinez FJ, Flaherty K. Pulmonary Function Testing in Idiopathic Interstitial Pneumonias. Proceedings of the American Thoracic Society. 2006;3(4):315-21.
52. du Bois RM, Nathan SD, Richeldi L, Schwarz MI, Noble PW. Idiopathic pulmonary fibrosis: lung function is a clinically meaningful endpoint for phase III trials. Am J Respir Crit Care Med. 2012;186(8):712-5.
53. Erbes R, Schaberg T, Loddenkemper R. Lung Function Tests in Patients With Idiopathic Pulmonary Fibrosis: Are They Helpful for Predicting Outcome? Chest. 1997;111(1):51-7.
54. Maher TM, Corte TJ, Kreuter M, Molina-Molina M, Axmann J, Gilberg F, et al. Home Spirometry as a Primary Endpoint in Clinical Trials: Sensitivity Analyses of a Randomized Controlled Trial of Pirfenidone in Patients with Unclassifiable Interstitial Lung Disease (UILD). A102 ILD DIAGNOSIS AND MONITORING. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2020. p. A2575-A.
55. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Ascertainment of Individual Risk of Mortality for Patients with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2011;184(4):459-66.
56. Moor CC, Wapenaar M, Miedema JR, Geelhoed JJM, Chandoesing PP, Wijsenbeek MS. A home monitoring program including real-time wireless home spirometry in idiopathic pulmonary fibrosis: a pilot study on experiences and barriers. Respir Res. 2018;19(1):105-.
57. Bois RMd, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced Vital Capacity in Patients with Idiopathic Pulmonary Fibrosis. American Journal of Respiratory and Critical Care Medicine. 2011;184(12):1382-9.
58. Collard HR, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis. American Journal of Respiratory and Critical Care Medicine. 2003;168(5):538-42.
59. Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. European Respiratory Journal. 2010;35(4):830.
60. Flaherty KR, Andrei A-C, Murray S, Fraley C, Colby TV, Travis WD, et al. Idiopathic Pulmonary Fibrosis. American Journal of Respiratory and Critical Care Medicine. 2006;174(7):803-9.
61. A Study to Characterize the Disease Behavior of Idiopathic Pulmonary Fibrosis (IPF) and Interstitial Lung Disease (ILD) During the Peri-Diagnostic Period. 2017.
62. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. New England Journal of Medicine. 2010;363(12):1128-38.
63. Leuschner G, Behr J. Acute Exacerbation in Interstitial Lung Disease. Front Med (Lausanne). 2017;4:176.

64. Swigris JJ, Swick J, Wamboldt FS, Sprunger D, du Bois R, Fischer A, et al. Heart Rate Recovery After 6-Min Walk Test Predicts Survival in Patients With Idiopathic Pulmonary Fibrosis. Chest. 2009;136(3):841-8.
65. Seemungal TAR, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of Exacerbation on Quality of Life in Patients with Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine. 1998;157(5):1418-22.
66. Shah SA, Velardo C, Farmer A, Tarassenko L. Exacerbations in Chronic Obstructive Pulmonary Disease: Identification and Prediction Using a Digital Health System. Journal of medical Internet research. 2017;19(3):e69.
67. Wu W, Jordan S, Becker MO, Dobrota R, Maurer B, Fretheim H, et al. Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. Annals of the Rheumatic Diseases. 2018;77(9):1326.
68. Bahmer T, Kirsten AM, Waschki B, Rabe KF, Magnussen H, Kirsten D, et al. Clinical Correlates of Reduced Physical Activity in Idiopathic Pulmonary Fibrosis. Respiration. 2016;91(6):497-502.
69. Wallaert B, Monge E, Le Rouzic O, Wémeau-Stervinou L, Salleron J, Grosbois J-M. Physical Activity in Daily Life of Patients With Fibrotic Idiopathic Interstitial Pneumonia. Chest. 2013;144(5):1652-8.
70. Root ED, Graney B, Baird S, Churney T, Fier K, Korn M, et al. Physical activity and activity space in patients with pulmonary fibrosis not prescribed supplemental oxygen. BMC Pulmonary Medicine. 2017;17(1):154.
71. Bahmer T, Kirsten A-M, Waschki B, Rabe KF, Magnussen H, Kirsten D, et al. Prognosis and longitudinal changes of physical activity in idiopathic pulmonary fibrosis. BMC pulmonary medicine. 2017;17(1):104-.
72. Jha S, Topol EJ. Adapting to Artificial Intelligence: Radiologists and Pathologists as Information Specialists. JAMA. 2016;316(22):2353-4.
73. Dilsizian SE, Siegel EL. Artificial intelligence in medicine and cardiac imaging: harnessing big data and advanced computing to provide personalized medical diagnosis and treatment. Curr Cardiol Rep. 2014;16(1):441.
74. Neill DB. Using Artificial Intelligence to Improve Hospital Inpatient Care. IEEE Intelligent Systems. 2013;28(2):92-5.
75. Esteban C, Moraza J, Esteban C, Sancho F, Aburto M, Aramburu A, et al. Machine learning for COPD exacerbation prediction. European Respiratory Journal. 2015;46(suppl 59):OA3282.
76. Topalovic M, Das N, Burgel P-R, Daenen M, Derom E, Haenebalcke C, et al. Artificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests. European Respiratory Journal. 2019;53(4):1801660.
77. Sanchez-Morillo D, Fernandez-Granero MA, Leon-Jimenez A. Use of predictive algorithms in-home monitoring of chronic obstructive pulmonary disease and asthma: A systematic review. Chron Respir Dis. 2016;13(3):264-83.
78. Finkelstein J, Jeong IC. Machine learning approaches to personalize early prediction of asthma exacerbations. Annals of the New York Academy of Sciences. 2017;1387(1):153-65.
79. Orchard P, Agakova A, Pinnock H, Burton CD, Sarran C, Agakov F, et al. Improving Prediction of Risk of Hospital Admission in Chronic Obstructive Pulmonary Disease: Application of Machine Learning to Telemonitoring Data. J Med Internet Res. 2018;20(9):e263.

80. Darcy AM, Louie AK, Roberts LW. Machine Learning and the Profession of Medicine. JAMA. 2016;315(6):551-2.
81. Janson C, Johansson G, Larsson K, Ställberg B, Mueller M, Luczko M, et al. Use of Machine learning to predict asthma exacerbations. European Respiratory Journal. 2020;56(suppl 64):4802.
82. Peng J, Chen C, Zhou M, Xie X, Zhou Y, Luo C-H. A Machine-learning Approach to Forecast Aggravation Risk in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease with Clinical Indicators. Scientific Reports. 2020;10(1):3118.
83. Young AL, Bragman FJS, Rangelov B, Han MK, Galbán CJ, Lynch DA, et al. Disease Progression Modeling in Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine. 2019;201(3):294-302.
84. Noth I, Maher TM, Johannson KA, Chaudhuri N, Jouneau S, Michael A, et al. Adherence to home spirometry among patients with IPF: results from the INMARK trial. European Respiratory Journal. 2019;54(suppl 63):PA2241.
85. Velardo C, Shah SA, Gibson O, Clifford G, Heneghan C, Rutter H, et al. Digital health system for personalised COPD long-term management. BMC Medical Informatics and Decision Making. 2017;17(1):19.
86. Swigris J, Nathan S, Tighe R, Nagra S, Rabe C, Kelkhoff D, et al. STARMAP: an observational study to assess disease-relevant outcomes using home-monitoring devices in patients with idiopathic pulmonary fibrosis (IPF). European Respiratory Journal. 2019;54(suppl 63):PA1333.
87. Lenferink A, Brusse-Keizer M, van der Valk P, Frith PA, Zwerink M, Monninkhof EM, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2017(8).
88. Wijsenbeek MS, Bendstrup E, Valenzuela C, Henry MT, Moor C, Jouneau S, et al. Interim analysis of patients with ILD enrolled in the STARLINER study. European Respiratory Journal. 2019;54(suppl 63):PA1335.
89. Nakshbandi G, Moor CC, Johannson KA, Maher TM, Kreuter M, Wijsenbeek MS. Worldwide experiences and opinions of healthcare providers on eHealth for patients with interstitial lung diseases in the COVID-19 era. ERJ Open Research. 2021:00405-2021.
90. Wijsenbeek M. An International Patient-led Registry in Fibrotic Interstitial Lung Diseases Using eHealth Technology. 2020.
91. Kreuter M. Early Detection of Acute Exacerbation in Patients With Idiopathic Lung Fibrosis - a Pilot Study
2019.

Home monitoring of physiology and symptoms to detect interstitial lung disease exacerbations and progression: a systematic review

SUPPLEMENTARY APPENDIX

Malik A. Althobiani[1], Rebecca A Evans[2], Jaber S Alqahtani[1], Abdulelah M Aldhahir[1], A. M. Russell[3] , John R Hurst [*1], Joanna C. Porter [*1]

Affiliation

1. UCL Respiratory, University College London
2. University College London Hospitals NHS Foundation Trust
3. University of Exeter College of Medicine and Health.

*Joint senior authors

Tables S1 and S2 provide details of the Embase Search Strategy and search concepts .Tables S3 and S4 provide detailed summaries of the included papers. Table S5 and S6 shows the quality assessment of studies.

Table S1. Embase Search Strategy

#	**Searches**	Results
1	exp interstitial lung disease/	78520
2	interstitial lung disease.mp.	27269
3	ILD.mp.	10264
4	exp fibrosing alveolitis/	24962
5	Idiopathic pulmonary fibrosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	15936
6	IPF.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	13338
7	ILD.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	10264
8	Interstitial lung disease.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	27269
9	Sarcoidosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	39987
10	lung sarcoidosis/ or sarcoidosis/ or sarcoidosis.mp.	39987
11	exp asbestosis/	4426
12	asbestosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	5002
13	Interstitial pneumonia.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	19871
14	exp interstitial pneumonia/	15797
15	Nonspecific interstitial pneumonitis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	164
16	Lung Diseases, Interstitial/	11329
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	128045
18	telemedicine/	26831
19	(telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	43430
20	(e-health or ehealth or m-health or mhealth or mobile health).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	15862
21	exp telemetry/ or exp telephone telemetry/	28159

22	Monitoring, Ambulatory/	11045
23	(monitoring adj4 (ambulatory or home$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	34975
24	Domiciliary.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3199
25	mobile application/ or app/ or software/	85222
26	Home monitoring.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	5796
27	Spirometry.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	45509
28	exp spirometry/	40687
29	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	239677
30	disease exacerbation/	122010
31	(exacerbat* or deteriorat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	431808
32	Progression.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	854808
33	predict*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2272713
34	detect*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3074247
35	early diagnosis/	108538
36	((respirat* or breath*) adj3 rate*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	59941
37	((heart* or pulse* or cardiac) adj3 rate*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	342488
38	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	6356485
39	17 and 29 and 38	1154
40	conference abstract/	1001899
41	39 not 40	924
42	limit 41 to human	874

Table S2: Database Search Strategy

Table S2: Database Search Strategy		
Database	**Subject Heading**	**Keyword**
MEDLINE	Interstitial Lung Disease	exp interstitial lung disease/. interstitial lung disease.mp. ILD.mp. exp fibrosing alveolitis/. Idiopathic pulmonary fibrosis.mp. IPF.mp. ILD.mp. Sarcoidosis.mp. lung sarcoidosis/ or sarcoidosis/ or sarcoidosis.mp. exp asbestosis/. asbestosis.mp. Interstitial pneumonia.mp. exp interstitial pneumonia/. Nonspecific interstitial pneumonitis.mp. Lung Diseases, Interstitial/.
	Home Monitoring	telemedicine/. (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine).mp. (e-health or ehealth or m-health or mhealth or mobile health).mp exp telemetry/ or exp telephone telemetry/. Monitoring, Ambulatory/. (monitoring adj4 (ambulatory or home$)).mp. Domiciliary.mp. mobile application/ or app/ or software/. Home monitoring.mp. Spirometry.mp. exp spirometry/
	Exacerbation	disease exacerbation/. (exacerbat* or deteriorat*).mp. Progression.mp. predict*.mp. detect*.mp. early diagnosis/. ((respirat* or breath*) adj3 rate*).mp. ((heart* or pulse* or cardiac) adj3 rate*).mp.

Table S2 Continued		
Database	Subject Heading	Keyword
CINAHL	(MH" Interstitial Lung Disease”) OR (MH"Interstitial pulmonary disease") OR (MH"Idiopathic pulmonary fibrosis") OR (MH"Fibrosing alveolitis") (MH"Sarcoidosis" OR (MH"Lung Sarcoidosis") (MH"Asbestosis") (MH"Interstitial pneumonia") OR (MH"Nonspecific interstitial pneumonitis")	TX Interstitial Lung Disease* TX (ILD) TX Idiopathic pulmonary fibrosis* TX (IPF) TX Fibrosing alveolitis* TX Sarcoidosis* TX Lung Sarcoidosis* TX Asbestosis* TX Interstitial pneumonia* TX Nonspecific interstitial pneumonitis*
	(MH "Home Monitoring") OR (MH"telemedicine") OR (MH"telemonitor") OR (MH"tele-monitor") OR (MH"tele-health") OR (MH"telehealth") OR (MH "Heart rate OR pulse OR respiratory rate OR Spirometry")	TX Telemedicine* OR telemonitor* or tele-monitor* or tele-health* or telehealth* TX E-health* or ehealth* or m-health* or mhealth* or mobile health*) TX telephone* TX Monitoring* TX Domiciliary* TX mobile application* TX Home monitoring* TX Spirometry*.
	(MH"Exacerbation") OR (MH" Deterioration") OR (MH" Progression") OR (MH"Predict") OR (MH "Detect")	TX disease exacerbation* OR exacerbate* OR deteriorate* OR Progression* TX Predict* OR detect* OR Early diagnosis* TX Heart rate* pulse* respiratory rate*

Table S2 Continued		
Database	Subject Heading	Keyword
Cochran	[mh "Interstitial Lung Disease"] OR [mh "Interstitial pulmonary disease"] [mh "Idiopathic pulmonary fibrosis"] [mh "Fibrosing alveolitis"] [mh "Sarcoidosis"] [mh "Lung Sarcoidosis"] [mh "Asbestosis"] [mh"Interstitialpneumonia"] [mh "Nonspecific interstitial pneumonitis"]	Interstitial Lung Disease* (ILD) Idiopathic pulmonary fibrosis* (IPF) Fibrosing alveolitis* Sarcoidosis* Lung Sarcoidosis* Asbestosis* Interstitial pneumonia* Nonspecific interstitial pneumonitis*
	[MH "Home Monitoring"] [mh "telemedicine"] [mh "telemonitor"] [mh "tele-monitor"] [mh "tele-health"] [mh "telehealth"] [mh "Heart rate OR pulse OR respiratory rate OR Spirometry"]	Telemedicine* OR telemonitor* or tele-monitor* or tele-health* or telehealth* E-health* or ehealth* or m-health* or mhealth* or mobile health*) telephone* Monitoring* Domiciliary* mobile application* Home monitoring*Spirometry*.
	[mh "Exacerbation"] [mh "Deterioration"] [mh "Progression"] [mh "Predict"] [mh "Detect"]	disease exacerbation* OR exacerbate* OR deteriorate* OR Progression* Predict* OR detect* OR Early diagnosis* Heart rate* pulse* respiratory rate*

Table S2 Continued		
Database	Heading	Keyword
Google Scholar		(Interstitial Lung Disease) OR (Interstitial pulmonary disease) OR (Idiopathic pulmonary fibrosis) OR (Fibrosing alveolitis)(Sarcoidosis) OR (Lung Sarcoidosis)(Asbestosis) (Interstitial pneumonia) OR (Nonspecific interstitialpneumonitis
		(Home Monitoring) OR (telemedicine) OR (telemonitor) OR (tele-monitor) OR (tele-health) OR (telehealth) OR (Heart rate OR pulse OR respiratory rate OR Spirometry)
		(Exacerbation) OR (Deterioration) OR (Progression) OR (Predict) OR (Detect)