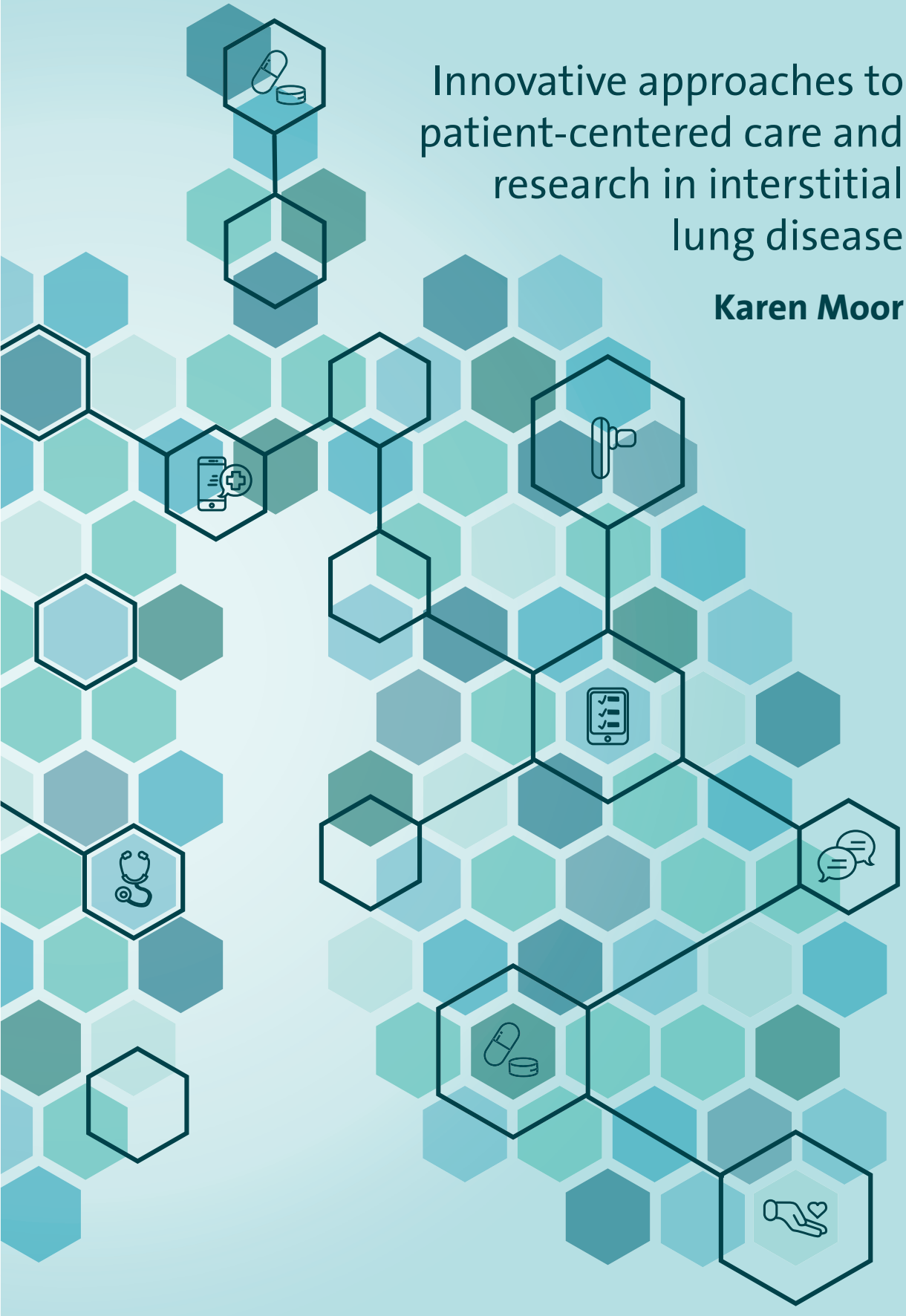
Innovative approaches to patient-centered care and research in interstitial lung disease

Karen Moor



Innovative Approaches to Patient-centered Care and Research in Interstitial Lung Disease

Catharina Christina Moor

The work described in this thesis was conducted at the Department of Respiratory Medicine, Erasmus MC, Rotterdam, the Netherlands.

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Innovative Approaches to Patient-centered Care and Research in Interstitial Lung Disease

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onderzoek in interstitiële longziekten

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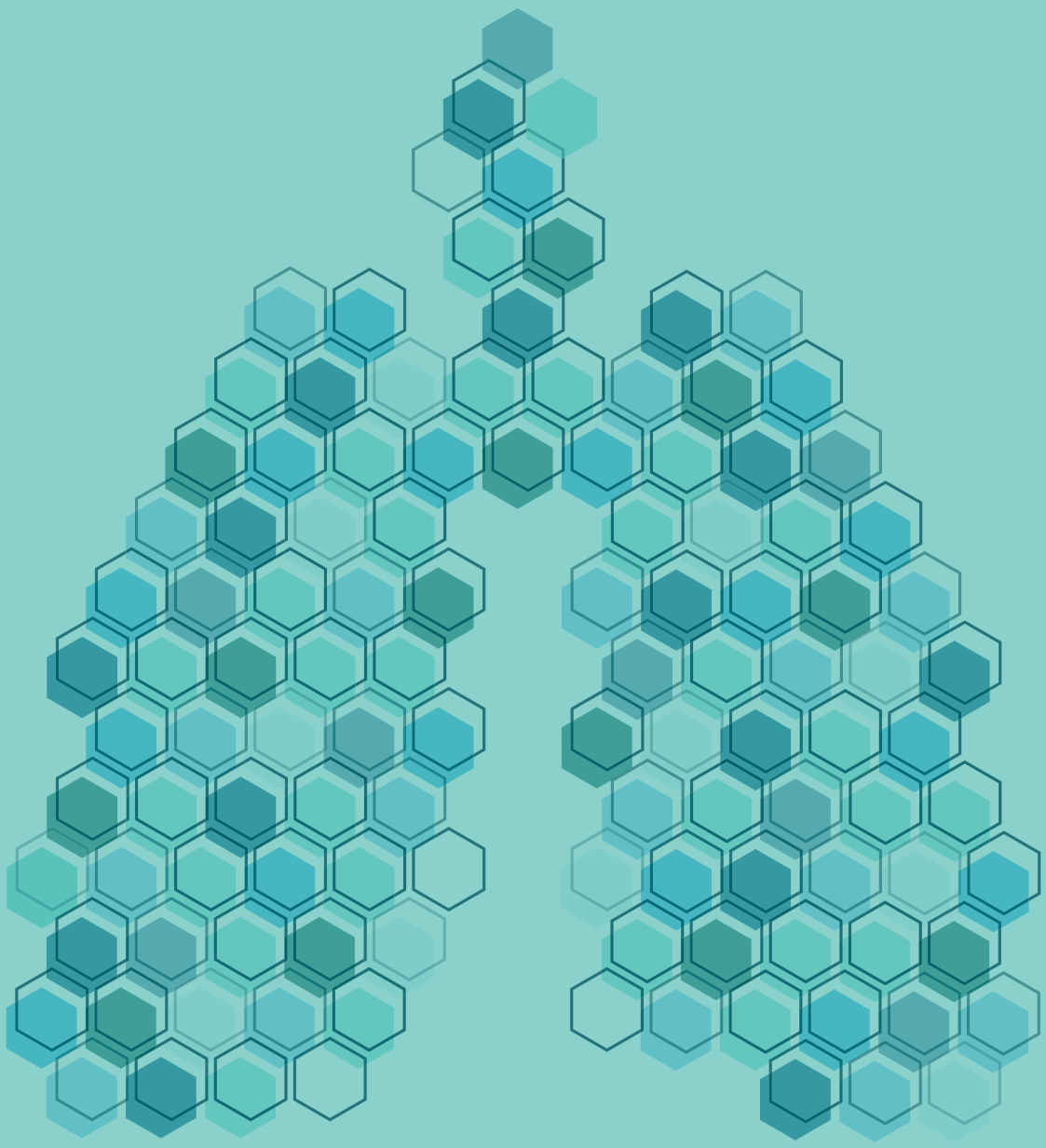
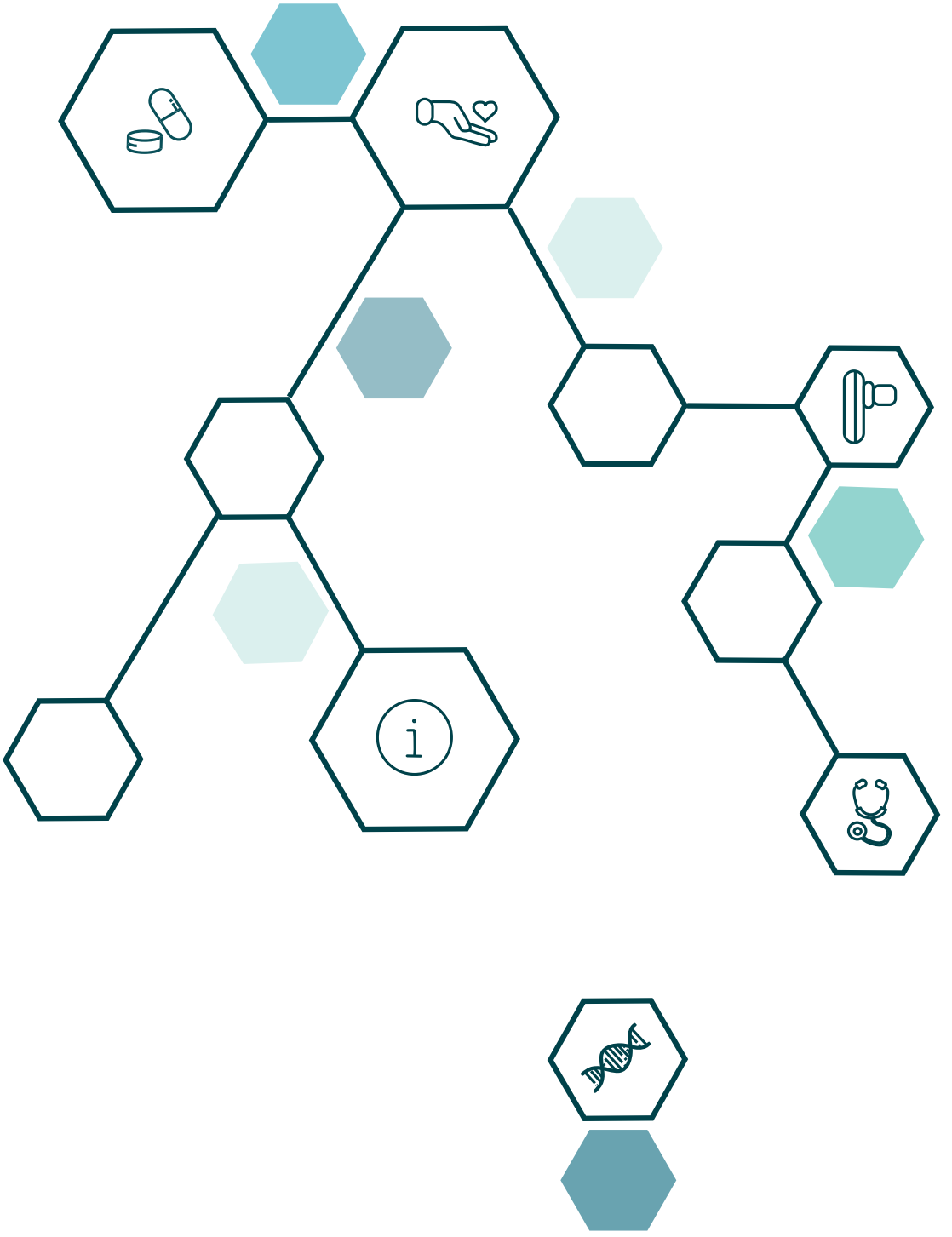


PART 1

Introduction



General introduction

Interstitial lung diseases

Interstitial lung diseases (ILDs) are a large, heterogeneous group of more than 200 diseases, that diffusely affect the lung (1). These diseases are often characterized by interstitial inflammation, interstitial fibrosis, or a combination of both (2). ILDs can broadly be classified in four groups. The first group encompasses ILDs with a known cause, such as underlying connective tissue disease or drug-induced ILD. The second and largest group are the idiopathic interstitial pneumonias (IIPs); the most common IIP is idiopathic pulmonary fibrosis (IPF). The third group consists of granulomatous disorders, of which sarcoidosis is the most prevalent entity. Sarcoidosis is a multi-organ, granulomatous disease of unknown etiology, with pulmonary involvement in around 90% of patients (3). The last group comprises rare ILDs, such as lymphangioleiomyomatosis.

The disease course of different ILDs varies considerably. Sarcoidosis spontaneously resolves in around two thirds of cases, and becomes chronic in one third of patients (4). A small subgroup of patients with chronic sarcoidosis develops pulmonary fibrosis and progressive disease (3). IPF is by definition progressive, and has the worst prognosis of all ILDs, with a mean survival of 3-5 years after diagnosis (2, 5). IPF may have an unpredictable disease course; some patients have a slow disease progression, others experience a rapid decline or a disease trajectory with acute deteriorations (6). A subgroup of other fibrotic ILDs can also have a progressive phenotype (**Figure 1**) (5, 7). So far, there are no good (bio)markers to predict disease course in individual patients (5). Even though the individual diseases are rare, ILD is the 40th most common cause of death worldwide (8, 9).

Achieving an early and accurate diagnosis remains challenging in the field of ILD, because symptoms such as dyspnea, cough, and fatigue are non-specific (10). The current "gold standard" for diagnosis is a multidisciplinary team discussion (MDT), based on a combination of clinical, radiological and sometimes pathological features (11). However, in a significant minority of patients diagnostic certainty is low, or they may even be "labeled" as unclassifiable ILD. Thus, there is a major need for minimal invasive biomarkers that may guide diagnosis and treatment decisions.

Guidelines for IIPs and IPF have been regularly updated in the past decades, as a consequence of evolving insights and emerging treatment options (1, 12-16). The only curative treatment option in progressive fibrotic ILDs is lung transplantation, which is only a possibility for a selected subgroup of patients (17). For IPF, two antifibrotic drugs (nintedanib and pirfenidone) are available (18, 19). These drugs slow down disease progression and seem to prolong survival (20-22). Up to now, other ILDs are primarily treated with immunomodulatory agents, but recently the FDA has approved nintedanib

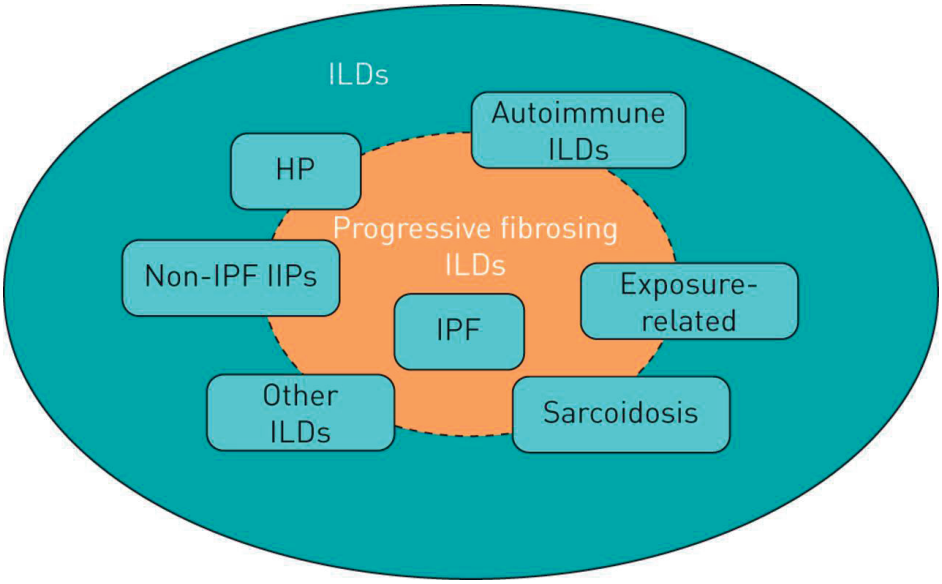


Figure 1. Interstitial lung diseases that can develop a progressive phenotype. ILD = interstitial lung disease, IPF = idiopathic pulmonary fibrosis, IIP = idiopathic interstitial pneumonia, HP = hypersensitivity pneumonitis. Reproduced with permission of the © ERS 2020 (5)

for the treatment of progressive fibrotic ILDs other than IPF (23, 24). This will significantly change care for patients with these diseases in the coming years; however, much is still unknown about the timing and position of antifibrotic drugs and immunosuppression in non-IPF progressive fibrotic ILDs. As diagnosis, treatment, and follow-up of patients with ILD require specific expertise, care for ILD in the Netherlands is organized in collaboration with ILD expert MDTs and specialized treatment centers.

This thesis will primarily focus on IPF, fibrotic ILD and sarcoidosis.

Disease burden

Most common symptoms of ILD are cough, dyspnea, and fatigue, which often deteriorate over time in patients with progressive disease. Living with a chronic disease, with a high symptom burden and uncertain prospects has a major impact on daily lives of most patients with ILD and their families (25). Quality of life (QOL) can be influenced by multiple factors, such as symptoms, comorbidities, physical deterioration and certain patient characteristics (26-32). In order to optimize QOL for ILD patients, a comprehensive, multidisciplinary approach to care is essential (33, 34) (**Figure 2**). Next to disease-modifying treatment, treatment should also be focused on symptom relief and supportive measures (e.g. supplementary oxygen, pulmonary rehabilitation and psychological support) (8, 35). In recent years, a number of qualitative studies in

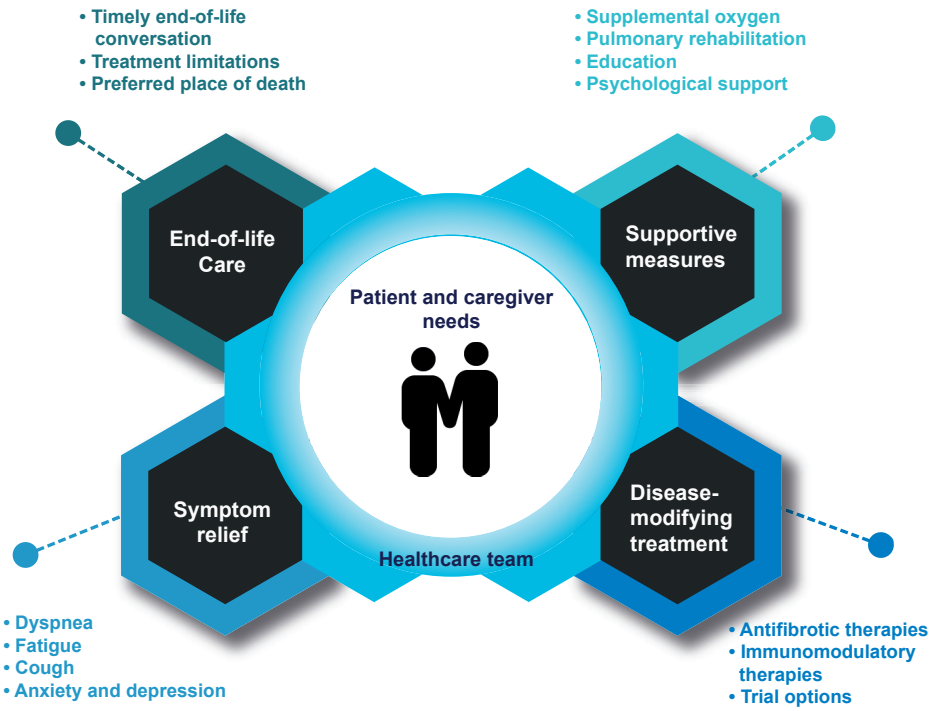


Figure 2. Comprehensive care for patients with (fibrosing) interstitial lung diseases. Patient and caregivers needs should play a central role in disease management. Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society (35).

IPF have evaluated the (unmet) needs of patients and their caregivers (25, 36-40). In sarcoidosis, needs of patients and their partners have not been investigated until now. It remains to be elucidated whether unmet needs and patient experiences with care have changed during the last years. In part 2 of this thesis, we aim to gain novel insights in the current unmet needs and gaps in care in ILD, in order to optimize comprehensive care for patients.

Home monitoring and eHealth

In the Netherlands, patients are regularly followed up at the outpatient clinic of ILD expert and specialized treatment centers, which means that they might have to travel considerable distances to the hospital. In other countries access to ILD care may be even more difficult for patients. These frequent hospital visits can be burdensome for patients, mainly because of (increasing) dyspnea, fatigue and sometimes supplementary oxygen needs. Furthermore, unexpected care needs may arise in between visits. For instance, patients can experience increasing symptoms, burdensome side-effects, or disease deterioration. Early identification and management of these inter-current problems

could potentially improve health outcomes and quality of life. As antifibrotic treatment is now also available for patients with progressive fibrotic ILDs other than IPF, it becomes increasingly important to timely identify those patients that show disease progression. Hence, home monitoring of symptoms and physiological parameters can bring major advantages and possibilities to improve quality of care for patients with ILD.

Home monitoring, or remote patient monitoring, is a broad term which entails the monitoring of patients at a distance. A few examples of home monitoring are self-recording of blood pressure, temperature, and glucose levels at home. In chronic lung diseases, home monitoring of lung function by means of home spirometry is increasingly used for research purposes (41-43). In lung transplant recipients, home spirometry is even incorporated in daily clinical practice in order to enhance early detection of lung function decline (44). In the field of ILD, home spirometry is not used in daily practice, and only a few studies investigated the feasibility and reliability of home spirometry in IPF and sarcoidosis (45-47). In sarcoidosis, home monitoring of lung function enabled early detection of corticosteroid treatment effects (47). Two studies in IPF revealed that home spirometry yielded reliable results, predicted disease progression better than hospital spirometry, and could potentially decrease sample size for future clinical trials (45, 46). Lung function data collected by patients in these studies were written in a paper-based diary or stored in a central database, without an option to share the measurements directly with healthcare providers. The collection of data at home via novel eHealth technologies would allow for direct data transfer to the hospital, and thereby broaden the applicability of home monitoring in ILD.

More than 50 definitions of eHealth exist (48). The World Health Organization (WHO) defines eHealth as "the use of information and communication technologies for health", with the goal of improving health outcomes for patients and increasing healthcare efficiency (49, 50). During the last 20 years, the number of published studies on eHealth have rapidly increased (50). Examples of eHealth technologies are wide-ranging and include health websites, apps, wearables, electronic and video consultations, devices to collect data at home, and online personal health records. In 2018, an estimated number of 325.000 eHealth-apps were available online; however, only a small part of these applications have been thoroughly investigated with regard to their efficacy and reliability (51). In other chronic lung diseases, such as chronic obstructive pulmonary disease and asthma, an increasing number of studies have evaluated the effects of eHealth on health outcomes and quality of life (52-54). Until now, studies on eHealth in the field of ILD are lacking. We hypothesized that online home monitoring would improve health outcomes and quality of life for patients with ILD. Hence, we developed a home monitoring program together with ILD patients, including home spirometry, online collection of

patient-reported outcomes, and low threshold communication with the hospital. In part 3 of this thesis, we aim to evaluate the feasibility and reliability of this comprehensive home monitoring program, and its impact on quality of life, patient satisfaction, psychological wellbeing, and medication use.

OUTLINE AND AIMS OF THIS THESIS

Part 1 is the general introduction of this thesis.

Chapter 1 introduces the concept of comprehensive care in ILD, especially in fibrotic ILD and IPF.

Chapter 2 focuses on comprehensive care for sarcoidosis.

Part 2 aims to evaluate patient experiences, patient perspectives, unmet needs and gaps in care for patients with ILD.

Chapter 3 evaluates gaps in care in pulmonary fibrosis, from the perspective of patients and healthcare providers throughout Europe. Furthermore, we assess whether care needs for patients have changed during the last years. These novel insights can be considered for future healthcare decisions.

Chapter 4 reviews methods to integrate patient perspectives in care for patients with IPF, in order to enhance personalized medicine and individually-tailored treatment.

In **chapter 5**, a recently developed and validated questionnaire is used to assess patient expectations, experiences and satisfaction with antifibrotic medication in IPF.

Chapter 6 reports on needs, experiences and perspectives of patients with sarcoidosis and their partners.

Chapter 7 reviews the current state-of-the art knowledge on fatigue in ILD, and provides a comprehensive approach to management of this debilitating symptom.

Part 3 describes novel innovations in ILD. The first aim of part 3 is to develop and evaluate an eHealth intervention for ILD. The ultimate goal of this eHealth intervention is to improve quality of life and health outcomes for patients, by addressing gaps in care identified in part 2. The second aim is to assess whether exhaled breath analysis using

electronic nose technology could be a novel non-invasive biomarker for the diagnosis of ILD.

Chapter 8 shows the initial steps in the development of the eHealth tool IPF-online, and a first evaluation of patient experiences.

Chapter 9 describes the further development of IPF-online into a comprehensive home monitoring program, integrated with real-time home spirometry. In this pilot study, feasibility, reliability and patients' experiences with home monitoring are evaluated.

Chapter 10 discusses qualitative patient experiences and feasibility of a comprehensive home monitoring program in sarcoidosis. This home monitoring program for sarcoidosis has been adjusted from the IPF version.

In **chapter 11**, the home monitoring program is used to assess diurnal variation in forced vital capacity (FVC) in patients with fibrotic ILD, and its relation with activity, measured with a wrist-worn activity tracker.

Chapter 12 describes a randomized controlled trial (RCT) with the home monitoring program IPF-online. This RCT evaluates whether a comprehensive home monitoring program on top of standard care improves quality of life for patients with IPF, compared with standard care alone.

Chapter 13 focuses on the reliability of exhaled breath analysis by use of eNose technology to discriminate between ILD and healthy controls, and to distinguish ILD subgroups.

Part 4

Chapter 14 provides a general discussion and future perspectives on patient-centered, comprehensive care and innovative novel technologies to improve outcomes for patients with ILD.

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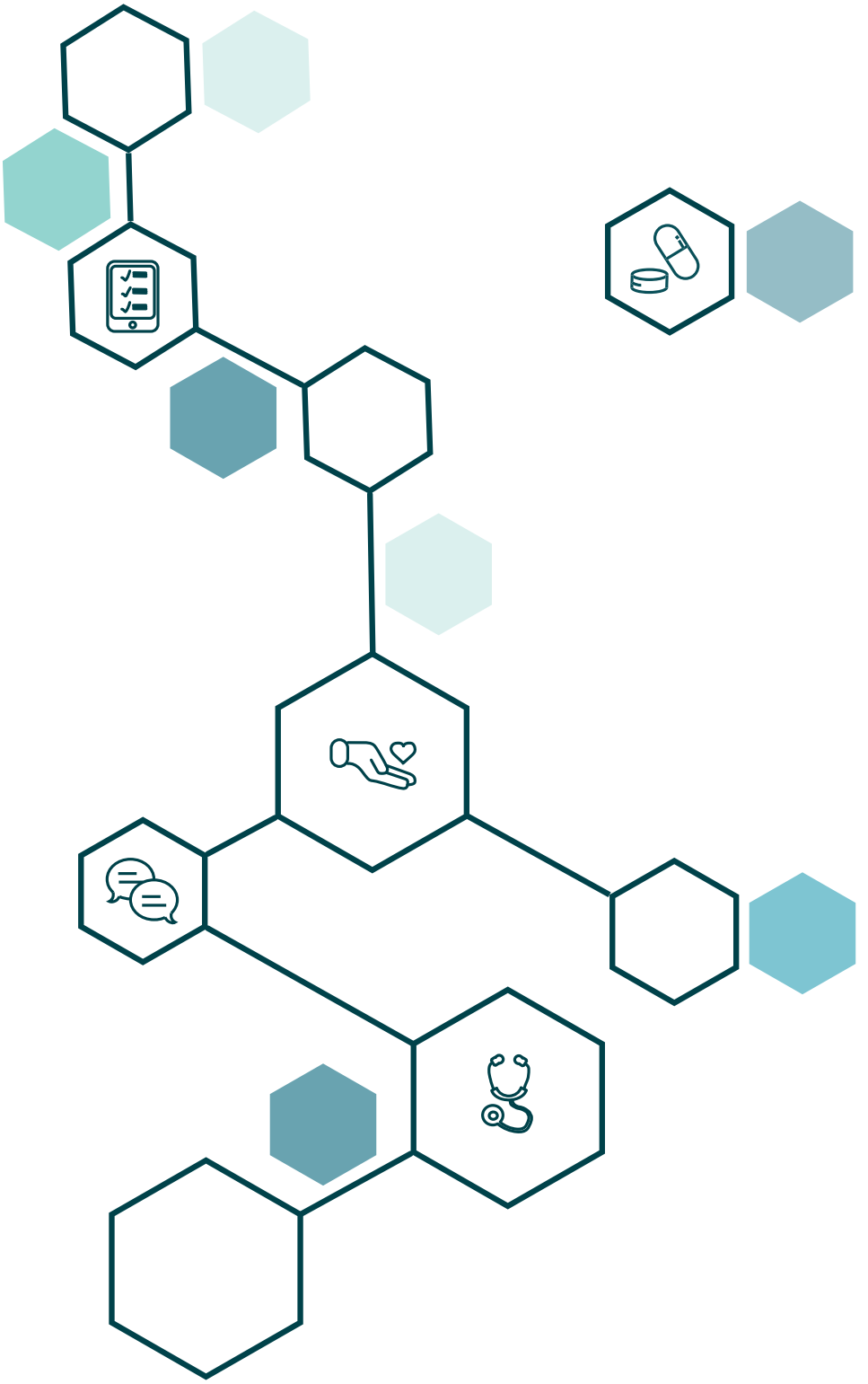

Chapter 1

Comprehensive care of interstitial lung disease

Encyclopedia of Respiratory Medicine

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ABSTRACT

Interstitial lung diseases comprise a heterogeneous group of diseases, which often have a major impact on the lives of patients. Optimal management of patients with interstitial lung disease requires a comprehensive approach to care, which encompasses disease-modifying treatment, symptom-centered management, education and self-management strategies. Especially in the more progressive and fibrotic forms of ILD, treatment should not only be aimed at prolonging life, but also at improving quality of life for patients. Symptom-centered management in ILD includes, amongst others, supplemental oxygen, pulmonary rehabilitation and palliative care. In order to optimize individually tailored treatment, patients' needs and preferences should regularly be assessed during the disease course.

Keywords

Interstitial lung disease; idiopathic pulmonary fibrosis; symptom relief; palliative care; supplemental oxygen; pulmonary rehabilitation; education; self-management; disease-modifying treatment; lung transplantation; end-of-life care

INTRODUCTION

Interstitial lung diseases (ILDs) are a diverse group of disorders affecting the interstitium of the lung. Historically, ILDs are classified in four groups: ILDs with a known cause, idiopathic interstitial pneumonias (IIPs), granulomatous disorders and rare ILDs. The disease course and prognosis significantly vary between different ILDs. Some ILDs are reversible, other ILDs have the potential for stabilization, but fibrotic ILDs are often progressive and ultimately fatal, especially idiopathic pulmonary fibrosis (IPF) (1). Therefore, pharmacological and non-pharmacological treatment strategies differ between ILDs and even within the same diagnosis, care needs may largely differ between patients. In this chapter, the comprehensive management of ILDs will be described. Different models exist to facilitate a systematic approach to comprehensive care. In this chapter the "ABCDE of ILD care" is used as a guidance to facilitate tailored care for the individual ILD patient (**Figure 1**) (2, 3).

Impact of disease

ILDs often have a major impact on the lives of patients, especially in progressive fibrotic disorders. Symptoms of cough, dyspnea, impaired exercise tolerance, fatigue, anxiety and depression, significantly impair (health-related) quality of life ((HR)QOL) (4-7). HRQOL can be defined as the influence of a medical condition on the well-being of a patient, whereas QOL is a broader concept which also encompasses factors such as personal beliefs, culture and social relationships. Dyspnea, cough and depression are assumed to be the main drivers of quality of life in IPF (4, 6, 8-10). Furthermore, fatigue, forced vital capacity (FVC), age, gender and the presence and number of comorbidities also influence quality of life in ILD (5-7, 9). HRQOL independently predicts mortality in IPF according to one study (11). The high disease burden emphasizes the importance of holistic care aimed both at prolonging survival as well as improving QOL in patients with ILD. In the end, prolonging life at an acceptable quality is what most people strive for.

ASSESS

Correct diagnosis

There is a lack of awareness about ILD in the general public and among healthcare providers such as general practitioners, radiologists, pathologists and general pulmonologists (12). Patients frequently feel misunderstood because people do not know what pulmonary fibrosis is (13). Lack of knowledge about ILDs may also lead to a delay in diagnosis and adequate treatment. Misdiagnosis and a long diagnostic trajectory can have a negative impact on QOL (14, 15). Symptom-based algorithms for general practitioners

ABCDE of ILD care

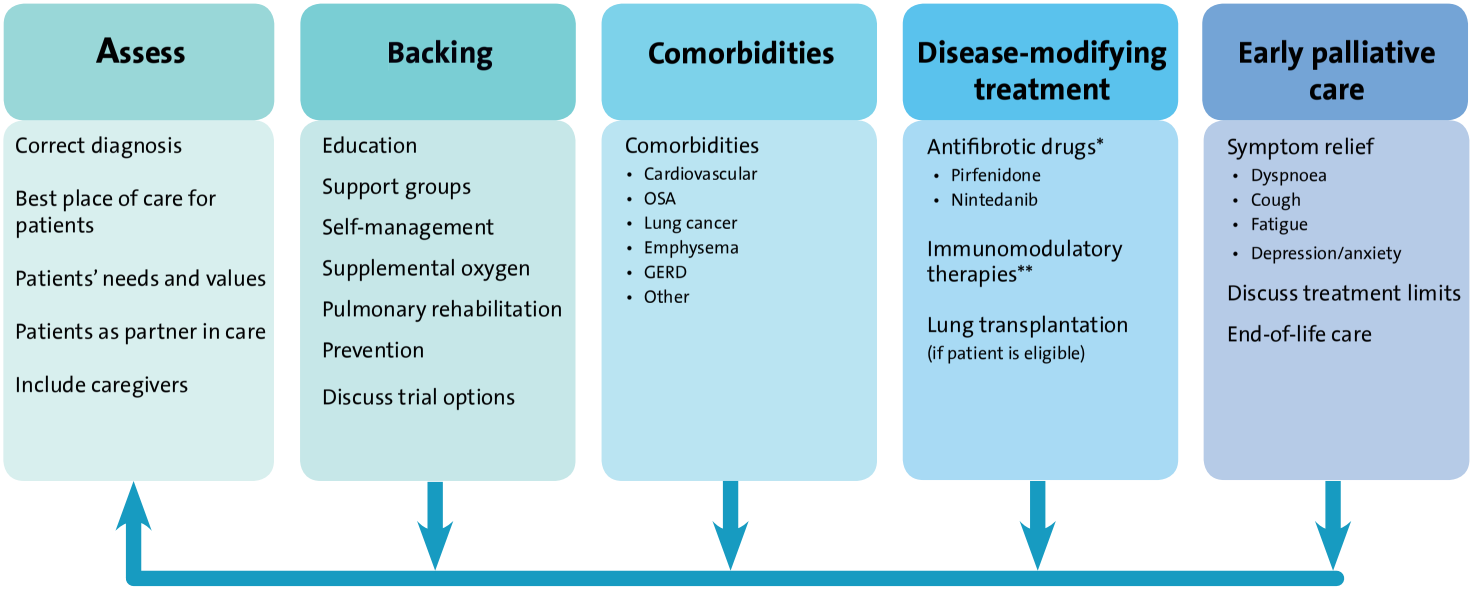

Figure 1. The ABCDE of interstitial lung disease care. The ABCDE model provides a structured approach to comprehensive care in ILD. OSA = obstructive sleep apnea, GERD = gastro-esophageal reflux disease. Adapted from Kreuter, M., Bendstrup, E., Russell, A. M., Bajwah, S., Lindell, K., Adir, Y., Brown, C. E., Calligaro, G., Cassidy, N., Corte, T. J., Geissler, K., Hassan, A. A., Johannson, K. A., Kairalla, R., Kolb, M., Kondoh, Y., Quadrelli, S., Swigris, J., Udwadia, Z., Wells, A. & Wijsenbeek, M. 2017a. Palliative care in interstitial lung disease: living well. *Lancet Respir Med,* 5**,** 968-980.

and awareness campaigns could improve knowledge of ILD and possibly enhance early diagnosis and treatment (16). Access to an ILD specialized multidisciplinary team (MDT) is essential to establish an accurate diagnosis and has shown to reduce the number of unclassifiable disease states. During multidisciplinary discussions in a specialized ILD center, the diagnosis is often changed, which regularly leads to adjustments in pharmacological and non-pharmacological management and other clinical trial options (17, 18).

Best place of care for patients

Early referral to a tertiary center seems to increase the perceived quality of care for patients (13, 19, 20). In IPF, delayed referral to a specialist center has been associated with a higher mortality, which emphasizes the need for early referral (21).

In an increasing number of countries, patients have access to ILD specialist nurses for practical and emotional support. The ILD specialist nurse often functions as the main contact for patients and can play an important role during the disease course. ILD specialist nurses provide information about the disease and medication, and help patients with the management of side-effects. Furthermore, they can direct patients to patient advocacy groups, offer practical help with supplemental oxygen and give advice about housing and employment issues, disability parking, physiotherapy and lifestyle changes (13, 14, 22-24). The availability of ILD specialist nurses can potentially improve quality of care and quality of life for patients and their partners (23, 25).

In some countries, patients have to travel long distances to visit an ILD specialist center. This can be very burdensome for patients with invalidating symptoms, impaired exercise tolerance and oftentimes high oxygen needs. When visits to the specialist center become too intrusive for patients, it could be an option to share the care between specialist center and local community center. Studies show that some patients prefer collaborative care between specialist and community centers (13, 16).

Patients' needs and values

For tailored treatment, it is essential to assess individual patients' needs, preferences and wishes. Several qualitative studies, mainly in IPF, evaluated unmet needs of patients and their partners. The most frequently reported unmet needs of patients with pulmonary fibrosis included adequate information about the disease, improved access to diagnosis, treatment and ILD specialists, psychological support, supplemental oxygen, pulmonary rehabilitation and end-of-life care, better general awareness for ILD, and more involvement of partners (12-14, 16, 20, 22, 26-35). Individual patients often have different needs, and personal circumstances, preferences, expectations and experiences may influence disease behavior and treatment success (36, 37). Furthermore, patients' needs and preferences may change during the disease course, and therefore regular reassessment of patients' needs is essential for optimal treatment (26).

Patients as a partner in care

A strong collaboration and mutual trust between the patient and healthcare provider is the foundation of comprehensive care in ILD. Patient engagement in care and self-management is essential to maintain or improve quality of life in ILD, but patients can only function as partners in care if they are well-educated about their disease and its prospects (3, 38). Effective communication and shared-decision making is important through the whole disease trajectory, from the moment of diagnosis to end-of-life.

When patients' preferences and wishes are taken into account before they start on pharmacological treatment, side-effects and non-adherence to medication may possibly be reduced (36, 38, 39). One study evaluated outcomes of a patient-centered care program in IPF. This program consisted of frequent phone calls and patient-led discussions with ILD nurses and was aimed at empowering patients and improving treatment adherence. Results indicated that patients felt more in control of their disease and highly valued the tailored information and support (23).

Inclusion of caregivers

A frequently overlooked part of comprehensive care in ILD is engaging the patient's support network in care (25). For most patients, partners and other family members are the main source of emotional and practical support during their disease trajectory. Partners can help patients adjust to a new lifestyle and cope with changes in everyday life due to their disease (26). Having a family member with ILD poses a major burden on caregivers and may lead to anxiety, frustration, limitations in daily and social activities and disturbed relationships (28, 34, 40). Caregivers of patients with ILD express the need to be more involved in care, and to receive better disease education, emotional support and practical advice (13, 26, 28, 35, 40). To improve engagement in care, partners should be more actively involved during outpatient consultations and be part of support groups and other educational activities (26, 28, 40).

BACKING

Education

The need for more accurate information and education about their disease is one of the most frequently reported unmet needs of patients and caregivers. A better understanding of the disease and its prospects could enhance self-management and help patients to cope with their disease (35). Patients with ILD are often unsatisfied with the amount and quality of available information and do not know which information sources are reliable. Online information is frequently outdated, not accurate or difficult to find for patients (22, 41, 42). Most of the online sources mainly contain information about IPF,

making it hard for patients with other ILDs to obtain specific and accurate information about their disease (41).

Patients and caregivers do not only wish to receive disease-specific information, but also individualized information about supplemental oxygen, insurance issues, alarming symptoms, prevention of infection and medication management (35). Informational needs of patients can change during their disease course. Patient's needs and wishes should be reassessed regularly by their healthcare providers, in order to provide individualized and tailored information (26). Educational patient meetings can be used to inform patients about ILD, but also to update them about new medications and clinical trials (13).

Support groups

The need for practical, emotional and psychological support is regularly reported in chronic ILD. A substantial group of patients think that psychological support is lacking in current care (12, 13, 22). Only a minority of ILD patients receive psychological care (13, 22, 41). One option to provide emotional and psychological support to patients and their caregivers is a (multidisciplinary) support program, led by a specialist nurse or psychologist. Studies showed that patients highly value these support group meetings, feel less lonely and could better place their disease in perspective. Furthermore, these programs can improve quality of life, psychological wellbeing and decrease stress for patients and/or partners (43-45). Composition and content of the program of these support groups is variable and no evidence-based directives for support groups exist to date.

Patient advocacy groups may play an important role in improving care for patients with ILD, by raising more awareness in society, providing disease-specific information, and offering practical and emotional support to patients (12). In some countries, patient advocacy organizations have established peer support groups. Meeting others with similar experiences and difficulties might be beneficial for patients, not only for emotional support but also for practical advice (14, 27). Nonetheless, it is important to keep in mind that some patients might have negative feelings towards peer support groups because it could be distressing to meet other patients with more severe disease (26).

Self-management

Self-management strategies may help patients to stay in control of their own disease, make realistic choices and prepare for the future (3). Self-management strategies are diverse and include, amongst others, self-monitoring of disease, acting on changes, medication management, oxygen use, dietary measures and exercise.

Innovative new techniques, such as eHealth solutions may be used to enhance self-management in ILD. eHealth is defined as "the use of information and communication

technologies for health". Use of eHealth has the potential to improve the quality of care by promoting self-management and by having a lower threshold to communicate with patients, using constant disease monitoring and direct feedback (46-48). In ILD, home monitoring experiences are limited, and eHealth solutions are not yet implemented in routine daily care. However, several studies have shown that home monitoring of lung function is feasible and reliable in this elderly patient population and potentially allows for earlier detection of disease deterioration or bothersome side-effects (47-50). One study evaluated a home monitoring program, including real-time wireless home spirometry and online reporting of symptoms and side-effects in IPF. Patients had access to an information library and electronic consultations, and were directly provided with feedback if their lung function significantly declined or bothersome side-effects were reported. Adherence to the program and patient satisfaction were high. Patients reported that home monitoring helped them to feel more in control, absorb information at their own pace and facilitated easier communication and interaction with healthcare providers (47, 48).

Another self-management tool for patients with ILD is to maintain a healthy diet. If needed, patients can be referred for dietary evaluation and support (25). It is not clear whether a specific diet could be beneficial for patients with ILD, since the influence of diet on disease course has never been assessed in clinical trials. However, being overweight and being underweight has been associated with worse outcomes in ILD (51, 52). Two studies showed that weight loss (>5% body mass index (BMI) decline or >5% bodyweight loss) was significantly associated with worse survival in ILD (53, 54). In these studies, BMI at baseline did not predict survival.

Supplemental oxygen

Among ILD patients, IPF patients are most likely to receive supplemental oxygen, independent of disease severity (55). The 2011 ATS/ERS/JRS/ALAT guideline for diagnosis and management of IPF provides a strong recommendation for the use of long-term supplemental oxygen in IPF patients with resting hypoxemia. This recommendation is mainly based on evidence from studies in chronic obstructive lung disease, and therefore the quality of evidence is deemed very low. According to this guideline, the timing of supplemental oxygen treatment is left up to the discretion of the treating physician. No clear peripheral oxygen saturation (SpO2) cut-off value for the use of supplemental oxygen has been advised, although most studies use a cut-off value of < 88%. The guidelines do not provide recommendations on the use of supplemental oxygen in patients with isolated exertional hypoxemia (56).

One of the aims of oxygen therapy in interstitial lung diseases is to maintain adequate SpO2 levels, and thereby prevent potential complications of chronic hypoxemia. Other

goals of supplemental oxygen are to alleviate dyspnea, increase physical activity and improve quality of life. Several studies have evaluated whether oxygen therapy could improve these parameters. Two reviews could not provide any good-quality evidence for or against the use of ambulatory oxygen in ILDs due to the low quality or retrospective nature of studies (57, 58). In the short term, oxygen therapy showed positive effects on exercise capacity, but no improvement in subjective dyspnea, although the total number of patients in these studies was low. No conclusions could be drawn regarding the impact of long-term oxygen therapy on survival in ILD (58).

Only one cross-over randomized controlled trial assessed the effect of ambulatory oxygen on HRQOL in patients with ILD who had isolated exertional hypoxemia (59). In this study, ambulatory oxygen improved short-term HRQOL and dyspnea scores. Qualitative interviews indicated that patients' quality of life improved because they felt less impaired in their daily activities. The attitude of most patients who initially had negative feelings regarding oxygen, changed because they experienced a beneficial effect from the supplemental oxygen (59). Results from other qualitative studies indicate that oxygen therapy can have a major impact on the lives of patients and their partners. Oxygen therapy is often seen as an indication of disease progression by patients and could probably be the first time that their disease becomes visible. Furthermore, oxygen therapy may also lead to practical issues and limitations in daily life (14, 26, 27, 34).

These data suggest that in ILD patients with exertional hypoxemia, the initiation of supplemental oxygen should be discussed during outpatient clinic visits and regularly reassessed during follow-up visits. The decision whether or not to start supplemental oxygen should be an individualized and shared decision between patients and their healthcare providers. SpO2 measurements at rest, oxygen desaturation during six-minute walk test, and assessment of dyspnea over time through patient-reported outcomes could help determine the need and timing for oxygen prescription (55). It should be acknowledged that guideline directions on supplemental oxygen use in ILD are lacking and access to supplemental oxygen may vary throughout the world (12).

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) can be defined as a comprehensive intervention, which includes exercise training, as well as education and self-management strategies. The main goals of PR are to improve the physical condition and quality of life of patients with chronic respiratory diseases. The content of the program should be tailored to individual patients' needs and wishes, type of disease, disease severity and comorbidities (60). PR has been extensively studied in chronic obstructive pulmonary disease (COPD) and has proven to be effective in this disease. The ATS/ERS statement about pulmonary

rehabilitation suggests that PR leads to a short-term improvement in exercise capacity, quality of life and dyspnea in ILDs, but that the beneficial effects are generally smaller than in COPD (60). The 2011 ATS/ERS/JRS/ALAT guideline on IPF provides a weak recommendation for pulmonary rehabilitation in patients with IPF, based on the results of two controlled trials (56, 61, 62). The beneficial effects of PR on exercise capacity, dyspnea and quality of life in patients with ILD were also reported in two systematic reviews (63, 64) There is no current evidence regarding the optimal duration and specific content of PR programs in ILD, and the long-term effects have not completely been elucidated(61, 65, 66).

Data regarding predictors of benefit after PR are somewhat conflicting. One observational study showed that patients with IPF have more benefits from PR in early disease stages, while other studies suggest that patients with lower walking distance at baseline had more improvement in 6MWD after PR (66-69). In other ILDs, there is no evidence that disease severity predicts outcomes after PR (67). Therefore, it is advised to discuss referral to PR with ILD patients in early disease stages, but to also consider PR for patients with more severe disease. Especially in the latter group, the balance between burden and gain of PR should be carefully discussed with the patient.

There are some differences in PR in patients with ILD compared to other respiratory diseases. Patients with fibrotic ILDs have significantly more desaturation during exercise compared with matched COPD patients, when adjusted for pulmonary physiology and demographic features (70). Exercise training in ILDs should therefore take place in a facility where supplemental oxygen therapy can be provided. Extra-pulmonary manifestations of ILD and comorbidities may limit the possibilities for exercise training. For example, patients with an underlying connective tissue disease may require modifications in their training program due to musculoskeletal pain, stiffness or weakness (71). Further, the educational content of PR programs is mostly focused on COPD. Hence, part of the program content in PR is not applicable for ILD patients. Both patients and clinicians reported the need for ILD specific content in PR programs, such as management of symptoms, oxygen use and end-of-life care. Education sessions in PR programs could be an ideal opportunity to educate patients with ILD and their partners (41, 72).

Prevention

In ILD, not much emphasis has been placed on prevention strategies, although it certainly has a role in preventing morbidity and mortality. In the pathogenesis of many ILDs, external triggers are thought to play a role. Examples of such triggers include smoking, medications, work and environmental exposures, infectious causes and mechanical stress. In some diseases, removal of the trigger may result in improvement of disease, for

instance in acute hypersensitivity pneumonitis or Langerhans cell histiocytosis, whilst in other diseases the effect is limited to possibly preventing further decline (73).

In current clinical practice, patients are advised to get an influenza vaccination once yearly and pneumococcal vaccination once every five years (3). Studies in ILD patients reported no acute exacerbations after vaccination, suggesting that influenza and pneumococcal vaccination are both safe in ILD (74, 75). Further, ILD patients with and without immunosuppression had normal vaccination responses (74-76).

Smoking cessation plays an important role in primary and secondary prevention of ILDs. Some chronic ILDs mainly develop in smokers. This group includes respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia and pulmonary Langerhans cell histiocytosis, also called smoking-related ILDs. In these smoking-related ILDs smoking cessation is the initial and most important therapy. Furthermore, there is a relationship between smoking and acute eosinophilic pneumonia, pulmonary hemorrhage syndromes, IPF and rheumatoid arthritis-associated ILD, though the association is less obvious than in smoking-related ILDs. In contrast, smoking appears to be protective in sarcoidosis and hypersensitivity pneumonitis (77). Cigarette smoking leads to worse outcomes in ILD and has a negative impact on survival. Smoking also increases the likelihood of development of comorbidities such as emphysema and lung cancer, which impact survival as well (77-79). In IPF, smoking reduces treatment efficacy in patients treated with pirfenidone. Pirfenidone is primarily metabolized in the liver by the CYP1A2 enzyme; smoking incudes CYP1A2 and thereby reduces bioavailability of pirfenidone (80). Consequently, cessation of smoking is strongly advised in all patients with ILD (77).

Mechanical stress, such as in mechanical ventilation or pulmonary surgery, may increase the risk for acute exacerbations in ILD (81-83). In patients with fibrotic ILDs, the risks and benefit should always be weighed and discussed with patients, also if the reason for mechanical ventilation is non-pulmonary (56).

Discuss trial options

Evidence-based treatment options in ILD are limited and often not curative. There is a major need for better treatments across the spectrum of ILDs and many trials are ongoing (clinicaltrials.gov). The majority of ILD patients wish to participate in clinical trials, and would also like to be involved in the development of studies (13). Healthcare providers should discuss the possibility of participating in a clinical trial with patients after a diagnosis has been established (3, 16). Participation in trials may empower patients to play a more active role in their disease, gain access to potential new treatments and contribute to medical research (3). Patients who participate in a clinical trial are more hopeful than others (14). A report about IPF in the UK indicated that only a minority of patients (42%) are informed about ongoing or future clinical trials (84). These findings were also reported in a qualitative study in IPF patients and caregivers (14).

COMORBIDITIES

Comprehensive care in ILD also means looking beyond the lungs (36). Assessment and treatment of co-morbidities should not be overlooked. Comorbidities are highly prevalent in ILDs and may have an influence on quality of life and survival (85-88). In IPF, a higher number of reported comorbidities is significantly associated with poorer survival (85). Early recognition and adequate treatment of comorbidities is essential and has the potential to improve outcomes in patients with ILD (88).

DISEASE-MODIFYING TREATMENT

Pharmacological management

ILDs comprise a large and heterogeneous group of diseases, characterized by variable presence of inflammation and fibrosis, or a combination of both, depending on the underlying disease and time of assessment. Historically, all ILDs were thought to start off with inflammation and ultimately result in fibrosis of the lung parenchyma. On the basis of these ideas, all patients with ILD were initially treated with immunomodulatory therapies (89, 90). However, it has become clear that not all patients with ILD will benefit from immunosuppressive therapies and in some ILDs this may even be harmful (91). In the past decade, new insights in the pathogenesis of ILDs together with an increasing number of well-designed clinical trials, have led to the first evidence-based recommendations for the use of disease-modifying agents in some ILDs (92, 93). However, none of these new drug developments have led to curative treatment options. Furthermore, in many ILDs, therapeutic decisions are still based on case-series or expert opinion, leaving a major unmet need to find better disease-modifying treatment for ILDs.

Antifibrotic therapies

In patients with IPF, the use of high dose immunosuppression has been abandoned since the study that showed that the combination of azathioprine, high dose corticosteroids and N-acetylcysteine was not only ineffective, but also associated with an increased risk of mortality (91). Subsequently, large randomized controlled trials showed that the use of the anti-fibrotic therapies, nintedanib and pirfenidone, had a favorable effect on the decline in lung function, as measured by FVC (92, 93). Pre-specified analysis of the pooled data for the respective drugs also showed a positive effect on survival and a decrease in acute exacerbations (92, 94). The treatment guideline for IPF includes recommendations for the conditional use of nintedanib and pirfenidone (95).

Several other ILDs may also present with a progressive fibrotic phenotype, such as rheumatoid arthritis related ILD, hypersensitivity pneumonitis, systemic sclerosis ILD

(SSc-ILD) and unclassifiable ILD. The communality in disease pathogenesis and behavior with IPF suggests a potential for a common treatment (96, 97). Currently, clinical trials are underway investigating the use of antifibrotic therapies in other progressive fibrotic diseases, both as single agents or along with immunomodulatory therapies (clinicaltrials.gov).

Immunomodulatory therapies

Although immunosuppression is considered the mainstay of treatment in many ILDs, this is largely supported by findings from retrospective and observational studies (98). In SSc-ILD, there is evidence that the use of both cyclophosphamide and mycophenolate mofetil (MMF) resulted in significant short-term lung function improvement, although MMF is better tolerated (99). For many other ILDs, such as connective tissue disease-associated ILD, drug-induced ILD and hypersensitivity pneumonitis, the optimal treatment strategies have not been determined (78, 100). Details on current treatment recommendations can be found in the disease specific chapters.

Future developments

Increasing insights into the pathogenesis of different pathways involved in ILD have led to a fast expanding field of randomized controlled trials with new compounds and combinations with existing drugs (101). In current practice, patients are treated with either antifibrotics or anti-inflammatory therapy. In the future, this paradigm may shift towards more combined or targeted therapy based on the individual patient profile, in which genetic/molecular endotypes, environmental factors and behavioral aspects are likely to play a role (36, 96, 102). Collaboration between researchers, physicians, patients and pharmaceutical companies will need to guide these developments.

Lung transplantation

In progressive, non-reversible ILDs, especially IPF, lung transplantation is the only treatment option with significant survival benefit. The number of ILD patients receiving a lung transplant has steadily increased after adaptation of the lung allocation system. The lung allocation score (LAS) was introduced in the USA in 2005 and in 2011 within the Eurotransplant countries. Prior to the LAS, lung allocation was based on time on the wait list, whereas the LAS uses a complex scoring system which allocates lungs to patients with a higher urgency due to more severe disease(103, 104). Between 1995 and 2017, 37% of all lung transplantations were performed in patients with idiopathic interstitial pneumonias, according to data from the international society for heart and lung transplantation (105). Among the ILDs, IPF is the most common indication for lung transplantation, but a small percentage of lung transplants are carried out in patients with other forms of ILD. In the US, ILD is currently the most common indication for lung

transplantation (106). However, only a small minority of patients with ILD are eligible for lung transplantation due to their older age and higher likelihood of comorbidities. The upper age limit for lung transplantation has increased over time. There are some data showing that patients aged over 70 years have comparable outcomes post lung transplantation compared to patients between 60 and 69 years of age, after the implementation of the LAS system (107). If this trend continues, it is expected that more ILD patients will become eligible for lung transplantation (104).

Due to the variable disease course of different ILDs, the optimal timing for referral to lung transplantation screening is not completely elucidated. In IPF, early referral for lung transplantation screening is strongly advised because of poor survival rates and the possibility for rapid deterioration (103, 104, 108). In other ILDs, patients are generally referred for lung transplantation screening when the disease progresses despite optimal treatment (104, 109).

EARLY PALLIATIVE CARE

Palliative care is an important component of comprehensive care in progressive ILDs and is directed at symptom relief and improving quality of life. The phrase "palliative care" is often associated with end-of-life care. This hampers referral to palliative care due to negative connotations and misconceptions (110-112). Palliative care does not solely include end-of-life care, but also comprises symptom-centered pharmacological and non-pharmacological treatment (25). Palliative care can be initiated in parallel with other interventions and should not lead to discontinuation of disease-modifying treatment (25). The balance between symptom-centered and disease-centered management varies throughout the disease course. When the disease progresses, symptom-centered management becomes increasingly important(3).

According to the World Health Organization, palliative care is a holistic and multidisciplinary approach which addresses the needs of patients and their family members and helps patients to live actively for as long as possible (113). Worldwide, many cultural, social and financial barriers to palliative care exist, and only a minority of patients who need palliative care have access to it (113). Palliative care research has almost completely focused on cancer during the last decades (114). Hence, underuse of palliative care is more pronounced in ILDs and other chronic lung diseases than in oncology. Discussions regarding prognosis and treatment limitations were less frequently reported in patients with ILD and COPD than in cancer patients (115). Two retrospective studies showed that palliative care services are involved in a small minority of patients with progres-

sive fibrotic ILDs. Furthermore, referral to palliative care occurred in a very late stage of disease in ILD patients (116, 117).

One of the main barriers to palliative care in ILD is the lack of knowledge about palliative care among pulmonary physicians and the lack of (inter)national guidelines (25, 114). Moreover, there is significant variability in disease course and prognostic uncertainty, which complicates referral to palliative care and optimal timing of palliative care discussions (25, 114). Initiation of palliative care in ILD is not required in all patients, since not all ILDs have a high symptom burden or poor outcome. A disease behavior –based algorithm can be helpful in assessing whether palliative care should be considered in individual patients (**Figure 2**) (25). In all patients with inevitably progressive ILD, especially IPF, palliative care should be discussed early in the disease course. In patients with cancer, early referral to palliative care improves quality of life and prolongs survival (118-120). Further, early and integrated palliative care with a breathlessness support service improved mastery of dyspnea and survival in patients with refractory dyspnea, including those with ILD (121). In patients with fibrotic interstitial lung disease a "palliative care case conference" intervention was feasible and improved anxiety and quality of life in patients and caregivers (122).

Symptom relief

Dyspnea

Dyspnea is the most prevalent symptom in interstitial lung disease. More than 90% of ILD patients report dyspnea at diagnosis (123, 124). Dyspnea is strongly associated with QOL in ILD and is reported to be the main contributing factor to impaired QOL in this population (5, 9, 125). Increasing dyspnea may influence all aspects of daily life. Many patients with dyspnea avoid exertion, which can lead to impairment in physical activity and decline in functional capacity. Moreover, breathlessness often leads to anxiety, which in turn may worsen the dyspnea. Dyspnea has a major impact on the caregiver too, and may lead to more care dependency and social limitations (126).

Several studies have shown that dyspnea independently predicts mortality in IPF. Increasing dyspnea also predicts disease progression in non-IPF ILDs (127-129). Two studies demonstrated that dyspnea severity is independently associated with depression and frailty in patients with IPF (130, 131). Comorbidities, such as pulmonary hypertension, cardiac disease, obstructive sleep apnea, infection and psychological disorders, may also contribute to dyspnea and should be identified and optimally treated (25).

Though breathlessness is a major symptom, only a few studies in ILD have been specifically aimed at dyspnea relief. Opioids and benzodiazepines are frequently prescribed for

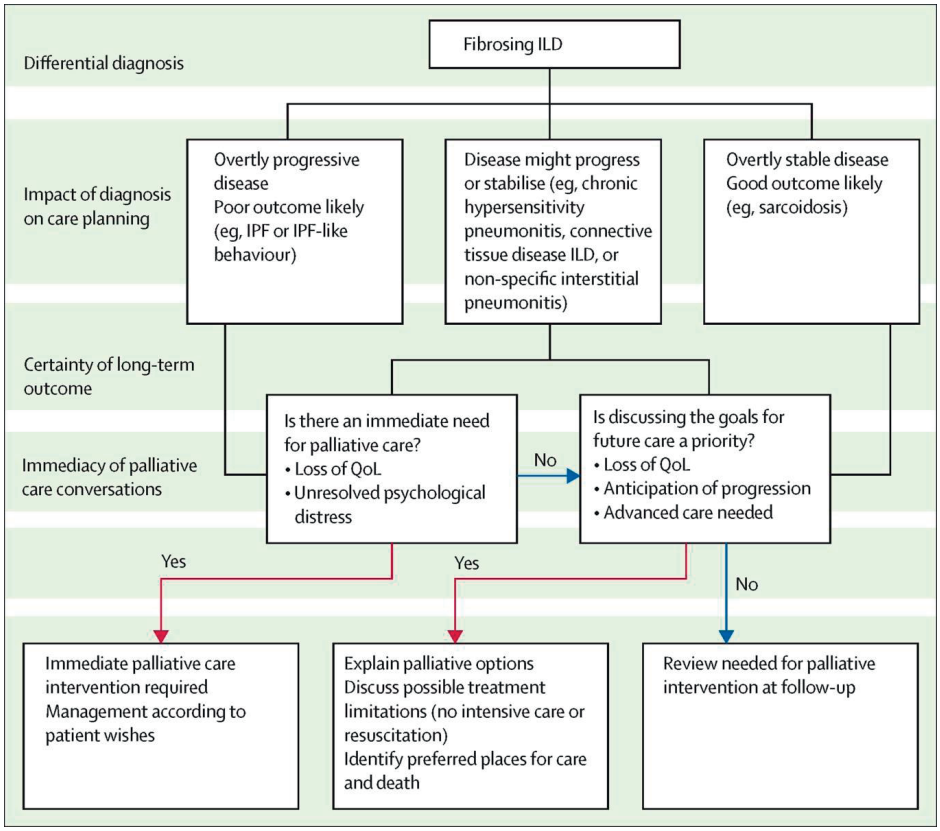

Figure 2. Disease-behavior based algorithm for referral to palliative care in ILD. ILD = interstitial lung disease, QOL = quality of life, IPF = idiopathic pulmonary fibrosis
Permission to use from Kreuter, M., Bendstrup, E., Russell, A. M., Bajwah, S., Lindell, K., Adir, Y., Brown, C. E., Calligaro, G., Cassidy, N., Corte, T. J., Geissler, K., Hassan, A. A., Johannson, K. A., Kairalla, R., Kolb, M., Kondoh, Y., Quadrelli, S., Swigris, J., Udwadia, Z., Wells, A. & Wijsenbeek, M. 2017a. Palliative care in interstitial lung disease: living well. *Lancet Respir Med,* 5**,** 968-980.

dyspnea relief in ILD according to a retrospective study about specialist palliative care (116). All patients in this study reported a benefit with benzodiazepines and opioids. Opioids may reduce the perception of dyspnea centrally in the brain (132). One review article evaluated the role of opioids to alleviate dyspnea in ILDs. Most of the included studies in this review primarily focused on COPD, and only 32 of the included patients had an ILD diagnosis. Results from these studies were inconsistent, but suggest that low-dose oral opioids may have a beneficial effect in patients with ILD. No serious adverse events, such as respiratory depression were reported, but constipation was common (132). The effect of nebulized morphine on dyspnea in ILDs has not yet been clarified (133). There are no studies in ILD assessing the role of benzodiazepines in dyspnea relief. A Cochrane review in cancer and COPD concluded that benzodiazepines may be used as

second or third-line therapy, especially if anxiety is present. A consensus statement on palliative care in ILD included opioids and benzodiazepines as potential symptom-based therapies in ILD (25). In IPF, anti-fibrotic drugs have not shown to alleviate dyspnea, and the combination of nintedanib with sildenafil in IPF also demonstrated no beneficial effect on dyspnea (92, 93, 134).

Use of a hand-held air fan can reduce dyspnea in patients with chronic breathlessness. Since the costs of this intervention are very limited and there are no known side-effects, the use of a hand-held fan may be advised to ILD patients with refractory breathlessness (135-137). The favorable effect of supplemental oxygen and pulmonary rehabilitation on dyspnea is discussed in separate paragraphs.

Cough

Cough is one of the most common and bothersome symptoms in ILD and is reported to be present in up to 87% of patients (138-141). The prevalence of cough is assumed to be highest in IPF, but cough is also highly prevalent in other fibrotic ILDs such as chronic hypersensitivity pneumonitis (up to 83% of patients) and scleroderma related ILD (up to 68% of patients) (140). Cough often leads to a major impairment of quality of life and may limit social activities (4, 6, 140).

Studies regarding the predictive role of cough in ILDs show contradictory results. One study in IPF stated that cough independently predicts mortality (141). A study in scleroderma related ILD showed a correlation between cough and ILD severity, as well as a correlation between lung function improvement and reduction of cough (142). Two other studies suggested that there was no association between cough and disease severity or progression in fibrotic ILDs (139, 140).

The pathogenesis of cough in ILDs remains incompletely understood. Furthermore, it is unclear whether distinct mechanisms play a role in cough pathogenesis in different (fibrotic) ILDs (139, 143). Co-morbidities such as gastro-esophageal reflux disease, obstructive sleep apnea, emphysema or lung cancer, may cause or worsen cough in ILDs. Other possible causes such as ACE inhibitor use, sinusitis and postnasal drip, should be recognized and adequately treated (25, 138, 144).

Cough in ILD is difficult to treat and is often refractory to regular antitussive treatment (138, 140). Consequently, effective therapeutic options for chronic cough in ILDs are lacking. One single-center randomized trial in 20 IPF patients showed that low-dose thalidomide improved patient reported cough and cough-related quality of life (145). Seventy-seven percent of patients in the treatment arm experienced adverse events,

compared to 22% in the placebo arm. Further research is needed to assess benefits and risks related to thalidomide (138, 143, 145). A phase 2 trial showed that sodium cromoglicate (PA101) reduced cough frequency by 31% after 14 days in patient with IPF and was generally well tolerated (146). PA101 had no significant beneficial effects in a group of patients with chronic idiopathic cough (146). Results from an observational study in IPF suggested that pirfenidone reduced cough and improved cough-related quality of life in patients with IPF (147). An older study in a limited number of patients with IPF, showed an effect of high dose corticosteroids on cough (148). However, with the current knowledge on the detrimental effects of high-dose immunosuppression in IPF, this practice is discouraged. The effect of anti-acid therapy on gastro esophageal reflux-related cough in ILD remains a matter of debate. One observational study showed that cough frequency did not change after high-dose acid suppression therapy, although the number of acid reflex events significantly declined, non-acid reflux paradoxically increased (149). A study with laparoscopic anti-reflux surgery showed no effect on cough (150). In scleroderma-related ILD, treatment with mycophenolate mofetil and oral cyclophosphamide decreased the reported prevalence of frequent cough, but had no influence on cough-related quality of life (142). The beneficial effect on cough in this study might possibly be due to the improvement in ILD rather than the immunosuppressive therapy itself. So currently, there is a lack of good therapies for cough in ILD. Whether results from studies on chronic cough can be extrapolated to ILD remains unclear, which underlines the necessity for more research into cough relief in ILD.

Fatigue

Fatigue is one of the major symptoms of ILD and has a significant influence on HRQOL (5, 7, 8)). Furthermore, fatigue predicts reduced physical activity in patients with IPF, independent of disease severity (151). Poor sleep quality has regularly been reported in ILDs and may be one of the contributing factors to fatigue (152). Medications and co-morbidities may also influence fatigue and factors such as sleep apnea, anemia, thromboembolism, and hypothyroidism, should be identified and treated (25). Although fatigue can be very burdensome, limited research has been done into the etiology and treatment of fatigue in ILD. A small study suggested a potential benefit of pulmonary rehabilitation on fatigue (153). No effective pharmacological treatment options are currently available.

Depression and anxiety

Depression and anxiety are common symptoms among ILD patients and can negatively impact HRQOL (6, 10). The reported prevalence of depressive symptoms in ILD is up to 49% (9, 130, 154, 155). Mild to severe anxiety symptoms may occur in up to 58% of patients, and clinically significant anxiety has been reported in about 12% of patients

(44, 130). One study showed that the presence of anxiety and depression was not related to disease severity and type of ILD. Dyspnea and comorbidities may be the main contributing factors to anxiety and depression in ILD (130, 156); the authors suggested that optimal management of these coexisting conditions may reduce anxiety and depressive symptoms.

No studies have specifically assessed the effect of pharmacological treatment on anxiety and depression in ILD. Therefore, standard treatment for anxiety and depression (i.e. anxiolytics and antidepressants) is currently advised in patients with ILD (25). Disease support programs and pulmonary rehabilitation may reduce anxiety and depression in ILD patients (43, 66, 71). Cognitive behavioral therapy has also been suggested as treatment option, but the effects on anxiety and depressive symptoms in ILD have not been studied (44). It is advised to discuss referrals for professional psychological counseling and support with all ILD patients presenting with anxiety and/or depressive symptoms.

Treatment limitations and end-of-life care

While the prognosis in ILD may vary, most patients with progressive fibrotic diseases will ultimately die from these diseases. Palliative care not only aims to improve quality of life for patients and families, but also quality of dying (25). To facilitate a dignified end-of-life path, patients' preferences should be known in order to anticipate needs. Many patients with progressive ILDs prefer talking about end-of-life early in the disease course. Some patients prefer to receive more gradual information about prognosis and end-of-life care, which emphasizes the need for regular assessments of individual patients' preferences during the disease trajectory (12, 13, 26, 28, 32).

A cross-sectional study in patients with cancer, cardiac diseases and chronic lung diseases (including ILD), showed that most patients preferred to die at home (157). Nonetheless, the majority of patients with IPF worldwide died in a hospital and a substantial number of patients died in the Intensive Care Unit (ICU)(117, 158, 159). The mortality rate for IPF patients in the ICU is high and prognosis after an ICU admission is poor (159-161). The percentage of patients dying in the ICU is highly variable across different countries, suggesting cultural differences regarding end-of-life discussions and the preferred place of death (158). Several retrospective studies showed that only a minority of ILD patients were referred to palliative care before their ICU admission (117, 161). Other studies showed that in ILD patients, end-of-life decisions were often not made (115), and that most end-of-life decisions were reported in the last days of life (159). Moreover, the majority of patients received life prolonging therapy and diagnostic procedures during the last days of their lives (159). Patients with oxygen-dependent ILD had less access to end-of-life care compared to patients with lung cancer in the last week of life, although their symptom burden was higher (162). One of the reasons for the poor access to

end-of-life care might be that in ILD patients, death was more frequently reported as "unexpected" than in lung cancer (162). Due to the unpredictable disease course, risk of acute exacerbations and rapid deterioration, it is strongly advised to initiate end-of-life discussions early in the disease course. During end-of-life conversations, issues such as treatment limitations (regarding intensive care, intubation and resuscitation) and the preferred place of dying, should be discussed with patients and caregivers (20, 25).

A decision aid tool facilitated communication and improved documentation of end-of-life decisions in ILD. Furthermore, it had the ability to identify patients in need of palliative care and led to earlier palliative care referrals (163). A multidisciplinary care program in IPF, which aimed at advanced care planning, reduced emergency room visits and hospitalizations in the last year of life. Patients who participated in the program died significantly more often at home (164). Although this was a retrospective study, the results are promising and may be used to improve end-of-life care in progressive ILDs. Though little structured research has been done in ILD about practical measures of symptom control in the dying phase, in practice many doctors will use similar approaches as for other respiratory diseases.

CONCLUSION

ILDs comprise a heterogeneous group of diseases, which often have a major impact on the lives of patients. Optimal management of patients with interstitial lung disease requires a comprehensive approach to care, which encompasses disease-modifying treatment, symptom-centered management, education and self-management strategies. Especially in the more progressive and fibrotic forms of ILD, treatment should not only be aimed at prolonging life, but also at improving quality of life for patients. Symptom-centered management in ILD includes, amongst others, supplemental oxygen, pulmonary rehabilitation and palliative care. In order to optimize individually tailored treatment, patients' needs and preferences should regularly be assessed during the disease course.

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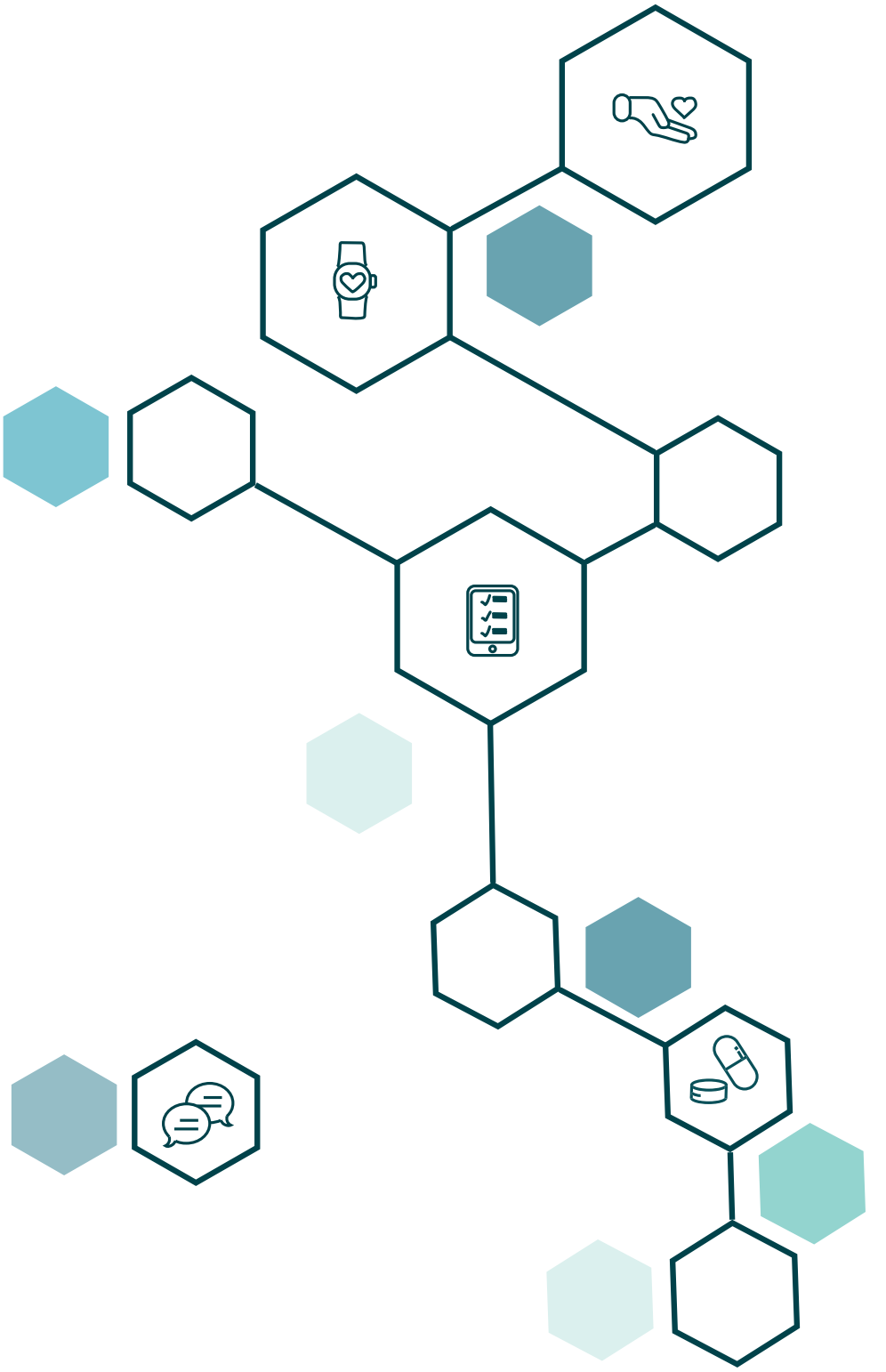

Chapter 2

Comprehensive care for patients with sarcoidosis

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disease, associated with significant morbidity and impaired quality of life. Treatment is aimed at recovering organ function, reducing symptom burden and improving quality of life. Because of the heterogeneity and variable disease course a comprehensive, multidisciplinary approach to care is needed. Comprehensive care includes not only pharmacological interventions, but also supportive measures aimed at relieving symptoms and improving quality of life. The purpose of this review is to summarize the most recent knowledge regarding different aspects of care and propose a structured approach to sarcoidosis management.

Keywords

Sarcoidosis; quality of life; comprehensive care; holistic management

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease of unknown cause, that can affect almost any organ. The past decade we have gained more insights in the dysregulation of the immune system, which is thought to play an important role in the etiology of sarcoidosis (1). Patients may present with a wide range of organ-specific symptoms, such as cough and dyspnea, or non-organ manifestations including fatigue, depression, and reduced exercise tolerance (1). In about 60 percent of patients, remission occurs spontaneously or after treatment within 10 years after diagnosis (2). In approximately 10-40% of patients, sarcoidosis becomes chronic and progressive. Mortality is around 1-5%, and is higher in African-American patients and elderly patients (3). In general, sarcoidosis leads to a substantial economic burden and societal impact, mainly because of hospitalizations, medication costs and inability to work (3, 4). For individual patients, high symptom burden often leads to psychological problems and an impaired quality of life (QoL) (5).

Current pharmacological treatment of sarcoidosis is usually immunosuppressive and directed at decreasing granulomatous inflammation (2). Overall, treatment is aimed at recovering organ function, reducing symptom burden and improving quality of life (6). Pharmacological interventions are not curative and in a subgroup of patients symptoms or disease progression may persist (2). A comprehensive approach to care is needed for patients with sarcoidosis, especially because of the heterogeneity in symptoms and organ involvement and variable disease course (7). This review is written from a pulmonologist's perspective, as in many hospitals the pulmonologist is the central care coordinator. However, we would like to stress the importance of multidisciplinary care as extrapulmonary disease is present in the majority of patients.

The aim of this review is to summarize the most recent knowledge regarding different aspects of care in sarcoidosis and propose the "ABCDE model for sarcoidosis", which is an adaptation of the ILD version (8, 9).

ABCDE MODEL

The importance of comprehensive care in sarcoidosis is generally acknowledged (10, 11). Here, we describe the ABCDE model that can be used to structure comprehensive sarcoidosis management in order to improve QoL and outcomes for patients (**Figure 1**). This model includes the following components: **A**ssessment of symptoms and patient's needs, **B**acking patients by providing support and education, treatment of **C**omplaints

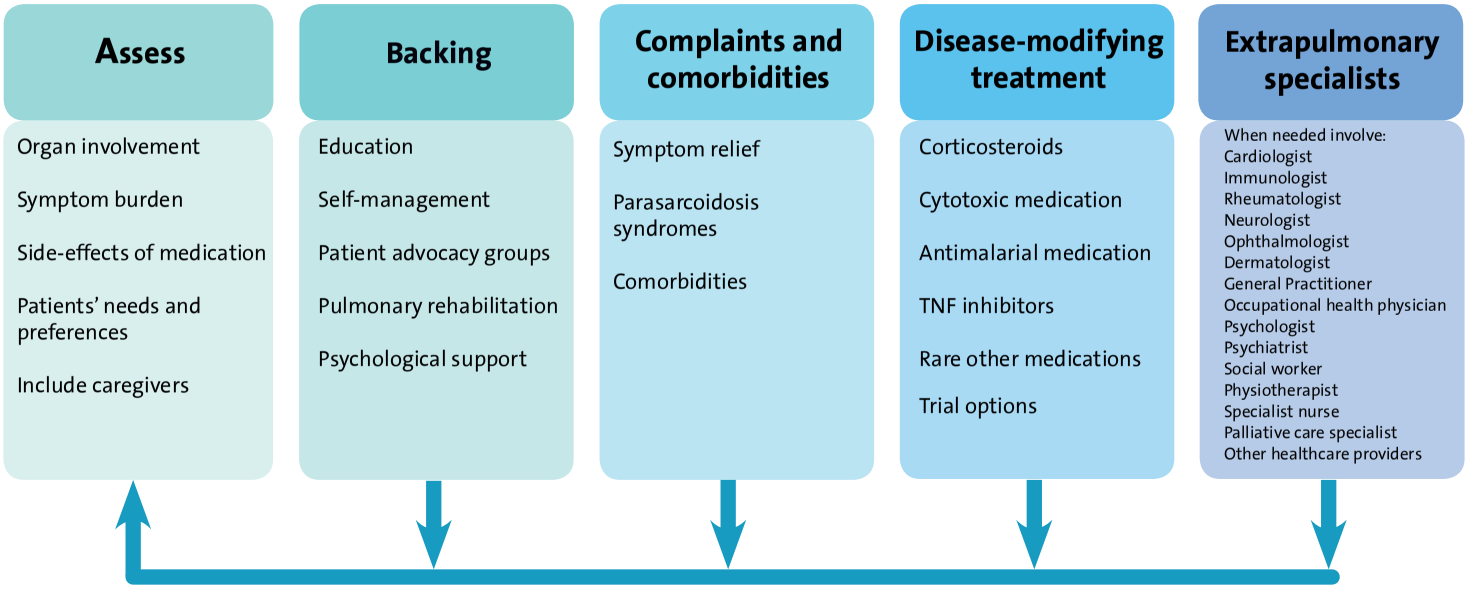

Figure 1. Structured approach to comprehensive care in sarcoidosis. The arrows show that individual patient's symptoms, needs, and treatment should regularly be reassessed. TNF = tumor necrosis factor

and **C**omorbidities, **D**isease-modifying treatment, and involvement of **E**xtrapulmonary specialists. As disease activity, organ involvement, and patients' preferences may vary during the disease course, regular reassessment is essential. The ABCDE model can provide guidance to clinicians during the first work-up and follow-up of patients with sarcoidosis. Different components of the model are discussed in more detail in the following paragraphs.

ASSESS

In all sarcoidosis patients, organ involvement should be carefully assessed in the diagnostic process and during follow-up. The degree of organ damage and disease activity is often difficult to quantify, as no gold standards exist and symptoms are often non-specific (3, 12, 13). Percentages of organ involvement in the literature vary, depending on whether only clinically overt or also asymptomatic organ involvement is taken into account. Further, organ involvement is depending on ethnic background and varies throughout the world. In individual patients, the number of involved organs may change over time and therefore diagnostic assessments have to be performed regularly, particularly if patients express new symptoms (1, 14). The frequency in which different organ systems are affected in sarcoidosis is summarized in **figure 2** (1, 15).

Furthermore, non-organ manifestations of sarcoidosis, such as fatigue, small fiber neuropathy (SFN), cognitive impairment, and muscle weakness should not be overlooked. These symptoms often correlate poorly with physiological parameters (3, 11). Consequently, patients without apparent organ involvement could still have a high symptom burden (11). Hence, Drent et al. proposed four different domains that should be evaluated in the complete work-up of a patient; not only the severity, extent and activity of the disease, but also the impact of disease (11). In a recent survey with over 1000 respondents, 95% of patients reported sarcoidosis-related symptoms, and self-reported symptom burden of sarcoidosis was high (17). Due to this high symptom burden, uncertain prospects, and sometimes social isolation and inability to work, sarcoidosis has a huge impact on lives of patients (3, 11, 18). In a Dutch government survey, more than 60% of sarcoidosis patients (n=150) considered their general health moderately to severely impaired. Only 7% answered that their health problems had no influence on their social life (19). Furthermore, almost 50% of patients in a recent study (n=755) were partially or totally unable to work due to their sarcoidosis, highlighting the considerable impact of sarcoidosis on daily life (18). A Swedish national registry evaluation of 3347 sarcoidosis patients aged 25-59 years, suggested 8% lower income and 26 lost work days in the year of diagnosis compared with age matched controls (20). In a US registry

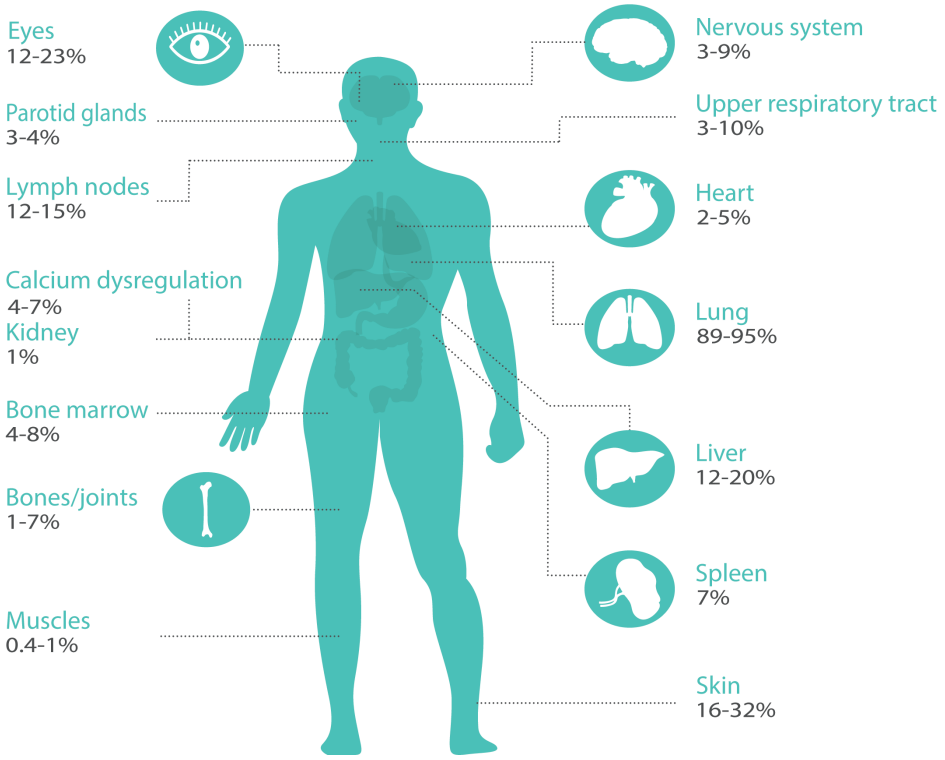

Figure 2. Organ involvement in sarcoidosis. Organ involvement is classified according to the ACCESS organ assessment instrument (16). Prevalence data are used from references (1, 15).

(n=2318), 44% of respondents reported a large effect on household finances, and 31% had to quit their job after the diagnosis of sarcoidosis (4).

Overall, sarcoidosis patients have an impaired QoL compared with the healthy population (5). Several studies analyzed the relation between symptoms and QoL in sarcoidosis. Symptoms predictive for QoL are depression, anxiety, fatigue, reduced exercise capacity, SFN-related symptoms, dyspnea, pain, and arthralgia (13, 21-26). Interestingly, partners of sarcoidosis patients also experience a reduced QoL compared with healthy controls (21). Moreover, partners tend to have increased anxiety levels and psychological distress (27). Both patients as well as their partners reported that there should be more support for partners of sarcoidosis patients (27).

QoL can be defined as "an individual's perception of their position in life" and is influenced by a persons' values, beliefs, culture, physical health, social and psychological state (28). QoL can be measured with patient-reported outcome measures (PROMs). PROMs are instruments that "collect self-reported information about a patients' health

condition, without any intervention from a healthcare provider" (29). PROMs can be either generic (applicable to the whole population), disease-specific (developed or validated in a specific disease) or domain-specific (assessing severity or burden of a specific symptom or organ). A wide range of PROMs are currently being used for sarcoidosis (30, 31). A number of these instruments, such as the King's Sarcoidosis Questionnaire (KSQ), Sarcoidosis Health Questionnaire (SHQ), Sarcoidosis Assessment Tool (SAT), and Fatigue Assessment Scale (FAS) have been specifically developed to measure QoL and symptom burden in sarcoidosis (31-34). Although PROMs are mainly used in clinical trials, well-validated PROMs could also be used in clinical practice to evaluate treatment effect and longitudinal changes in symptoms and QoL (31, 35). In other chronic diseases, the use of PROMs in regular care is associated with enhanced communication and shared-decision making, detection of unrecognized problems, higher patient satisfaction and improved QoL (36, 37). Future research could affirm whether this is also the case in sarcoidosis.

Other factors with a potential negative impact on QoL should not be forgotten in the assessment of sarcoidosis patients. For example, medication for sarcoidosis may lead to debilitating side-effects, such as weight gain, diabetes, osteoporosis and psychological problems (38-40). According to one study, patients with higher cumulative doses of prednisolone had a significantly lower QoL when adjusted for disease severity (4, 39). Moreover, medication-related events lead to a substantial number of hospitalizations in patients with sarcoidosis (41). Consequently, (dis)advantages of starting and continuing therapy should be weighted by healthcare provider and patient during every clinic visit.

Although it is increasingly acknowledged that patient perspectives are important for optimizing individually-tailored treatment (17, 27, 42), literature concerning (unmet) needs and preferences of patients with sarcoidosis is scarce. Recently, an international survey revealed that sarcoidosis patients considered QoL and functionality as the most important treatment outcomes (7). Blood tests and pulmonary function tests were considered the least important outcomes (7). These results are in contrast to the current focus of most clinicians on physiological outcome measures (5, 13, 17, 30). In a number of studies, patients reported the need for better information about sarcoidosis and shared decision making (19, 27). As treatment goals can obviously differ between patients, the first step in shared-decision making is identifying patients' needs and preferences. During the disease course, patients should be involved in their treatment plan and in the regular evaluation of benefits versus risks of (pharmacological) treatment (10, 14, 19). Including patients as a partner in care could lead to better QoL and adherence to treatment (43). Multidisciplinary management and improved access to sarcoidosis specialists and expert centers for sarcoidosis are other important needs for patients, although it must be acknowledged that not all sarcoidosis patients require tertiary care (6, 32).

BACKING

Several support measures to improve QoL for sarcoidosis patients have been suggested in the past years. Better information and education is vital to optimize care for sarcoidosis (11, 18, 27, 44, 45). Even in the current internet era patients state that they cannot find enough reliable information about their disease online (19, 27) Moreover, the complexity and heterogeneity of sarcoidosis may complicate communication and knowledge transfer between healthcare providers and patients (11). Currently, patients and their partners often feel misunderstood because of a lack of knowledge among healthcare providers and the general public (11, 27). Hence, awareness should be raised in society and among relevant healthcare providers. Patient advocacy groups could play an important role in providing understandable information and education, by organizing information meetings and awareness campaigns (46). Although support groups can have obvious benefits, effects on QoL have never been studied in sarcoidosis.

Self-management support is one of the main pillars of the chronic care model, developed to improve care for patients with chronic conditions (47). Many aspects of chronic disease care can only be managed by patients themselves. Self-management strategies cover all disease domains, and include for example behavioral changes, medication use, exercise, dietary strategies and home monitoring of disease (47, 48). To achieve skills for self-management, patients and families need to be adequately trained and supported by their healthcare providers (1). Use of novel eHealth solutions to enhance self-management has recently gained interest in sarcoidosis (44, 49). Self-monitoring of symptoms, side-effects, QoL, activity and pulmonary function at home has shown to be feasible and highly appreciated by patients with sarcoidosis (49, 50). A comprehensive home monitoring program may provide patients with more insights in their disease course, and thereby empower patients and enhance communication with healthcare providers. In a recent study, home monitoring of pulmonary function allowed for earlier detection of steroid treatment effects, suggesting that patient-managed steroid dosing regimens may be feasible (50).

While activity tracking at home could possibly help to stimulate exercise (49, 51-53), supervised training programs or multidisciplinary pulmonary rehabilitation might have more beneficial effects (11). Current evidence indicates that a structured, supervised exercise program can improve symptoms, QoL, exercise capacity, and muscle strength in patients with different stages of sarcoidosis (54-58). Although these studies showed promising results, no evidence-based guidelines exist to date. In a survey of international sarcoidosis experts, the vast majority of respondents considered physical training in sarcoidosis valuable and would recommend it as standard of care (54). Pulmonary in-

volvement, fatigue, and reduced exercise tolerance are the main indications for physical therapy in sarcoidosis (54). The long-term effects of physical therapy, optimal duration and content of exercise programs in sarcoidosis have never been investigated and need further study. Furthermore, reimbursement and distance to appropriate exercise programs vary between regions and countries and may limit access to physical therapy for sarcoidosis patients (54). Telerehabilitation could potentially be a solution for patients living in rural areas because distances are bridged online. A study evaluating the feasibility and effect of a telerehabilitation program in sarcoidosis is ongoing (NCT03914027).

The majority of patients would like to have better access to psychological support (7, 27). In clinical practice, patients are referred to a psychologist or psychiatrist for further counseling and treatment on indication, though some people advocate for standard psychological assessment (59). Cognitive behavioral therapy has been proposed as a promising method to offer psychological support; this therapy could potentially improve patients' coping strategies and thereby reduce stress, anxiety and depression (11, 23). To date, one study analyzed the impact of mindfulness-based exercise therapy on physical and psychological symptoms in sarcoidosis. Even though this was a modified training consisting of only one 45-minute workshop, symptoms significantly decreased after the session (60). A randomized controlled trial to assess the impact of an online mindfulness-based cognitive behavioral therapy on QoL, fatigue, stress, and anxiety is currently ongoing (https://www.trialregister.nl/trial/7816).

COMPLAINTS AND COMORBIDITIES

Symptom relief is a major aspect of sarcoidosis management. Dyspnea is among the most common symptoms in sarcoidosis and is an important indication for treatment (10). Dyspnea is often multifactorial and can be caused by pulmonary, musculoskeletal or cardiac involvement of sarcoidosis, or deconditioning. Other causes for dyspnea such as infection or pulmonary hypertension should also be evaluated (10). Non-pharmacological treatment options include physical training, multidisciplinary pulmonary rehabilitation and potentially cognitive behavioral therapy (56-58, 60) (**Table 1**). Cough is present in up to 53% of sarcoidosis patients (61). Patients with sarcoidosis have a significantly higher cough frequency compared with the normal population (62). Even though cough is often part of the disease, other causes such as reflux or post-nasal drip should always be excluded. One study showed that inhaled corticosteroids may be effective in reducing cough in sarcoidosis, but two other small studies showed no effects of inhaled corticosteroids on cough in sarcoidosis (63-65). Consequently, inhaled corticosteroids should not be routinely administered unless a trial demonstrates efficacy

Table 1. overview of pharmacological and non-pharmacological treatment options for common sarcoidosis symptoms

Symptom	Pharmacological treatment	Non-pharmacological treatment
Dyspnea	- Regular disease-modifying treatment - Treat other causes - Supplemental oxygen (in case of hypoxemia)	- Physical training, pulmonary rehabilitation (56-58) - Cognitive behavioral therapy (60)
Cough	- Regular disease-modifying treatment - Treat other causes - Inhaled corticosteroids*	Multimodality speech pathology therapy (66)
Fatigue	- Treat other causes and comorbidities - Neurostimulants: armodafinil, (dex) methylphenidate (68, 69) - TNF inhibitor treatment (70)	- Treat reversible causes i.e. obstructive sleep apnea, obesity, depression - Physical training or pulmonary rehabilitation (55-58) - Psychosocial counselling (11) - Cognitive behavioral therapy (60)
Depression and anxiety	- Antidepressants (11)** - Anxiolytics**	- Cognitive behavioral therapy (60) - Pulmonary rehabilitation (56) - Psychological counselling (45)
Small-fiber neuropathy	- Antidepressants - Anticonvulsants - Topical anesthetics - Opioids (45) - Intravenous immunoglobulin (71, 72) - TNF inhibitor treatment (72)	Mindfulness-based therapy (45)
Cognitive impairment	TNF inhibitor treatment (70)	

Many of these recommendations are expert opinion or based on small studies.*earlier studies showed conflicting results. **should only be initiated after an appropriate psychiatric evaluation. TNF = tumor necrosis factor

(66). In the recent CHEST guideline, speech therapy is recommended for patients with ILD and refractory cough, however, this therapy has not been specifically evaluated in sarcoidosis (66). Vasoactive intestinal peptide (VIP) inhalation seemed to reduce cough in sarcoidosis in one small open clinical phase II study, but has never been investigated in a randomized setting (67). Further studies regarding antitussive therapy in sarcoidosis are highly needed.

Non-organ manifestations or parasarcoidosis syndromes include symptoms as fatigue, depression, anxiety, pain, SFN, and cognitive impairment (45). As most of these symptoms are related to each other, it can be challenging to avoid a vicious circle. Fatigue is one of the most prevalent (up to 90% of patients) and burdensome symptoms for patients with sarcoidosis (17, 27). Fatigue is a complex, multifactorial problem (11). Symptoms as sleep disturbance, psychological problems, cognitive impairment, reduced exercise capacity, and muscle strength are all linked to fatigue (73-77). Moreover, comorbidities and medication use may also contribute to fatigue. Previously, it has been shown that

patients with multi-organ involvement and a higher number of comorbidities have increased fatigue levels (74). Comorbidities associated with fatigue are sleep apnea, pulmonary hypertension, diabetes mellitus, thyroid disorders, and obesity (74). Fatigue is often a chronic problem, which persists or worsens despite sarcoidosis treatment. Research into better pharmacological and non-pharmacological treatment options for sarcoidosis-associated fatigue is scarce. Two small randomized trials demonstrated that neurostimulants (armodafinil and methylphenidate) have the potential to reduce sarcoidosis-associated fatigue (68, 69). A number of other relatively small or retrospective studies showed the benefits of physical training and cognitive behavioral therapy on fatigue in sarcoidosis (55-58, 60). Larger studies investigating the etiology and better treatment options for sarcoidosis-associated fatigue are essential to improve symptom burden and QoL for patients.

Next to fatigue, SFN-related related symptoms were reported by the vast majority of patients (86%) in a recent European survey (17). SFN is difficult to diagnose and to treat (11). Patients may experience a myriad of symptoms, but frequently present with neuropathic pain or autonomic dysfunction (72). SFN is usually treated with anticonvulsants, antidepressants, topical anesthestics or opioids (45). However, these standard treatment options are often not effective (11). Retrospective studies showed that intravenous immunoglobulin (IVIG) and tumor necrosis factor (TNF) inhibitors might be effective in reducing SFN-related symptoms (71, 72). Furthermore, the erythropoietin agonist cibenitide (ARA290) showed promising results on corneal nerve fiber abundance in a phase 2b clinical trial (78). No statistical differences were found in patient-reported outcomes, probably due to the design of the study (78).

Other common non-organ manifestations of sarcoidosis are psychological problems. Previous studies reported anxiety in up to 33% of patients and depressive symptoms in up to 66% of patients (45, 79). In a study which used a comprehensive diagnostic interview, the prevalence of major depressive disorder remained strikingly high, at 25% (59). Most other studies used questionnaires to screen for depressive symptoms (5, 80, 81). Patients with depression or anxiety tend to have a higher symptom burden and different perception of disease severity (79). Pulmonary rehabilitation may have a beneficial effect on psychological wellbeing (56). Cognitive behavioral therapy also has the potential to improve stress, anxiety and depression in sarcoidosis (60). Furthermore, regular pharmacological therapy for depression and anxiety (antidepressants and anxiolytics) could be offered after an appropriate psychiatric evaluation (60).

Cognitive problems, including memory loss, concentration difficulties, and impaired short-term memory are reported by more than 50% of sarcoidosis patients (17, 77).

At present, the cause of cognitive failure is considered multi-factorial, and possibly related to chronic inflammation. Currently, no convincing therapies or interventions are available. An observational study indicated that TNF inhibitor treatment may have a beneficial effect on cognition, as measured by the cognitive failure questionnaire (CFQ) (70). Besides, treatment of associated symptoms may also ameliorate cognitive function.

Comorbidities may also importantly impact QoL and are more prevalent in patients with sarcoidosis compared to the normal population (41, 82, 83). A higher number of comorbidities is associated with more frequent hospitalizations and a higher mortality rate (83, 84). The development of new comorbidities, related either to steroid use or to sarcoidosis itself, after diagnosis of sarcoidosis is independently and strongly associated with a number of adverse outcomes, including worse QoL, risk of hospitalization, and financial impacts (4). One study showed that more than half of sarcoidosis patients have more than one comorbidity, with arterial hypertension, thyroid disorders and diabetes mellitus being the most prevalent comorbidities (82). Another study found a significant higher prevalence of chronic liver disease, autoimmune diseases, chronic pulmonary diseases and cancer in patients with sarcoidosis (83). A study in African-American sarcoidosis patients reported that 90% of patients had one or more comorbidities (85). The number of comorbidities is higher in older patients, multi-organ involvement and patients with lower incomes (4, 82). Patients with comorbidities obviously have a higher disease complexity, making multidisciplinary management of sarcoidosis even more essential (83). The presence of comorbidities should therefore be carefully (re)assessed during the disease course.

DISEASE MODIFYING-TREATMENT

Not all patients with sarcoidosis require pharmacological treatment, as the majority will have spontaneous regression of the disease (2). Treatment is primarily aimed at suppression of the immune system, and thereby preventing organ damage. The main reasons to start treatment are "to avoid danger or improve quality of life" (86). Factors which should be taken into account are the probability of spontaneous resolution, risk for disease progression, extent of disease, organ dysfunction, activity of sarcoidosis, symptom burden and patient' preferences (2, 5, 10, 14).

Pharmacological treatment of pulmonary sarcoidosis should be considered for patients with significant pulmonary symptoms and patients with an impaired or deteriorating lung function (14, 87). For extrapulmonary sarcoidosis, the ATS/ERS/WASOG guideline state that treatment should always be initiated in case of cardiac sarcoidosis, involve-

ment of the central nervous system, hypercalcemia and ocular sarcoidosis not responding to topical treatment (88). Other common indications for treatment are hepatic involvement (impaired liver function, portal hypertension), splenic involvement, bone marrow involvement (cytopenia), nephrolithiasis and skin involvement with disfiguring lesions (14). Treatment may be initiated in patients who have disabling symptoms without organ damage, however, this should always be a shared-decision with patients as medication can have debilitating side-effects (10, 14). Consequently, efficacy and side-effects of treatment should be assessed during every outpatient clinic visit.

The current guideline, dating from 1999, states that "the appropriate treatment has not been well-defined for all patients" (88). At the moment oral corticosteroids (e.g. prednisolone) are recommended as the first-choice therapy for sarcoidosis (88). This recommendation is mainly based on expert opinion and a few relatively small observational studies and low-quality randomized trials from over 20 years ago (87, 89). Older studies have demonstrated that corticosteroids lead to an improvement in lung function, especially in patients with initial severe impairment of lung function (90, 91). Although corticosteroid treatment leads to short-term improvement of lung function, radiological improvement, and symptom reduction, previous studies have not conclusively demonstrated a beneficial effect in preventing disease progression (14, 87). Disease relapse occurs in over 30% of patients after discontinuation of corticosteroids. Furthermore, due to the lack of larger randomized trials the optimal dosage and duration of treatment remains unclear (89).

Most frequently used second-line treatment is the folic acid antagonist methotrexate (92). Methotrexate has a significant steroid-sparing effect and improves lung function (93, 94). Methotrexate is increasingly used as first-line agent in case of (relative) contraindications for corticosteroids (92). A second choice second-line treatment is azathioprine. A retrospective study in the Netherlands and Belgium showed that azathioprine and methotrexate were equally effective, but azathioprine appeared to have more side-effects (93). Mycophenolate mofetil and leflunomide are other second-line alternatives (1). Antimalarial medication (chloroquine, hydroxychloroquine) is regularly prescribed in patients with cutaneous involvement or hypercalcemia (95, 96). In refractory sarcoidosis, TNF inhibitors can be prescribed as a third-line agent. Infliximab has been studied in randomized controlled trials and may have beneficial effects on both pulmonary and extrapulmonary sarcoidosis in a subgroup of carefully selected patients (97-99). Adalimumab also appears to be effective (100). Other treatment options have recently emerged for patients with progressive sarcoidosis. The INBUILD study showed that nintedanib is effective in reducing forced vital capacity decline in patients with fibrotic interstitial lung disease, including sarcoidosis (101). The efficacy of pirfenidone in progressive fibrotic

sarcoidosis is also being studied (NCT03260556). Recently, inhibition of the JAK-STAT signaling pathway has been identified as a novel promising treatment target in sarcoidosis; prospective research is ongoing (NCT03910543, NCT03793439) (102). Not only is more research needed for refractory sarcoidosis, but better evidence-based treatment for first-line therapy, aiming at a better balance between effects and side-effects, is also highly needed. A multicenter trial evaluating the efficacy and side-effects of prednisone and methotrexate as first-line treatment for pulmonary sarcoidosis has recently started in the Netherlands. A detailed description of medication for sarcoidosis is outside the scope of this review; for an extensive overview, we refer you to other published reviews specifically focusing on this topic (1, 2, 10, 14, 86, 89).

EXTRAPULMONARY SPECIALISTS

Pulmonary physicians play an important role in the management of sarcoidosis patients, as the lungs are affected in up to 90% of patients. Nevertheless, a multidisciplinary team is needed to improve efficiency of care and outcomes for patients, as many organs can be affected and symptoms are wide-ranging (7, 103). While it is quite obvious that other medical specialists contribute their expertise in case of extrapulmonary sarcoidosis, healthcare providers such as occupational health physicians, pain specialists or specialist nurses should not be forgotten (7, 18) (**Figure 1)**. Work participation is lower in patients with sarcoidosis; patients have more health-related sick days and a substantial income loss compared with the normal population (3, 4, 18, 20). Consequently, many patients undergo work capacity assessments and occupational health physicians need to be well-educated about sarcoidosis (11, 18). Although the role of specialist nurses is not as established as in other interstitial lung diseases, specialists nurses could function as coordinator of care in sarcoidosis and give patients practical and emotional support. In a small minority of patients, disease will progress despite all treatment lines. In a subgroup of these patients lung transplantation may be an option. And even though mortality is overall low in sarcoidosis, a multidisciplinary approach should also include palliative care specialists in end-stage disease or in case of a high disease burden.

CONCLUSIONS

A comprehensive, multidisciplinary approach is essential to treat patients with such a heterogeneous disease as sarcoidosis. Besides aiming at disease modification with pharmacological interventions, patients should also be offered supportive comprehensive care aimed at relieving symptoms and optimizing QoL. Patients' preferences should be

guiding all treatment decisions. To allow for better evidence-based treatment in the future, more research into both pharmacological and non-pharmacological treatment options is highly needed.

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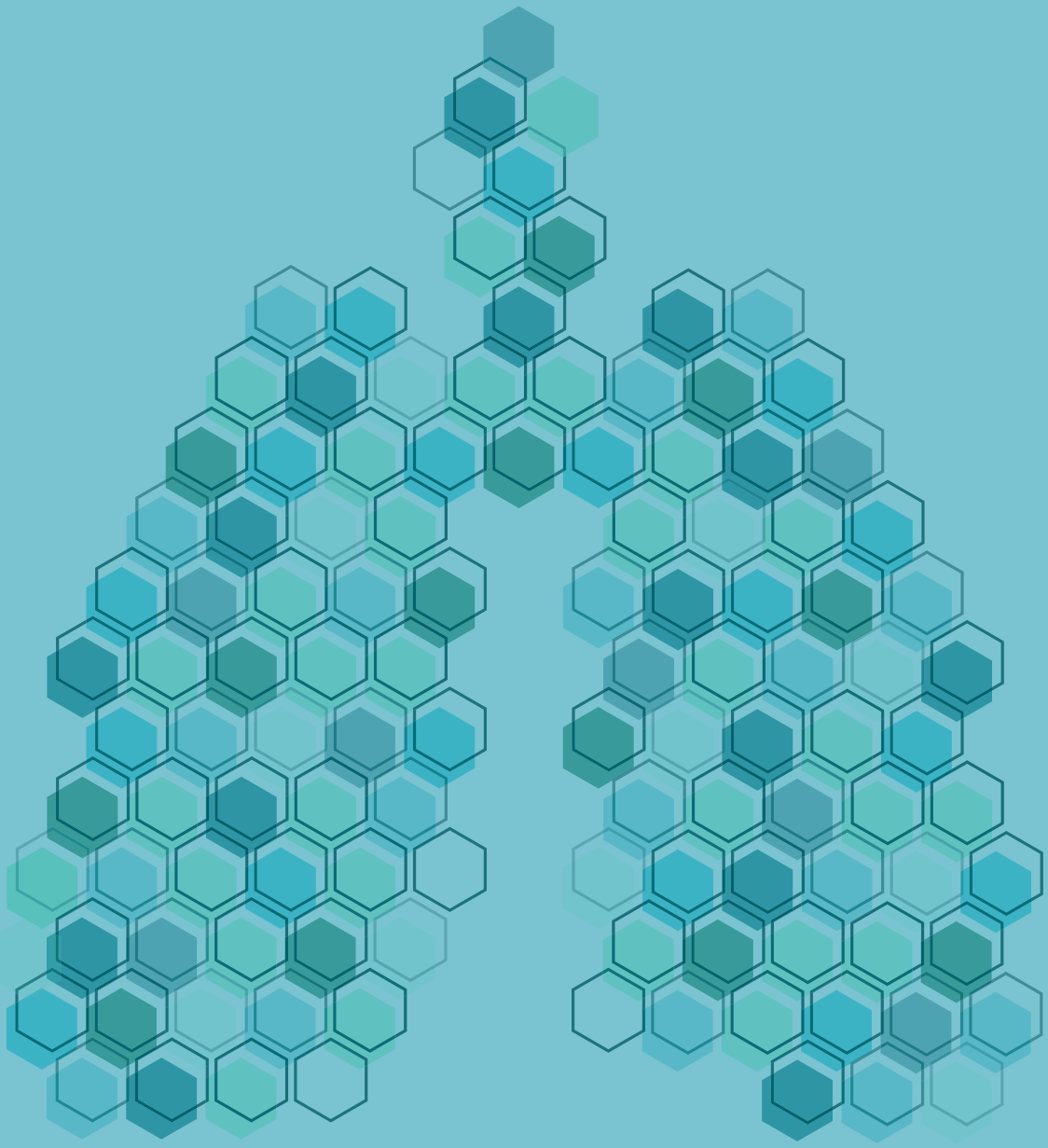
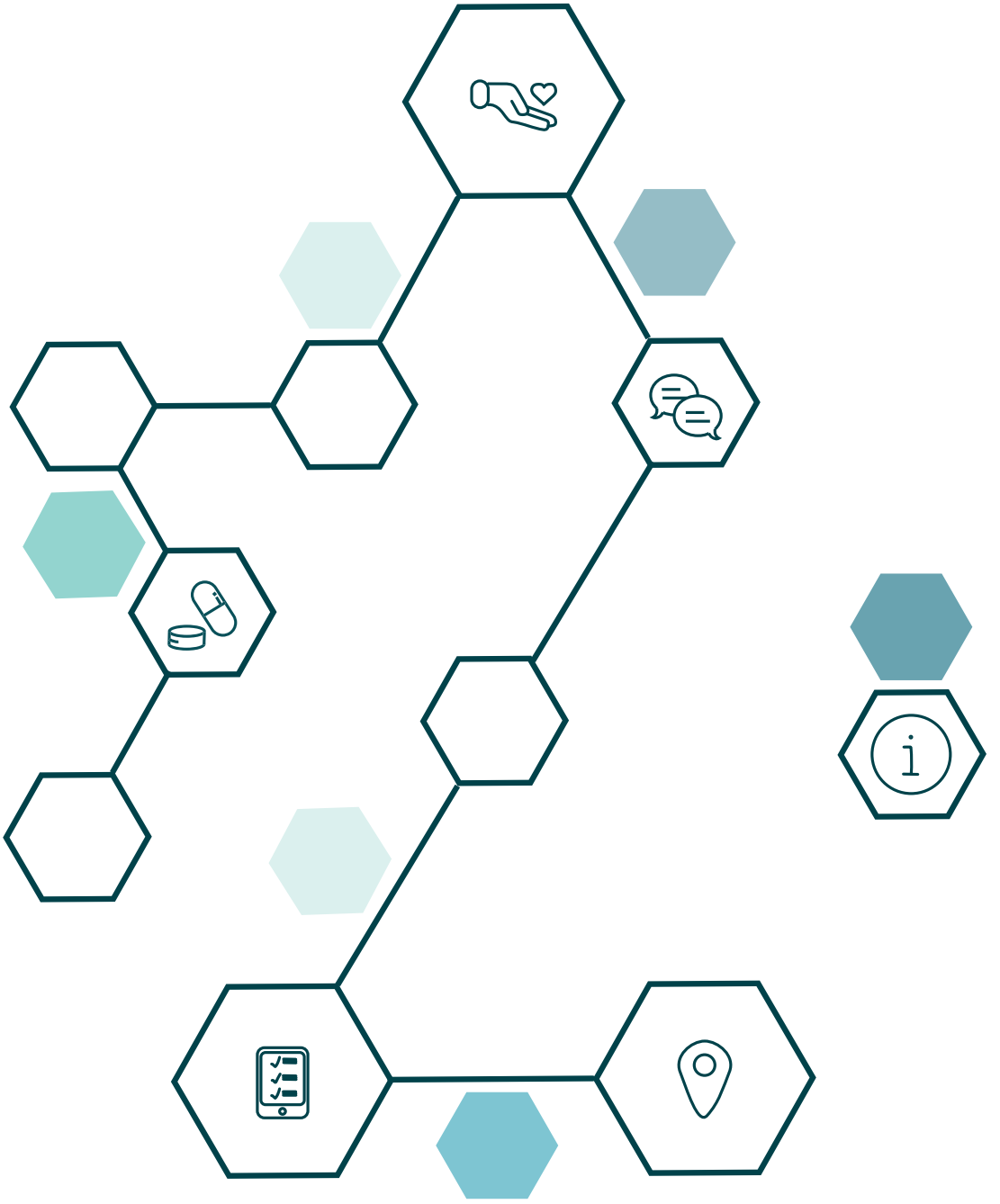


PART 2

Gaps in care in interstitial lung disease



Chapter 3

Gaps in care of patients living with pulmonary fibrosis: a joint patient and expert statement on the results of a Europe-wide survey

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ABSTRACT

Background

Pulmonary fibrosis (PF) and its most common form, idiopathic pulmonary fibrosis (IPF), are chronic, progressive diseases resulting in increasing loss of lung function, impaired quality of life and survival. The aim of this joint Expert and Patient Statement was to highlight the most pressing common unmet needs of patients with PF and IPF, putting forward recommendations to improve the quality of life and health outcomes throughout the patient journey.

Methods

Two online surveys for patients and healthcare providers were conducted by the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation (EU-IPFF) in 14 European countries.

Results

The surveys were answered by 286 patients and 69 healthcare professionals, including physicians and nurses. Delays in diagnosis and timely access to ILD specialists and pharmacological treatment have been identified as important gaps in care. Additionally, patients and healthcare professionals reported that a greater focus on symptom-centered management, adequate information, trial information, and increasing awareness of PF/IPF was required.

Conclusion

The surveys offer important insights into the current unmet needs of PF/IPF patients. Interventions at different points of the care pathway are needed to improve patient experience.

Keywords

IPF; Interstitial Lung Diseases/ Pulmonary Fibrosis; Doctor-Patient Relationship; Early Diagnosis; Treatment access; Health outcomes.

INTRODUCTION

Interstitial lung diseases (ILDs) comprise a diverse collection of more than 200 lung disorders, affecting the interstitium of the lung (1). A large subgroup of patients with ILD have pulmonary fibrosis (PF); most forms of PF are characterized by a progressive phenotype, are associated with a high burden of disease and have devastating consequences for patients and their families (2-4). Idiopathic pulmonary fibrosis (IPF) is the most frequent form and accounts for 17-37% of all ILDs (5). A cure for IPF does not currently exist, although there are two drugs approved that slow disease progression (6, 7). Non-pharmacological treatment options include lung transplantation to prolong life and measures such as pulmonary rehabilitation and supplemental oxygen to ameliorate exercise tolerance and quality of life (8-10).

In 2016, a collaborative effort of patient associations and healthcare providers was undertaken to gain insights in the needs of patients with IPF, which led to a European IPF Charter (11). This charter was presented at the European Parliament to improve awareness and equal access to care around Europe for patients with IPF. We hoped that this would lead to improvement in the care and treatment of patients with fibrotic lung diseases. One of the aims of the current study was to see whether this happened or not. To do so, we aimed to identify the most pressing common unmet needs of patients with PF and IPF throughout Europe and to put forward recommendations in an Expert Statement to improve quality of life and health outcomes throughout the patient journey.

PARTICIPANTS AND METHODS

The study was conducted by the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation (EU-IPFF) in association with the European Reference Network on Rare Lung Diseases (ERN-Lung). This Expert Statement is a result of the collaboration between patient representatives and medical experts. Two online surveys were developed: one for PF/IPF patients and one for practicing pulmonologists and nurses with ILD expertise. The questions for the surveys were developed by the EU-IPPF working group, consisting of four patient representatives and 14 ILD experts. The group met in person to discuss the topics of the surveys and to reach consensus on the questions. Both surveys contained 62 questions and were circulated between 29 June 2018 and 8 September 2018 in 14 countries. The survey has been created in SurveyMonkey (www.surveymonkey.com). An information sheet was developed to inform respondents about the purpose of the project. All respondents were asked to read and understand the terms of the questionnaire and provide their consent. The survey for healthcare profes-

sionals (HCPs) was distributed through the ERN-LUNG network and the patient survey through the EU-IPFF's 17 member organizations *via* an email that contained a link to the survey. Caregivers were allowed to respond to the survey on behalf of the patient. The surveys are available in the supplementary material. This study is exempt from ethics review because it solely consists of an online survey that was disseminated to patients *via* patient groups.

Results have been divided into four geographical sub-regions: Northern Europe (Denmark, Ireland and UK), Eastern Europe (Bulgaria, Czech Republic and Poland), Southern Europe (Greece, Italy and Spain), and Western Europe (Austria, Belgium, France, Germany, and the Netherlands) (12). Results were collected, tabulated in Excel (Microsoft, Redmond, WA, USA) and bar graphs were generated. Pearson chi-squared test has been used to compare between geographical sub-regions. Data were analyzed with R version 3.5.2 (www.r-project.org).

In addition, a literature search was conducted for articles about the care pathway and unmet needs of patients with PF/IPF. PubMed and Embase have been searched for articles published between January 2010 and March 2018, using the (MesH) terms "idiopathic pulmonary fibrosis", "pulmonary fibrosis", "interstitial lung disease" or "diffuse parenchymal lung disease" in combination with "care pathway", "unmet needs", and/or "barriers". The search was limited to adults and articles published in English. The reference lists of articles were manually screened for additional publications. Relevant articles were included in order to create an overview on the state of knowledge on the care pathway and unmet needs of patients with PF/IPF. Results of the literature search will be used to compare gaps in care from previous research with results of the current study.

RESULTS

Literature search

The literature search retrieved 1111 articles, of which 966 articles were excluded based on title and abstract. After full-text screening of the remaining articles and exclusion of studies without relevant information on unmet needs and the care pathway in PF/IPF, 22 studies were included (see the supplementary material for details). Unmet needs reported by patients and caregivers were extracted from these studies and displayed in **Table 1**.

Table 1. Unmet needs of patients with PF/IPF reported by patients and caregivers

	Reference(s)
Timely and accurate diagnosis	(11, 13-26)
More awareness of PF/IPF	(11, 13-15, 18-21, 23, 26, 27)
Adequate information and education	(11, 13-19, 22-24, 26-32)
Access to pharmacological treatment	(11, 14, 15, 19-21, 26)
ILD specialists	(11, 13-16, 18, 19, 22, 25-27)
Symptom relief	(17, 18, 20, 21, 23, 28, 30)
Psychological support	(11, 13-15, 17, 23, 26-28)
More involvement and support of partners	(14, 16, 17, 24, 28, 32, 33)
Non-pharmacological management (i.e. supplemental oxygen, pulmonary rehabilitation)	(11, 13, 15-17, 19, 21-23, 26, 30)
Access to a multidisciplinary team	(11, 16, 17)
End-of-life care	(11, 16, 19, 20, 22, 23, 26-30)

Survey results

Respondent characteristics

The patient survey was completed by 286 individuals from 14 different countries, of whom 79% were patients and 21% were caregivers (**Figure 1)**. The majority of patients had IPF (86%) and 14% of respondents had another type of PF. Patients reported diagnosis between 1987 and 2018. The mean age of patients was 66 years, and 70% were male. A fifth of respondents (21%) reported a history of PF/IPF in their families. The questionnaire for HCPs was completed by 69 respondents: 56 physicians (81%) and 13 specialist nurses (19%). Most HCPs (87%) were specialized in ILD and worked at recognized centers of expertise. There was a large variation in the reported number of patients with PF/IPF treated per center (range 5-3000). The estimated total number of patients managed per year among all participating centers collectively was 10,000-11,000 for IPF and 27,000-28,000 for other forms of PF.

Referral pathways and access to ILD specialist care

In order to assess the delay in access to a pulmonary physician, patients were asked to indicate how much time passed before their general practitioner referred them to a respiratory specialist. Almost half of patients (45%) reported that referral took place within one month. In contrast, time to referral was >1 year for 16% of patients. No evident differences in referral time were found across Europe (p=0.84) (**Figure 2**).

Furthermore, 33% of patients reported that their referral to a specialist center took <1 month, with 20% reporting a wait of >1 year. Fewer than half of patients (47%) reported that a referral to a specialist center was (very) easy to obtain, whereas 20% considered it a (very) difficult process. More than a third of PF/IPF patients (37%) reported at least one

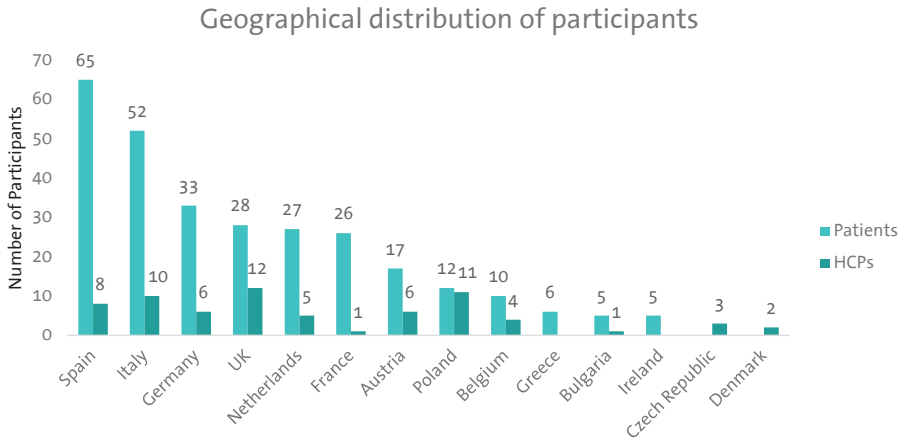

Figure 1. Number of participants (patients and HCPs) per country. HCP = healthcare professional

other diagnosis prior to being diagnosed with PF/IPF. Half of these patients indicated that >1 year passed before they were correctly diagnosed (**Figure 3**).

The vast majority of HCPs (94%) reported that there was access to a multidisciplinary team (MDT) for all IPF/PF patients in their center, but composition of the MDT varied greatly. In the patient survey, 58% of respondents stated that diagnosis has been confirmed in an MDT meeting. However, it is unknown if all patients were aware that their case was evaluated in an MDT. Around two-third of HCPs (65%) answered that ILD specialist nurses were available in their center, while 52% of PF/IPF patients responded that they had access to specialist nurses.

Reported access to genetic screening varied. Half of the participating HCPs (49%) stated that genetic screening was offered, either in their own center or *via* referral to another center. In total, 16% of surveyed patients underwent genetic testing; of these 45 patients, 42% stated that they did not receive enough information about their results of the genetic tests.

Access to pharmacological treatment for IPF patients

Both approved treatments for IPF, *i.e.* nintedanib and pirfenidone, were available in all participating countries. Almost all HCPs (93%) confirmed that antifibrotic drugs could be prescribed in their centers. The majority of respondents with IPF (82%) were treated with either nintedanib or pirfenidone at the time of the survey.

The time from diagnosis to initiation of treatment varied greatly, and this was reflected throughout Europe **(Figure 4)**. No statistical differences were found between sub-regions (p=0.16). Although antifibrotic treatment was initiated <1 month after diagnosis in 31% of patients, more than a quarter of patients (26%) reported that they

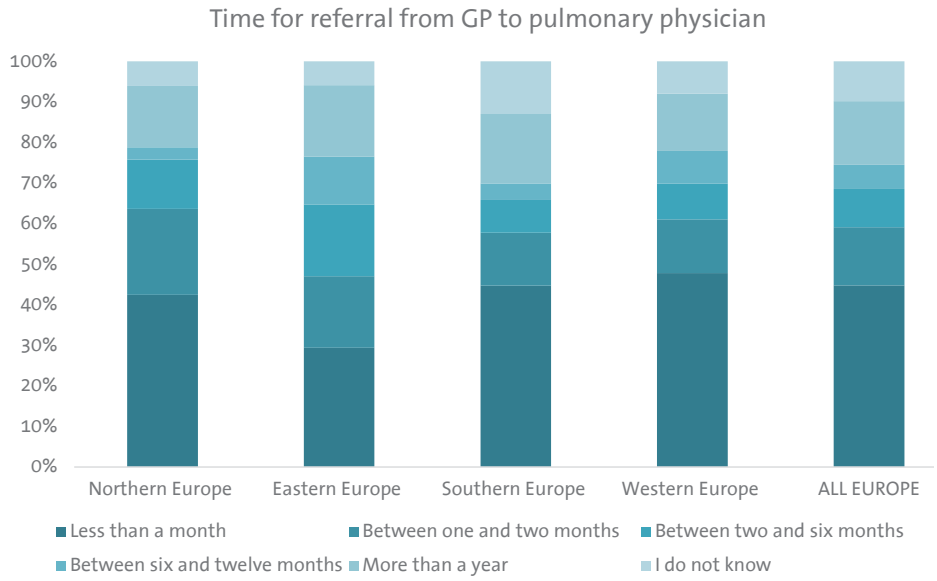

Figure 2. Time for referral from general practitioner (GP) to a pulmonary physician (patient survey)

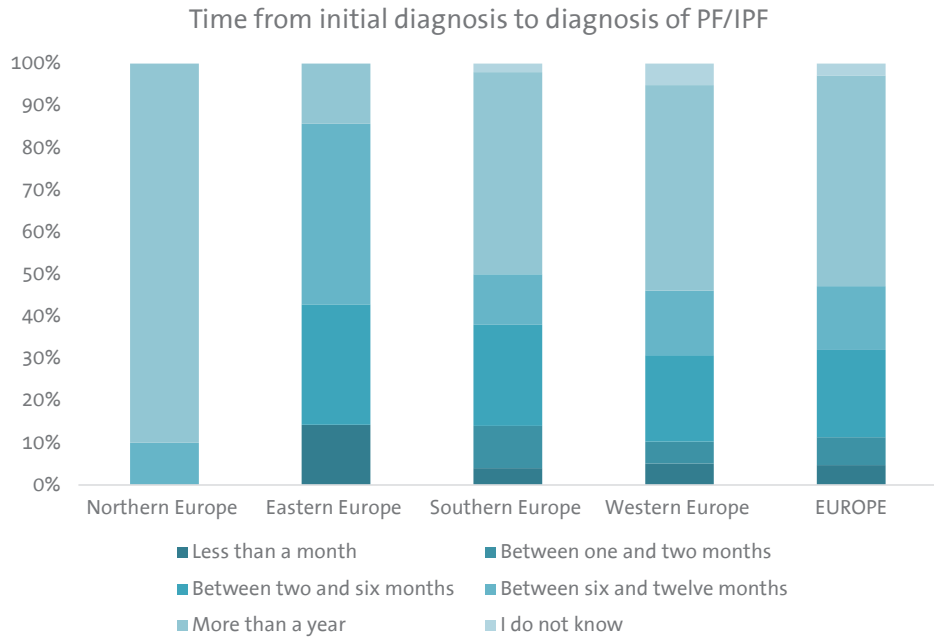

Figure 3. Time from initial diagnosis to diagnosis of PF/IPF (patient survey)

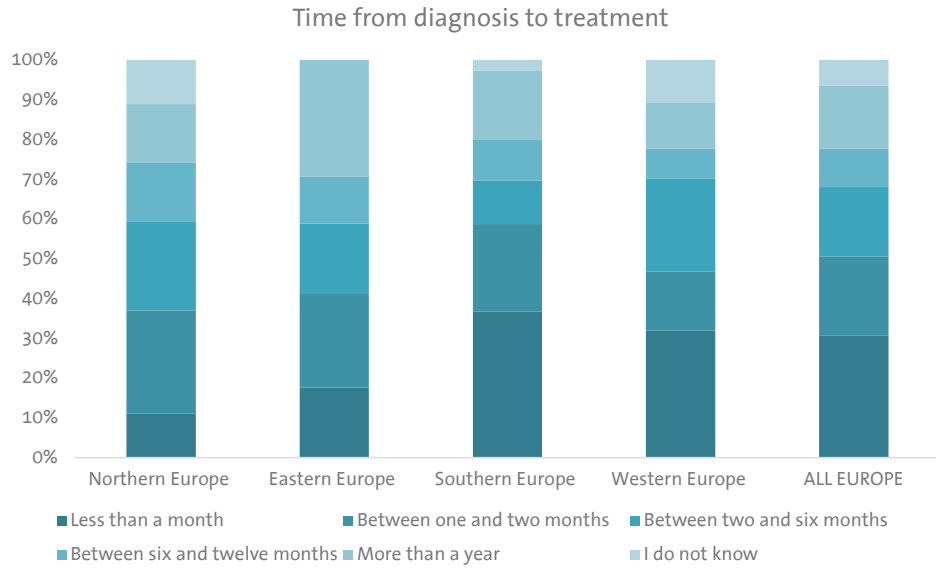

Figure 4. Time between diagnosis to start of antifibrotic treatment (patient survey)

had to wait >6 months before antifibrotic treatment was started. HCPs reported reimbursement restrictions as the main reason for this delay; 78% of respondents confirmed that reimbursement restrictions for prescription of antifibrotic treatment exist in their country. In some countries, antifibrotic drugs are only reimbursed when patients are diagnosed in an ILD specialist center, and in others lung function and/or age criteria exist. Specific lung function criteria were identified as the main barrier for prescription of antifibrotic medication by 70% of HCPs.

Access to non-pharmacological treatment

Almost all HCPs (97%) were able to prescribe oxygen therapy for PF/IPF patients. More than three quarters of patients (78%) reported full coverage for the costs of ambulatory oxygen therapy, and two-thirds of patients (64%) for the costs of oxygen at home.

The vast majority of HCPs (88%) could refer patients for pulmonary rehabilitation. A third of HCPs answered that pulmonary rehabilitation was not fully reimbursed in their country. Fewer than half of patients (42%) stated that they had access to outpatient pulmonary rehabilitation; 11% of patients also had access to inpatient pulmonary rehabilitation. Just over half of HCPs (58%) reported that their patients had access to psychological support at their center, with full reimbursement for 70% of patients. Patients were not specifically questioned about access to psychological support; however, 10% of patients spontaneously reported the need for (better) psychological support throughout their disease course.

The most reported eligibility criteria for lung transplantation concerned age and general health condition. Most HCPs (96%) reported that all eligible patients were referred for lung transplant. In one of the surveyed countries, lung transplantation was not possible at the moment of the survey.

Access to palliative care

Of the surveyed patients, 29% confirmed access to palliative care and 36% answered that they were involved in palliative care decisions. The majority of HCPs (88%) stated that they discuss possibilities for end-of-life care with patients, and almost all HCPs (93%) could prescribe (palliative) medication for symptom relief.

HCPs were asked to explain at which point in the disease course they initiate palliative care for their patients. Around one third answered that palliative care was started at an early stage of the disease if desired by patients. Most HCPs reported that palliative care is initiated in more advanced stages of PF/IPF. One fifth stated that palliative care was only initiated at the end-of-life.

Communication and education

The majority of patients (60%) had a positive experience while discussing their diagnosis with the pulmonary physician. However, a fifth of patients answered that they did not receive any information about their disease at the time of diagnosis. Three out of four patients (73%) and 60% of HCPs felt that there was enough time to discuss diagnosis and treatment options. Only 39% of HCPs reported that they received training on how to effectively communicate information on diagnosis and treatment of PF/IPF with their patients. Three quarters of patients received a treatment plan following their diagnosis, which was clearly explained in 73% of cases. Less than a third of patients (31%) were involved in development of their treatment plan; this involvement was mostly related to the selection and dosage of antifibrotic medication, initiation of non-pharmacological management and participation in clinical trials.

Patients were asked to give recommendations on how healthcare staff could work more effectively with them and their caregivers. Many patients answered that they would like to have more time allocated for their questions and concerns, and receive more information about PF/IPF including practical issues such as reimbursement. Furthermore, patients mentioned the need for timely referral to a specialist center and more awareness of PF/IPF amongst general practitioners, nurses and physicians in community hospitals. Around two-thirds of participating centers (65%) offered educational activities specifically for PF/IPF patients, such as nurse led education sessions, information meetings, eHealth programs and patient support groups. Among the surveyed patients, 39% attended educational sessions in their treating center.

Involvement in research

The majority of HCPs (95%) reported that their center participated in clinical trials and that they inform their PF/IPF patients on ongoing clinical trials. Half of patients (53%) were aware of ongoing clinical trials, 31% had been asked to participate and 25% had actually participated in a clinical trial. Patient registries for IPF and PF existed in 75% and 48% of centers respectively. A quarter of patients (27%) declared that they contributed to the collection of registry data.

General recommendations

In general, 61% of patients described that their experience with the healthcare system as either good or excellent. Both patients and HCPs were asked about suggestions to improve the patient experiences at different stages of the disease. Based on the answers on this question five recommendations by the expert panel were proposed **(Figure 5)**.

DISCUSSION

This is the first study investigating unmet needs of patients with pulmonary fibrosis in a Europe-wide survey. Despite recent advances in PF/IPF care and research, the unmet needs and gaps in care revealed in this study are in line with previous research (**Table 1**).

Referral pathways and access to specialist care

One of the major unmet needs in PF/IPF care is a timely and accurate diagnosis (13, 15, 19, 24, 25). In the current study, a significant number of patients received another diagnosis prior to being diagnosed with of PF/IPF; time from initial diagnosis to diagnosis of PF/IPF was often >1 year. This is in agreement with previous studies, which showed that many patients receive at least one misdiagnosis, consult more than three physicians before receiving a final diagnosis, and have a delay in diagnosis of >1 year (15, 25, 26, 34). Although the current study shows less delay than some previous reports, one out of five patients in this study still had to wait >1 year for referral to an ILD specialist center. It is of utmost importance to reduce delays in diagnosis and referral, since previous research indicated that a lengthy diagnostic trajectory can have an adverse effect on quality of life, and that delayed access to tertiary referral centers is associated with a higher risk of death in IPF (13, 25, 35). In fact, access to ILD specialist centers may increase the perceived quality of care (15, 26). Access to MDTs appears to have increased in recent years. In contrast to the European IPF patient charter in 2016 (11), almost all HCPs in the current study reported access to an MDT, while the composition of the MDT still widely varies.

Figure 5. General recommendations to improve the IPF/PF patient journey

One of the reasons for delayed diagnosis is the lack of knowledge regarding PF/IPF among the general public, GPs and physicians in community hospitals (5, 11, 15, 26). Improving knowledge about IPF, through education and awareness campaigns, could facilitate earlier diagnosis and referral (11, 13, 34). A prior study suggested to develop symptom-based algorithms for GPs, to help identify which patients should be referred for further analysis (19).

Pharmacological treatment

Although antifibrotic medication can be prescribed in all participating countries in this study, timely access to treatment has been highlighted as an issue by both patients and healthcare professionals. A recent study found that up to 40% of patients with a confirmed IPF diagnosis do not receive treatment with antifibrotic medication (36). Barriers

to pharmacological treatment include delayed access to specialist care and reimbursement restrictions (36). Moreover, a watch-and-wait approach is sometimes preferred in patients with mild or relatively stable disease, despite the fact that the importance of early treatment initiation has been emphasized in recent years (5, 36-39). Our results show that reimbursement restrictions continue to be an important cause of delayed access to antifibrotic treatment. Treatment delays vary due to different prescription criteria. To ensure equal access to antifibrotic medication across Europe, fewer reimbursement restrictions and uniform criteria acknowledging the patient needs reported in this statement are imperative.

Non-pharmacological treatment

Non-pharmacological treatment options, such as pulmonary rehabilitation, oxygen therapy, psychological support, and lung transplantation are a vital part of holistic care for patients with PF/IPF (2, 40, 41). Previous studies demonstrated that non-pharmacological treatment options are not equally available for patients in different European countries (11, 19). In the current survey, the vast majority of HCPs indicated that they could refer patients for lung transplantation and pulmonary rehabilitation, as well as being able to prescribe oxygen therapy. In contrast, fewer than half of the patients reported that they had access to pulmonary rehabilitation. This discrepancy could be due to the fact that pulmonary rehabilitation is often not fully reimbursed, that many patients are unaware that pulmonary rehabilitation programs exist for PF/IPF, and that patients often have to travel long distances for pulmonary rehabilitation (11). The need for better emotional and psychological support for patients and caregivers has been frequently reported and is underlined by the findings from our study (11, 13, 14, 17-19, 21, 23, 28, 33). Nevertheless, reimbursement and access to psychological support for PF/IPF patients remains restricted. If referral to a psychologist is not possible, other options for emotional support should be explored. Previous work shows that many patients also benefit from psychological and emotional support through peer support groups, pulmonary rehabilitation, and ILD specialist nurses (11, 13, 14, 23, 30, 42, 43). Strikingly, only half of the surveyed patients in this study had access to ILD specialist nurses, demonstrating that more specialist nurses should be trained.

Access to palliative care

As of yet, there are no (international) guidelines on palliative care in PF/IPF. This leads to underuse of and varying access to palliative care across Europe, which is also influenced by differences in local resources, cultural and religious beliefs, and misconceptions about the meaning of palliative care (2, 11). It is important to acknowledge that palliative care comprises more than just end-of-life care alone, and aims to improve quality of life during the whole disease course (2, 44, 45). Still, our results indicate that many HCPs

in Europe start palliative care in more severe stages of PF/IPF. The majority of HCPs in this study stated that they discuss end-of-life care with all patients. However, the optimal timing of end-of-life discussions and referral to palliative care services remains difficult in PF/IPF (16, 19, 29) and depends on various factors including culture, religion etc. Prior reports suggest that early palliative care can potentially reduce symptom burden for patients with IPF, but needs to be tailored to the preferences of individual patients (2, 28). Hence, palliative care should be an integral part of comprehensive care for patients with PF/IPF (2).

Communication and education

Education plays an important role in the management of PF/IPF. To enable shared-decision making and enhance communication, patients must be well informed about their disease and its prospects (40, 46). While our results show that three quarters of patients receive a treatment plan after their diagnosis, only a third of patients are actually involved in developing this plan. Possible reasons are the lack of time to discuss treatment plans with patients and the fact that patients need to be better educated to become more involved (46). Adequate information about PF/IPF, more education, and continuous counselling were among the frequently reported suggestions for improvement of the care pathway in the patient survey. The need for more information is in agreement with findings from previous surveys and interviews (11, 15-18, 23, 24, 27-29). Whereas two-thirds of centers in the current study offer education for patients, only a minority of patients attended any educational activity. This suggests that greater awareness of the educational activities amongst patients may be required, or that some patients might prefer to receive written information and/or use online resources (24, 31, 46). To improve experiences for patients and caregivers, educational material about PF/IPF needs to be easily accessible, understandable, updated frequently and adapted to individual patient's needs (14, 23, 24, 46).

Involvement in research

Results of this study highlight that patients should be better informed about clinical trials and patient registries. Only half of patients were aware of ongoing clinical trials and only a quarter actually participated in a trial. Previous research suggested that many patients wish to be informed about possibilities to participate in clinical trials and that patients treated in specialist centers were more likely to be participating in a clinical trial (13, 15, 27, 37). Moreover, one study reported that patients who participated in a clinical trial were more hopeful regarding treatment than other patients (13). Efforts should therefore be made to inform all PF/IPF patients about clinical trials, and to refer patients to specialist centers for participation in trials. Many countries have local or national registries for PF/IPF; however, only a quarter of patients indicated that they contribute data

to a registry. Improved collaboration with patients and between countries is needed to collect data and establish a multinational registry. Such a registry will not only enhance understanding of disease behavior, but may also provide insights to improve care and outcomes for patients with PF/IPF(47).

Limitations

This study has several limitations**.** First, the results are only representative of the situation in 14 EU-IPPF member countries; newer EU Member States, in particular, have been under-represented. Moreover, the HCP survey was distributed through the ERN-LUNG network. This resulted in a high number of responses from physicians in ILD specialist centers, representing an important bias. Similarly, the patients who participated in the survey may have better access to information and specialist care, because they were recruited *via* support groups. There may also have been a bias towards less impaired patients amongst the respondents, which makes it difficult to compare answers of HCPs and patients. Further limitations of this online survey distributed *via* patient member organizations were a self-reported diagnosis and an unknown response rate.

CONCLUSIONS

This survey and literature search offers important insights into the current unmet needs of PF/IPF patients in Europe and should be considered for healthcare decisions. Recommendations set out in this statement could provide a useful tool to healthcare providers and policy makers to improve the patient journey and overall care of these rare diseases. Better international collaboration between clinicians, researchers, patients, caregivers, industry partners, and governments should be established to solve unmet needs, improve outcomes, and develop evidence-based multidisciplinary care for PF/IPF patients.

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SUPPLEMENT

Supplementary file S1

Your experience of living with Idiopathic Pulmonary Fibrosis (IPF) or another form of Pulmonary Fibrosis (PF)

Thank you for agreeing to take part in this survey about living with IPF or PF. You can fill in the questionnaire yourself of your carer can do it for you. It will take about half an hour. The information you share will give EU-IPFF, the patients' European federation, a better understanding of the needs of IPF and PF patients and may help to improve services in the future. Your name will not be requested to complete this questionnaire.

English plain review
Translated in DE/FR/EL/ES/BG/IT/NL/PT/PL
Time to complete: 25 minutes
Online distribution
Consent form requested before questionnaire is completed

General information

1) I am a patient / carer. (If you are a carer or family member, please answer on behalf of the person you care for).
2) I have IPF or another type of PF
3) I am male / female
4) My age:
5) Country I live in

Information about your PF/IPF

6) Is there a history of IPF or PF in your family?
7) In which year were you diagnosed with IPF?
8) Some countries have a national registry which collects health information from patients and uses it to improve knowledge and treatment of the disease.
9) Do you know if there is an IPF (not PF) registry in your country? Yes / No / I don't know
10) Do you know if there is a registry for PF (not IPF) in your country? Yes / No / I don't know
11) Do you contribute to the collection of registry data? Yes / No

Your experience of interacting with doctors

12) Did your doctor give you information on your disease when you were diagnosed?

13) If yes, what type of information did you receive?
14) Did you understand the information you were given?
15) Did you have enough time to discuss your diagnosis with your doctor? Yes/ No
16) How would you describe your experience of discussing your diagnosis with your doctor? (scale 1 to 5: 1= strong positive; 2=positive; 3=neutral; 4=negative; 5=strong negative)
17) Besides your family doctor, did you have access to any other healthcare professionals to discuss your diagnosis? Yes / no
18) If yes, please say which of the following you spoke with :
    - respiratory (lung) doctor (also known as a pulmonologist)
    - radiologist
    - specialist respiratory nurse
    - physiotherapist
    - rheumatologist
    - psychologist
    - thoracic (chest) surgeon
    - other (please specify)
19) Did you get training or educational activities from your treating centre? Yes / No
20) How could health care staff work more effectively with you and your carers? Please give us your suggestions and recommendations

Genetic screening

21) Did you have a genetic test? This is a test to examine your genes to find out how likely you are to get IPF or PF. Yes / No
22) If yes, did you get enough information about this test?

Your referral

23) How much time passed before your family doctor referred you to a respiratory doctor?
    - Less than a month
    - Between one and two months
    - Between two and six months
    - Between six and twelve months
    - More than a year
24) How much time passed between the first consultation with your family doctor and your referral to a specialist lung centre?
    - Less than a month
    - Between one and two months
    - Between two and six months

- Between six and twelve months
- More than a year

25) Did you get a wrong diagnosis before you were diagnosed with IPF or PF? Yes / No
26) If yes, how much time passed between your first (wrong) diagnosis and your diagnosis with IPF or PF?
    - Less than a month
    - Between one and two months
    - Between two and six months
    - Between six and twelve months
    - More than a year
27) In your country, how it easy is it to get a referral to a specialist lung centre? Please choose from the following scale where 1=very easy; 2= easy; 3=neither easy nor difficult; 4=difficult; 5=very difficult.
28) How far is your centre from your home?
    - Less than 10 km (about 6 miles)
    - Between 10 km and 30 km (between about 6 miles and 18 miles)
    - Between 30 km and 50 km (between about 18 miles and 31 miles)
    - Between 50 km 100 km (between about 31 miles and 62 miles)
    - More than 100 km (more than 62 miles)
29) Do you have access to a multidisciplinary team? Yes / No
30) Do you have access to a specialist lung nurse? Yes / No
31) Which healthcare professional has been monitoring your IPF or PF since your diagnosis?
    - Respiratory doctor (pulmonologist) from the specialist lung centre
    - Family doctor
    - Specialist nurse
    - Physiotherapist
    - Palliative care doctor or nurse
    - Other, please specify:
32) On average, how often do you meet your multidisciplinary team to discuss your condition?
    - Once a month
    - Every 3 months
    - Every 6 months
    - Every 12 months
    - Other, please specify:
33) Following your diagnosis, did you get a treatment plan for your disease? Yes / No
34) Was your treatment plan explained clearly to you? Yes / No If no, please tell us more.

35) Were you involved at any stage in the development of your treatment plan? Yes / No

If yes, how were you involved (please describe)?

36) Were you given different options for your treatment? Yes / No

If yes, please say which options.

37) Do you feel you got enough support from your doctors and healthcare team? Yes / No

If no, please tell us what support you would have liked to get.

Access to medicines (only for IPF patients)

38) Are you being treated with medicines for your IPF? Yes / No

If no, were you treated with any medicines in the past? Yes / No

39) In what year did you start taking medicines for your IPF?

40) Did you have to change your medicines at any point? Yes / No

If yes, please say why you had to change.

41) Overall, how long did you have to wait from diagnosis to receiving treatment?
    - Less than a month
    - Between one and two months
    - Between two and six months
    - Between six and twelve months
    - More than a year

42) In case you started late taking medicines, what are the main reasons?
    - Late diagnosis
    - Not referred in time to a specialist lung centre
    - Treatment not available for sale in your country
    - Treatment is not paid for
    - Treatment is only partially paid for
    - Treatment is not reimbursed for your type of IPF
    - Treatment is not prescribed by your centre
    - Other, please explain

43) Are you fully (100%) covered for the costs of medicines by health insurance or the health service in your country? Yes / No

44) If no, how much do you have to pay for medicines out of your own pocket each year?
    - Less than €200
    - Between €200 and €500
    - Between €500 and €1,000
    - Between €1,000 and €2,000
    - Between €2,000 and €5,000

- More than €5,000

45) In your opinion, what would help increase the use of medicines for treating IPF? Please choose all that apply.
    - Making the prescription of medicines easier for doctors
    - Encouraging family doctors to refer more patients to specialist lung centres
    - Making the procedures for reimbursement easier
    - Cheaper medicines
    - Other, please explain

Access to other treatments

46) Has your doctor prescribed portable oxygen therapy for you? Yes / No
47) Is the cost of portable oxygen paid for by your health insurance or the health service in your country?
    - Yes, fully (100%)
    - Yes, in part
    - No
48) What do you have to do to be fully or partially reimbursed? Please describe.
49) Has your doctor prescribed oxygen therapy for you to use at home? Yes / No
50) Is the cost of oxygen at home paid for by your health insurance or the health service in your country?
    - Yes, fully (100%)
    - Yes, in part
    - No
51) What do you have to do to be fully or partially reimbursed for home oxygen therapy? Please describe.
52) What are the main difficulties you face in accessing portable and home oxygen therapy? Please choose all that apply.
    - High cost
    - No availability of liquid oxygen portables
    - No availability of portable oxygen concentrators
    - Oxygen therapy was not prescribed
    - Other, please specify
53) Do you have access to a pulmonary (lung) rehabilitation programme?
    - Yes, out-patient
    - Yes, in-patient
    - No, none at all
54) Is the cost of the pulmonary rehabilitation programme paid for by your health insurance or the health service in your country?
    - Yes, fully (100%)

- Yes, in part
- No

55) What do you have to do to be fully or partially reimbursed for pulmonary rehabilitation? Please describe.
56) Do you have access to palliative care? Yes / No
57) Is palliative care paid for by your health insurance or the health service in your country?
    - Yes, fully (100%)
    - Yes, in part
    - No
58) What do you have to do to be fully or partially reimbursed for palliative care? Please describe.
59) Are you and your family involved in decisions about palliative care?
60) Who supported you during your treatment (whatever type of treatment you had)? Please choose all that apply.
    - respiratory doctor (pulmonologist)
    - radiologist
    - pathologist
    - specialist nurse
    - multidisciplinary team coordinator
    - physiotherapist
    - rheumatologist
    - immunologist
    - thoracic surgeon
    - interventional pulmonologist (who uses minimally invasive endoscopic techniques)
    - psychologist
    - patient organisation or peer group
    - other, please indicate
61) Do you have access to a patient organisation to support you during your treatment? Yes / No
62) How would you describe your overall experience with the healthcare system in relation to your IPF or PF? Please choose from the following scale where 1= excellent; 2=good; 3=neither good nor bad; 4=bad; 5=very bad.

Research

63) Are you aware of any ongoing clinical trials? Yes / No
64) Were you ever asked to be involved in a clinical trial? Yes / No
65) Have you ever taken part in a clinical trial? Yes / No

General suggestions

66) Please tell us how you feel the experience of patients and carers could be improved at different stages of the disease.

Thank you for completing this survey

SUPPLEMENTARY FILE S2

Questionnaire for healthcare professionals on the patient's journey through Idiopathic Pulmonary Fibrosis (IPF) and other forms of Pulmonary Fibrosis (PF)

Time to complete: 30 minutes

English only

Online distribution

1) General information
2) Indicators
3) I am a doctor / nurse
4) Your organisation's name and location
5) Your country of residence
6) Is your organisation a recognised Centre of Expertise specialising in interstitial lung diseases (ILDs)? Yes / No
7) Is your organisation a member of ERN-LUNG? Yes / No

Epidemiological data

8) How many patients with Idiopathic Pulmonary Fibrosis (IPF) are managed in your centre each year?
9) How many patients with Pulmonary Fibrosis (PF), but excluding IPF, are managed in your centre each year?
10) How many new patients were diagnosed with IPF within the past 12 months at your centre?
11) How many new patients have been diagnosed with other forms of PF within the past 12 months at your centre?
12) Is there a national registry for IPF in your country? Yes / No
13) Is there a registry for IPF in your centre? Yes / No
14) Is there a national registry for other forms of PF in your country? Yes / No
15) Is there a registry for PF in your centre? Yes / No
16) Do you contribute to the collection of registry data? Yes / No

Interactions between patients and doctors

17) Have you received training to effectively communicate information on diagnosis and treatment to IPF and PF patients and carers? Yes / No
18) If yes, please specify the training.
19) Do you feel equipped to give clear and easy-to-understand information to IPF and PF patients and carers? (Please choose from the following scale where 1=strongly agree; 2=agree; 3=neither agree nor disagree; 4=disagree; 5=strongly disagree)

20) Do you feel you have enough time to discuss their diagnosis with patients? (Please choose from the following scale where 1=strongly agree; 2=agree; 3=neither agree nor disagree; 4=disagree; 5=strongly disagree)
21) Do you feel you have enough time to discuss their treatment with patients? (Please choose from the following scale where 1=strongly agree; 2=agree; 3=neither agree nor disagree; 4=disagree; 5=strongly disagree)
22) Does your centre offer training or educational activities to IPF and PF patients? Yes / No. If yes, please specify.
23) How do you think interactions with patients could be improved?

Screening

24) Does your centre have access to genetic testing to diagnose IPF and PF? Yes / No
25) If yes, is the test provided to IPF and PF patients in your centre or in another centre?
    - In my centre
    - In another centre
26) Does your centre have access to genetic counselling? Yes / No. Please specify for both answers. If yes, is it provided to IPF and PF patients?

Referral

27) In your country, how easy is it to identify a centre of expertise specialising in ILDs for IPF and PF patients? (Please choose from the following scale where 1=very easy; 2=easy; 3=neither easy nor difficult; 4=difficult; 5=very difficult).
28) Do IPF and PF patients have access to a multidisciplinary? Yes / No
29) Do IPF and PF patients have access to a specialist ILD nurse? Yes / No
30) Which of the following professionals is part of the multidisciplinary team or supportive interdisciplinary team? (Please tick all that apply)
    - consultant respiratory physician or pulmonologist
    - consultant thoracic radiologist
    - consultant pathologist
    - interstitial lung disease specialist nurse
    - multidisciplinary team coordinator
    - physiotherapist
    - rheumatologist
    - immunologist
    - thoracic surgeon
    - pharmacist
    - other (please describe)
31) On average, how often do you or the multidisciplinary team review an IPF or PF patient's case?

- Once a week
- Twice a month
- Once a month
- Every 3 months
- Every 6 months
- Every 12 months
- Other (please specify)

32) On average, how often do you or the multidisciplinary team invite the IPF or PF patient to the clinic to discuss their case?
    - Once a month
    - Every 3 months
    - Every 6 months
    - Every 12 months
    - Other (please specify)
33) Are IPF and PF patients involved in developing their treatment plan? Yes / No If yes, how?
34) Do you provide different treatment and support options to your IPF and PF patients? Yes / No
35) How are IPF and PF patients referred to you? Please indicate the top-two options that apply:
    - General practitioner
    - Pulmonologist
    - Other pulmonologist
    - Self-referral
    - Other (please specify)

Access to pharmacological treatment (specific to IPF)

36) The following treatments for IPF are approved by the European Medicines Agency (EMA). Please indicate if they are prescribed in your country
    - Active substance Available Not available
    - Pirfenidone
    - Nintedanib
37) Please indicate if the following EMA-approved treatments for IPF are available for prescription in your centre
    - Active substance Available Not available
    - Pirfenidone
    - Nintedanib
38) Please indicate if the following EMA-approved treatments for IPF are fully (100%) reimbursed or not in your country

- Pirfenidone Yes / No
- Nintedanib Yes / No

39) If no, please elaborate.

40) Are there any inclusion or exclusion criteria when administering the following treatments:
    - Pirfenidone Yes / No
    - Nintedanib Yes / No

41) If yes, please specify.

42) Are there any barriers to prescribing EMA-approved IPF treatments in your centre? Please select all that apply
    - Severity of disease (mild, moderate, severe)
    - Disease progress
    - Patient clinical status
    - Age
    - Other, please explain

43) What is the average time from suspected diagnosis to starting treatment with Nintedanib or Pirfenidone?
    - Less than a month
    - Between 1 month and 6 months
    - Between 6 months and 1 year
    - More than a year

44) If IPF patients in your centre experience delays in accessing treatment, what are the main reasons for the delay? Please select all that apply
    - Wrong recognition of symptoms and signs
    - Time from suspected diagnosis to confirmed diagnosis
    - Delays in referral to a centre specialising in ILDs
    - Treatment not available for sale in your country
    - Treatment not reimbursed
    - Treatment only partially reimbursed
    - Treatment not reimbursed for all types of IPF or PF
    - Treatment not prescribed by your centre
    - Other, please explain

45) Do you have patients who might benefit from access to pharmacological treatment but who are not eligible?
    - No
    - Less than 10%
    - Less than 30%
    - More than 30%

46) In your opinion, what would improve access to treatment for IPF patients?

- No limitations for prescription
- Reimbursement
- Timely referral to specialist ILD centre
- Better pricing policies
- Other, please explain

Access to non-pharmacological treatment

47) Does your centre prescribe ambulatory oxygen for IPF and PF patients? Yes / No
48) Is ambulatory oxygen reimbursed? Yes / No / Partially
49) Can your centre prescribe oxygen for IPF and PF patients to use at home? Yes / No
50) Is oxygen for use at home reimbursed? Yes / No / Partially
51) Can your centre prescribe pulmonary rehabilitation for IPF and PF patients? Yes / No
52) Is pulmonary rehabilitation reimbursed? Yes / No / Partially
53) Can your centre prescribe medication for palliative care or symptom relief for IPF and PF patients? Yes / No
54) When do you start palliative care or symptom relief for IPF and PF patients? Please specify according to the stage of progression of the disease.
55) Is end-of-life care discussed with IPF and PF patients and their families? Yes / No
56) In your country, what are the eligibility criteria for a lung transplant? Please select all the criteria that apply.
    - Age, please specify
    - General health condition
    - Likelihood of developing risks associated with transplant (for example, infections, rejection of new lung)
    - Severity of IPF or PF
    - Progression of IPF or PF
    - Availability of organs
    - Surgical procedure not available
    - Other, please specify
57) In patients eligible for lung transplantation, do you refer these patients for a lung transplant? Yes / No
58) Do patients in your centre have access to psychological support such as counselling? Yes / No.
59) If yes, please specify if psychological support is reimbursed: Yes / No / Partially
60) Do patients in your centre have access to educational materials on IPF and PF?

Research

61) Are you aware of current IPF and PF clinical trials? Yes / No If yes, please state which trials.
62) Do you tell IPF and PF patients that they could take part in clinical trials? Yes / No
63) If yes, please specify if:
    - your centre participates in trials
    - your centre refers patients for trials to another centre
    - you refer to the patient association

General recommendations

64) Please share your suggestions for improving the patient's experience of the IPF or PF journey.

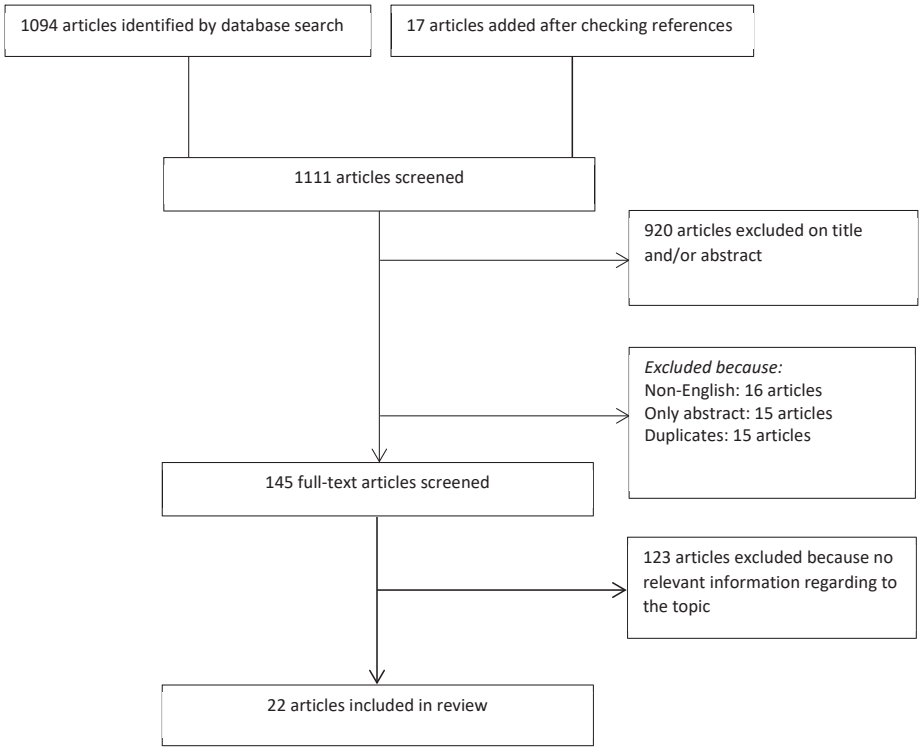
Thank you for completing this survey.

SUPPLEMENTARY FILE S3

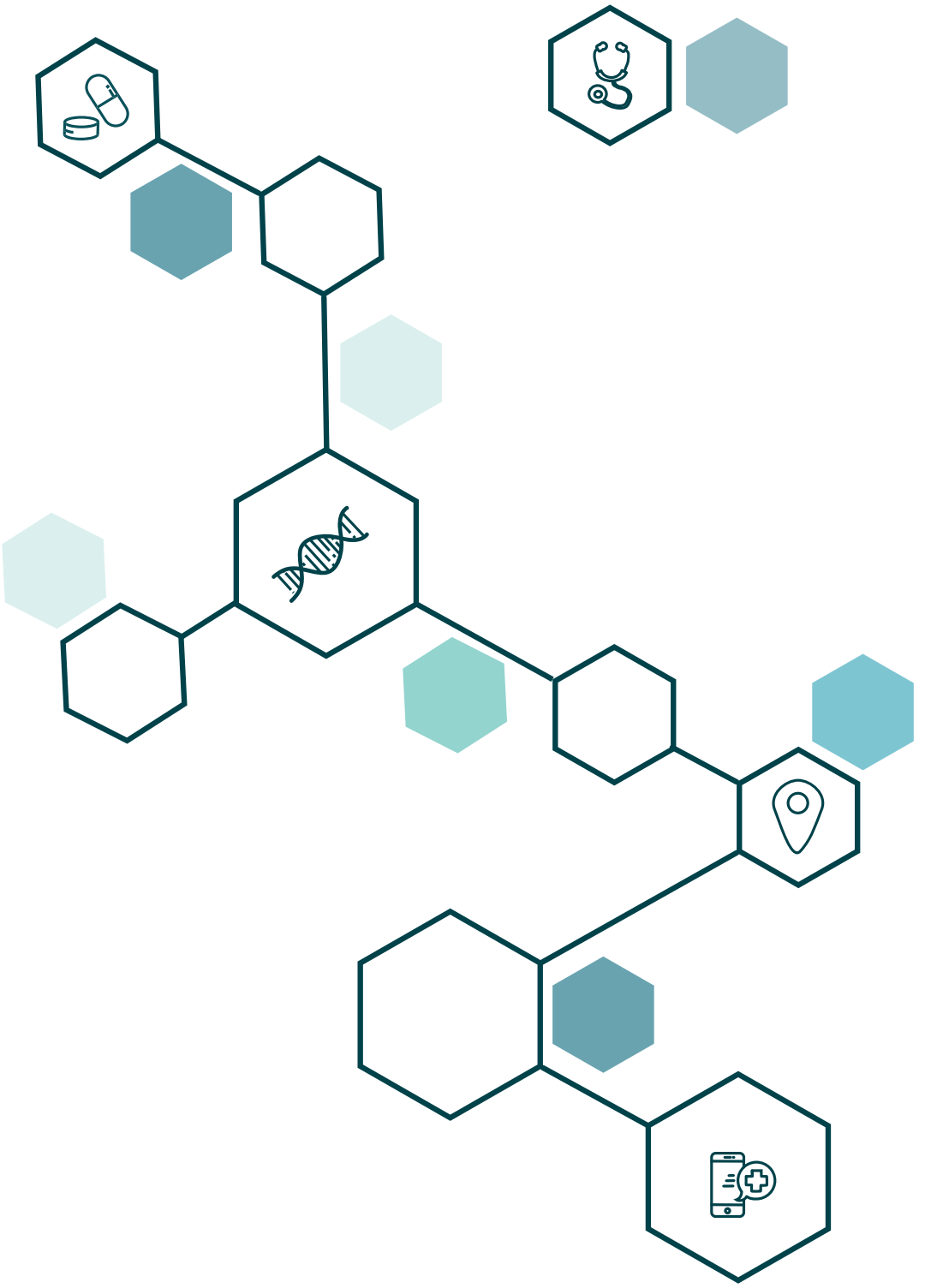
Literature search

A systematic literature search was performed using PubMed and Embase for studies that evaluated the care pathway for pulmonary fibrosis patients, published between January 2010 and March 2018. For this search the following (MeSH) terms were used: ("idiopathic pulmonary fibrosis" OR "pulmonary fibrosis" OR "interstitial lung disease") AND ("care pathway" OR care OR barrier OR need OR unmet need). Additionally, references of included articles were checked to identify other potentially relevant articles.

This search retrieved 1094 articles and 17 articles were added after checking references. These 1111 articles were screened on title and abstract by three authors (DB, CM and LP). 145 potentially relevant articles have been fully assessed by the reviewers, and in case of disagreement the article has been discussed until consensus was reached. Non-English articles and abstracts were excluded. After exclusion of studies not related to the topic, 22 articles were included (see flowchart in figure 1).



Supplementary file S3: Literature search flow diagram



Chapter 4

Integrating patient perspectives into personalized medicine in idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal disease which has a major impact on patients' quality of life. Except for lung transplantation, there is no curative treatment option. Fortunately, two disease-modifying drugs that slow down disease decline were recently approved. Though this is a major step forward, these drugs do not halt or reverse the disease, nor convincingly improve health-related quality of life. In daily practice, disease behavior and response to therapy greatly vary among patients. It is assumed that this is related to the multiple biological pathways and complex interactions between genetic, molecular and environmental factors that are involved in the pathogenesis of IPF. Recently, research in IPF has therefore started to focus on developing targeted therapy through identifying genetic risk factors and biomarkers. In this rapidly evolving field of personalized medicine, patient factors such as lifestyle, comorbidities, preferences, and experiences with medication should not be overlooked. This review describes recent insights and methods on how to integrate patient perspectives into personalized medicine. Furthermore, it provides an overview of the most used patient-reported outcome measures in IPF, to facilitate choices for both researchers and clinicians when incorporating the patient voice in their research and care. To enhance truly personalized treatment in IPF, biology should be combined with patient perspectives.

INTRODUCTION

"Give different ones [therapeutic drinks] to different patients, for the sweet ones do not benefit everyone, nor do the astringent ones, nor are all patients able to drink the same things" - ***Hippocrates*** (1)

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia (IIP) (2). IPF is characterized by progressive decline of lung function, with a median survival of only 3-5 years (3). Common symptoms as breathlessness, cough and fatigue have a major impact on the quality of life (QOL) of patients (4). IPF occurs more often in men than women and usually affects elderly patients, aged 50 years and above (3). There are two approved anti-fibrotic drugs that slow down disease decline, but these drugs do not halt or reverse the disease, and ultimately IPF remains a fatal disease (5, 6). The heterogeneity in disease behavior and response to therapy in IPF has (further) stimulated research to identify possible distinct underlying genetic, molecular and environmental factors associated with IPF (7, 8).

The potential to enhance personalized treatment has prompted excitement also in the IPF field (7). Until now, the focus of personalized medicine has been on physiology and the use of this biological information to predict response to treatment and to develop targeted therapy (9). In this process, patient factors should not be overlooked. For real personalized treatment patient perceptions and preferences should also be taken into account. In this article, we describe recent insights and methods on how to integrate patient perspectives into personalized medicine.

Impact of disease

IPF is a heterogeneous disease, with a highly variable disease course (10, 11). Additionally, different phenotypes of IPF exist. Most patients have a slow disease progression, while some patients display relative stable periods followed by acute exacerbations and a small group of patients experiences a rapid decline in lung function (12). Uncertainty about the disease course and prognosis can cause emotional distress and anxiety, and, as a result, IPF has a major impact on most patients' health-related quality of life (HRQOL). HRQOL can be defined as a patient's perceived well-being affected by disease and treatment of the disease (13). IPF affects patients in almost every domain of life; hence, the burden of the disease is high, not just for patients but also for their partners and families. Patients often struggle with loss of independence because of functional limitations and deteriorating symptoms. Not only can breathlessness, cough and fatigue diminish quality of life, but also other symptoms such as sleep disorders, loss of appetite, and psychological problems can (14-18).

Most clinical trials in IPF that have been performed so far, have shown no convincing improvement of patient HRQOL (5, 6, 19). To date, the main focus in research has been to stabilize or improve physiological outcomes rather than HRQOL. Physiological parameters, such as lung function, do not correlate well with HRQOL measurements (20, 21). To our knowledge for parameters as imaging and biomarkers, relationships with HRQOL have not yet been established. Thus, decline in lung function does not adequately reflect the perceived impact of the disease on patients' lives.

Every person has a different lifestyle, personal circumstances, and coping strategies. These factors can play an important role in how a disease manifests itself; hence, the same disease affects each person in a different way (16, 22, 23). Medication may show promising results at group level in randomized controlled trials, but still in some individual patients, treatment may fail (22). For example, the side effects of medication may outweigh the positive effects of medication in daily practice, or the burden of treatment might be too high for patients. To improve and personalize treatment of IPF, we should also include patient perspectives and quality of life.

Personomics

Personalized, stratified or precision medicine is a broad term which can be referred to as "delivering the right treatment to the right patient at the right time" (24). Personalized medicine has gained increasing attention during the past decade (22, 25). However, the concept is not new; Hippocrates already mentioned the importance of a personalized approach to diagnosis and treatment in the 5th century BC, stating that "individuality of human beings affects predisposition to disease and response to treatment", and also noting that "not all patients are able to drink the same therapeutic drinks" (1, 26). His concepts already include the notion that experiences with treatment differ among patients. This idea is also acknowledged by Britten and colleagues, who suggest that because individuals are more than their genetic profile, the main concept of stratified medicine is too limited at the moment (22). Personalized treatment comprises not only "biology", but should also focus on patient perspectives, needs, experiences, personality, environment, lifestyle and other personal circumstances (**Figure 1**) (9, 22). Accordingly, the term "personomics" has been introduced to capture a patient's life circumstances that may alter disease behavior and response to treatment (23).

Current view of personalized medicine in IPF

In other fields, especially oncology, personalized medicine has dramatically changed clinical practice during the last few years. Biomarkers have been used to develop targeted therapy and allocate patients to individual treatment plans (27-29).

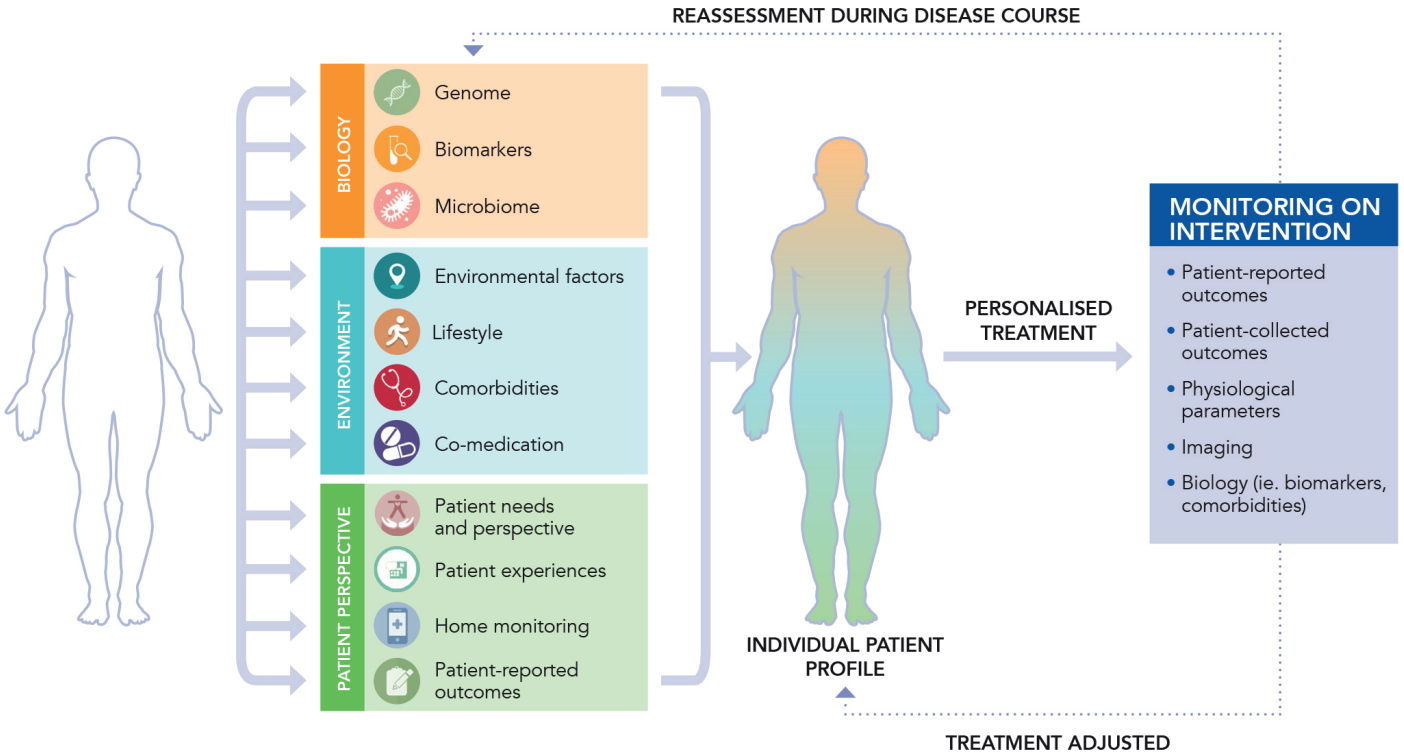

Figure 1. To enhance tailored treatment in IPF, "biology" should be combined with patient factors to generate an individual patient profile. Close monitoring, timely reassessment and treatment adjustment during the disease course are required to optimize personalized care.

Currently, the diagnosis of IPF is based on clinical, radiological and pathological findings (3). The exact etiology of IPF is however incompletely understood. One of the proposed hypotheses is the concept of dysfunctional wound healing: repeated epithelial injury and dysfunctional regeneration possibly in combination with a dysregulated immune system normally facilitating wound healing leads to fibrogenesis and, as a consequence, excessive scarring of the lung tissue (11, 30). Epithelial injury might be caused by risk factors such as cigarette smoking, micro-aspiration of gastric content, and lead to development of IPF in susceptible individuals (11). At present, it is assumed that multiple biological pathways and complex interactions between genetic, molecular and environmental factors are involved in the pathogenesis of IPF. Improved understanding of the pathogenesis of IPF has led to the identification of potential molecular biomarkers (7, 11, 31-33). Genome-wide association studies found genetic mutations that correlate with disease risk and possibly also disease progression (34-37); subsequently, the first examples of drug-gene interactions in IPF were found (38). To date, the value of biomarkers in IPF has not been fully clarified, and, therefore biomarkers or genetic endotyping are not yet used in clinical practice (7, 33).

Novel studies in IPF suggest that the 'respiratory microbiome' is also involved in IPF pathogenesis, disease progression and mortality (39-41). Patients with IPF have a higher bacterial burden and abundance of specific pathogens in the lung microbiome than the normal population. Furthermore, interactions have been found between specific gene expression and an altered lung microbiome in IPF, which is the first evidence for host-environmental interactions in IPF (42, 43). The lung microbiome may serve as a prognostic factor in the future, and clinical trials aimed at altering the microbiome of patients with IPF have already started (44). A detailed description of (molecular) biology and its current role and potential in the IPF field is beyond the scope of this review.

How to integrate personomics into personalized medicine

Patient needs and perspectives in IPF care

The importance of engaging patients in IPF care has gained increasing attention during the last several years (45). Recent qualitative studies have reported a need for better education about IPF, information about specific treatment options and palliative care, and access to specialist centers and specialist nurses. Additionally, more support for caregivers is warranted (16, 17, 46-48). These recommendations underscore the idea that not only pharmacological treatment but also non-pharmacological treatment options such as oxygen therapy, pulmonary rehabilitation, psychological support and palliative care, are an important part of personalized management. With regard to pharmacological treatment, it is important to assess the needs and perspectives of patients before starting treatment, thereby enhancing shared decision-making. For instance, some side

effects of disease-modifying drugs might have a devastating impact on one patient, but be far less bothersome to other patients (22). At the moment, over-use and under-use of medication, compliance problems and waste of medication are not unusual in IPF (22, 49, 50). Non-adherence to medication could therefore be prevented when patients' preferences and lifestyle are taken into account (9). Since patient preferences and needs may change because of disease progression or personal circumstances, an important aspect of disease management is iterative evaluation of the situation of individual patients (16, 46, 51). Only in this way can "holistic" personalized care be given in IPF.

Comorbidities and co-medication

Holistic care also means looking further than the lungs. IPF is associated with a number of pulmonary and extra-pulmonary comorbidities, such as pulmonary hypertension, respiratory infection, cardiovascular disease, emphysema, lung cancer, diabetes mellitus, venous thromboembolism and gastroesophageal reflux (52-56). Comorbidities are more prevalent in patients with IPF than in the normal population and have a negative influence on QOL and survival (54, 56-58). Hence, early identification and treatment of comorbid conditions have the potential to improve QOL, functional outcomes, and survival for patients with IPF (53). Kreuter et al. (54) proposed the "IPF comorbidome", which visually displays prevalence of comorbidities and their strength of association with mortality in patients with IPF. This comorbidome could be used to predict prognosis for individual patients with IPF, and thus enhance personalized treatment.

Moreover, extra attention should be paid to the frail, elderly patients who have multiple comorbidities and functional impairment (55). As a consequence, these patients might have a higher risk of harmful side effects of disease-modifying medication and should be closely monitored during treatment. Besides, polypharmacy may play an important role in this group of patients. It is generally known that polypharmacy decreases medication compliance, increases risk of adverse drug events, and might lead to impaired functional status and cognitive impairment in elderly patients (59). Furthermore, co-medication can also interfere with disease-modifying medication, and subsequently increase side effects or reduce treatment efficacy (60). Accordingly, co-medication could play an important role in the choice of pharmacological treatment in IPF. Expected risk-benefit ratio, comorbidities, and co-medication should be taken into account before pharmacological treatment is started in individual patients.

Measuring quality of life and monitoring treatment response

It remains challenging how to measure patients' disease burden, experiences and response to treatment in IPF. For this purpose, it is important to receive structured patient input throughout the whole disease course, starting already when the diagnosis is

established. At present, digital solutions can facilitate more collaboration with patients in monitoring disease behavior, their experiences, and response to therapy (**Figure 2**).

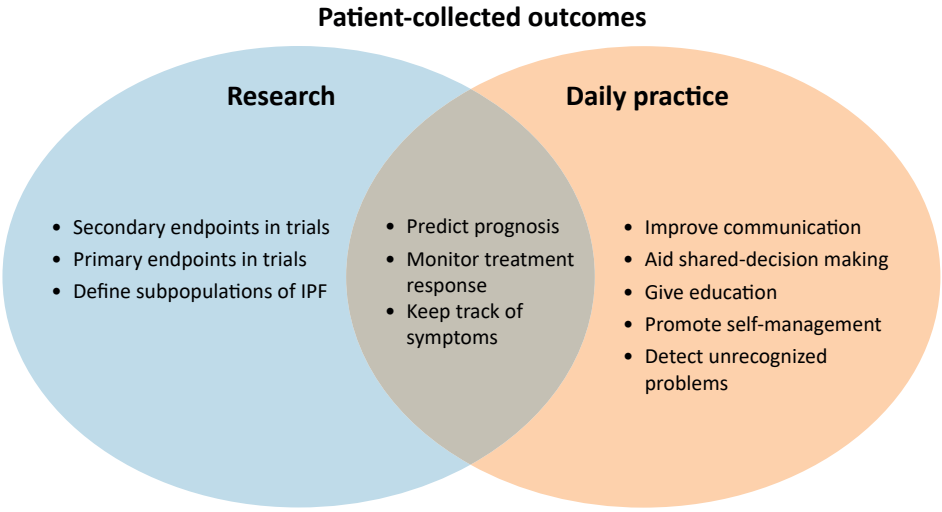

Figure 2. Patient-reported and recorded outcomes can be used to enhance personalized treatment

Patient-reported outcome measures in IPF

A patient-reported outcome (PRO) is defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (61). Patient-reported outcome measures (PROMs) can be used to measure (HR)QOL, assess symptoms and evaluate disease progression. There is a difference between generic and disease-specific PROMs. Disease-specific PROMs are developed to assess symptoms and (HR)QOL in a specific disease, whereas generic PROMs address more general questions and can be used in the whole population (62). One of the most commonly used generic PROMs in IPF trials are the Short-Form 36 (SF-36) and the Euroqol-5D (EQ5D), which is also a widely accepted instrument for economic evaluation in healthcare (63, 64). An overview of the most widely used PROMs in IPF is given in **Table 1**.

Disease-specific PROMs

Although PROMs can play an important role to improve care for IPF, only a few well-validated, disease-specific questionnaires have been developed (19). Until a few years ago, most questionnaires used in clinical trials in IPF were originally intended for other chronic diseases (64-66). The validity of these questionnaires, such as the Saint George

Table 1. Overview of most used patient-reported outcomes in IPF

Patient-reported outcome measure	Description	Validation studies and MCID	Advantages	Disadvantages
Disease-specific				
SGRQ (65)	50-item questionnaire with 3 domains assessing HRQOL in chronic respiratory diseases	Validated in IPF MCID in IPF: 5-8 points (67)	Used in many clinical trials in IPF	Originally developed for COPD and asthma; Lengthy, difficult questionnaire
SGRQ-I (68)	IPF-specific version of original SGRQ; Contains 34 items	Validity comparable to SGRQ	Questions more relevant for IPF than SGRQ	Responsiveness and MCID not known yet; Limited experience
CAT (66)	Composed of 8 symptom items on a 0-5 response scale	Validated in IPF	Simple and quick instrument	Originally developed for COPD; Limited experience in IPF
K-BILD (21)	15-item health status questionnaire in ILD with 3 domains	Validated in IPF MCID in IPF: 4 points (79)	Brief Developed in ILD including IPF patients	Limited experience in clinical trials, though increasingly used
L-IPF (69) (revised version ATAQ-IPF)	Contains 2 modules with different domains	Currently in validation process	Adapted with feedback from patients	Not available yet
IPF-PROM (70)	Concise questionnaire to assess QOL in IPF	Study is ongoing	Developed with patients and caregivers	Not available yet
PESaM (80)	Generic and disease specific module; evaluates patients' expectations, experiences and satisfaction with disease-modifying drugs	Currently in validation process	Developed together with IPF patients.	Not validated yet; Responsiveness unknown
IPF-PREM (81)	Questionnaire to assess experiences with care delivery	Study is ongoing	Measures experiences of patients	Not available yet
Domain-specific				
UCSD (74)	Contains 24 items on a 0-5 response scale assessing dyspnea in the last week	Validated in IPF; MCID in IPF: 8 points	Already used in different IPF trials; Valid to assess change in dyspnea in IPF	Takes considerably more time compared to other dyspnea measures; Not originally developed in IPF

Table 1. Overview of most used patient-reported outcomes in IPF (*continued*)

Patient-reported outcome measure	Description	Validation studies and MCID	Advantages	Disadvantages
mMRC (72)	Consists of one question with five grades for the level of dyspnea	Not validated in IPF	Quick, easy tool for use in daily practice; Relates to disease progression	Responsiveness in IPF unclear; Not originally developed in IPF
BDI-TDI (73)	BDI scores 3 components of dyspnea at baseline; TDI measures changes compared to baseline	Not validated in IPF; MCID in COPD: 1 point (73)	Measures both baseline and change over time	Only interview-administered or computerized version; Not originally developed in IPF
Borg Scale (71)	Level of dyspnea scored on a scale from 0-10	Not validated in IPF; MCID in COPD: 1 point (82)	Useful during 6-min walk test in daily practice	Only measures dyspnea during exertion, does not measure dyspnea over time; Not originally developed in IPF
HADS (77)	Consists of 14 items in the subscales anxiety and depression	Not validated in IPF; MCID in COPD: 1.5 points (77)	Reliable screening tool for anxiety and depression	Should not be used as diagnostic test; Not originally developed in IPF
CQLQ (76)	Consists of 28 cough-specific questions in 6 domains	Validated in IPF; MCID in IPF: 5 points	Comprehensive; Responsive outcome measure	Good validity for total score in IPF, but not for all domains; Limited experience in IPF; Not originally developed in IPF
LCQ (83)	Chronic cough quality of life questionnaire with 19 items in 3 domains	Not validated in IPF; MCID in chronic cough: 1.3 points(84)	High reliability; Ability to detect a response to change	Limited experience in IPF; Not originally developed in IPF

IPF: Idiopathic Pulmonary Fibrosis; MCID: minimal clinically important difference; ILD: interstitial lung disease; HRQOL: Health-related quality of life; SGRQ: Saint George Respiratory Questionnaire; K-BILD; Kings' Brief Interstitial Lung Disease health status questionnaire; L-IPF: Living with Idiopathic Pulmonary Fibrosis; ATAQ-IPF: a Tool to Assess Quality of Life in IPF; IPF-PROM: Idiopathic Pulmonary Fibrosis-Patient-reported outcome measure; PESaM: Patient Experiences and Satisfaction with Medication; IPF-PREM: Idiopathic Pulmonary Fibrosis – Patient-reported experience measure; UCSD: University of California San Diego shortness of breath; mMRC: modified Medical Research Council; BDI-TDI: Baseline and Transition Dyspnea Indexes; HADS: Hospital Anxiety and Depression Scale; CQLQ: Cough Quality of Life Questionnaire; LCQ: Leicester Cough Questionnaire

Respiratory Questionnaire (SGRQ) and COPD Assessment Test (CAT), has been confirmed in patients with IPF (66, 67). For the SGRQ, even an adapted version, the SGRQ-I, has been developed (68). This revised PROM consists of questions from the original SGRQ that were most relevant for patients with IPF. The reliability and validity of the SGRQ-I are comparable to the SGRQ. However, PROMs which are developed in a target population from the start, are thought to be more precise in capturing changes in HRQOL for this group of patients (58). One of the first questionnaires specifically developed in a population of patients with interstitial lung diseases (ILDs), among whom patients with IPF, is the Kings' Brief Interstitial Lung Disease health status questionnaire (K-BILD) (21). This is a brief, valid questionnaire that is increasingly used in IPF and other ILD clinical trials. One of the emerging PROMs in IPF is the 'Living with Idiopathic Pulmonary Fibrosis (L-IPF) questionnaire, which is a revised, electronic version of the ATAQ-IPF (a Tool to Assess Quality of Life in IPF). The L-IPF was adapted from the ATAQ-IPF following feedback from patients, and a validation study is underway at the moment (69). Another questionnaire which is currently being developed with the help of a multidisciplinary group of patients and carers is the IPF-PROM (70).

Domain-specific PROMs

Additionally, domain-specific PROMs, which are questionnaires related to a specific symptom or organ, can be used to capture and objectify different aspects of disease. A few measures to evaluate breathlessness, such as the University of California San Diego Shortness of Breath Questionnaire (UCSD), the modified Medical Research Council (mMRC) scale, the Baseline and Transition Dyspnea Indexes (BDI-TDI) and the Borg scale, are commonly used in IPF, although none were originally developed for IPF (71-74). Even though cough is a major problem in IPF, no specific cough questionnaires for IPF exist. However, the Leicester Cough Questionnaire (LCQ) and the Cough Quality of Life Questionnaire (CQLQ) are currently used instead (75, 76). A widely-known PROM to assess anxiety and depression is the Hospital Anxiety and Depression Scale (HADS), which is increasingly used in IPF (77). No specific fatigue questionnaires for IPF exist; however, the Fatigue Assessment Scale (FAS), originally developed for sarcoidosis, is used and might be adapted for IPF in the future (78).

Patient-reported outcomes in research and daily practice

PROs could be very helpful to enhance personalized treatment in IPF (Figure 2). Until now, PROMs have been mainly used for research purposes, as a secondary endpoint in clinical trials. The most used primary endpoint in IPF trials is forced vital capacity (FVC), which is accepted as a surrogate measure for mortality (85). One study showed that HRQOL, assessed with the SGRQ, is also an independent prognostic factor for mortality in IPF (86). PROMs probably reflect another dimension of disease compared with tra-

ditional physiological parameters (86). In the future, PROMs could possibly be used to predict treatment success in IPF.

PROM use in daily practice can allow healthcare providers and patients to gain more insight into the individual disease and patient behavior. In a study of Sampson et al. (46), most patients were uncertain about their own disease course and progression and had difficulties interpreting objective hospital-based parameters. PROMs could allow both patients and healthcare providers to keep track of symptoms and disease progression easily. PRO results can even be used as a simple tool to communicate with patients, educate them, promote self-management and aid shared decision making during the course of the disease (19, 87). A systematic review in oncology has shown strong evidence that routine collecting of PROs improved patient-centered care, patient satisfaction, and detection of unrecognized problems (88).

Patient-reported experience measures in IPF

Optimal treatment requires close monitoring of the balance between the effects and side effects of disease-modifying drugs. Nonetheless, to our knowledge, a reliable measure to assess patient experiences with medication in IPF is not yet available in clinical practice. For this reason, a consortium of doctors, scientists and patient representatives has joined forces to develop the Patient Experiences and Satisfaction with Medications (PESaM) questionnaire, which has a generic module and a disease-specific part for IPF (78). The PESaM questionnaire focuses on perceived effectiveness, side effects and ease of use of medication and its impact on patients' lives. This patient reported experience measure (PREM) could not only be used in future clinical trials, but also in clinical practice to help with better detection of side effects and adjustment of medication. Moreover, Russell and colleagues, together with patients, are currently developing the 'IPF-PREM'. This is a measure to assess patient experiences with healthcare and can possibly be used to improve the quality of care for patients (79).

Home monitoring

Ideally, for a better tailored treatment, frequent monitoring with a low burden for the patient is needed. In the last decade, the use of e-health in chronic diseases has been growing, and shows mostly promising results (89-91). E-health involves the exchange of data between a patient and a healthcare provider using information and communication technologies (ICT) (92). By using e-health tools, patients may better understand their health condition and become actively involved in the management of their own disease. It allows frequent monitoring in between regular visits and collection of PROs at home (93). Recently, a study showed that daily home spirometry in a population of patients with IPF was highly feasible and informative (94). Home-based spirometry pre-

dicts disease decline and mortality better than hospital-based measurements. Routine home spirometry could be very helpful to identify patients with rapid decline in lung function and to evaluate response to treatment. The authors suggest that daily home spirometry will allow for more individualized patient care. The feasibility of home-based spirometry in IPF was confirmed by Johannson et al. (95), who additionally showed that home spirometry might reduce sample size as well as the length of future clinical trials. Another promising example of home monitoring in IPF is the longitudinal follow-up of physical activity with activity trackers worn by patients at home (96). Decline in physical activity can provide reliable, objective data on disease progression and could be integrated into a home monitoring program. A comprehensive home monitoring program, consisting of an e-health tool combined with home spirometry and online collecting of PROs, has the potential to enhance trial design, stimulate self-management, allow for early treatment adaption to minimize side effects, prevent hospital admissions, and subsequently improve personalized management and quality of life for patients with IPF.

CONCLUSION

The potential to enhance personalized treatment has prompted excitement also in the IPF field. In the future, patients' genetic, biomarker and microbiome profiles may guide clinical trial design and treatment decisions. In this process, patient perspectives should not be overlooked. Only by integrating biological information with patient-reported and patient-collected information, will we be able to realize truly personalized treatment.

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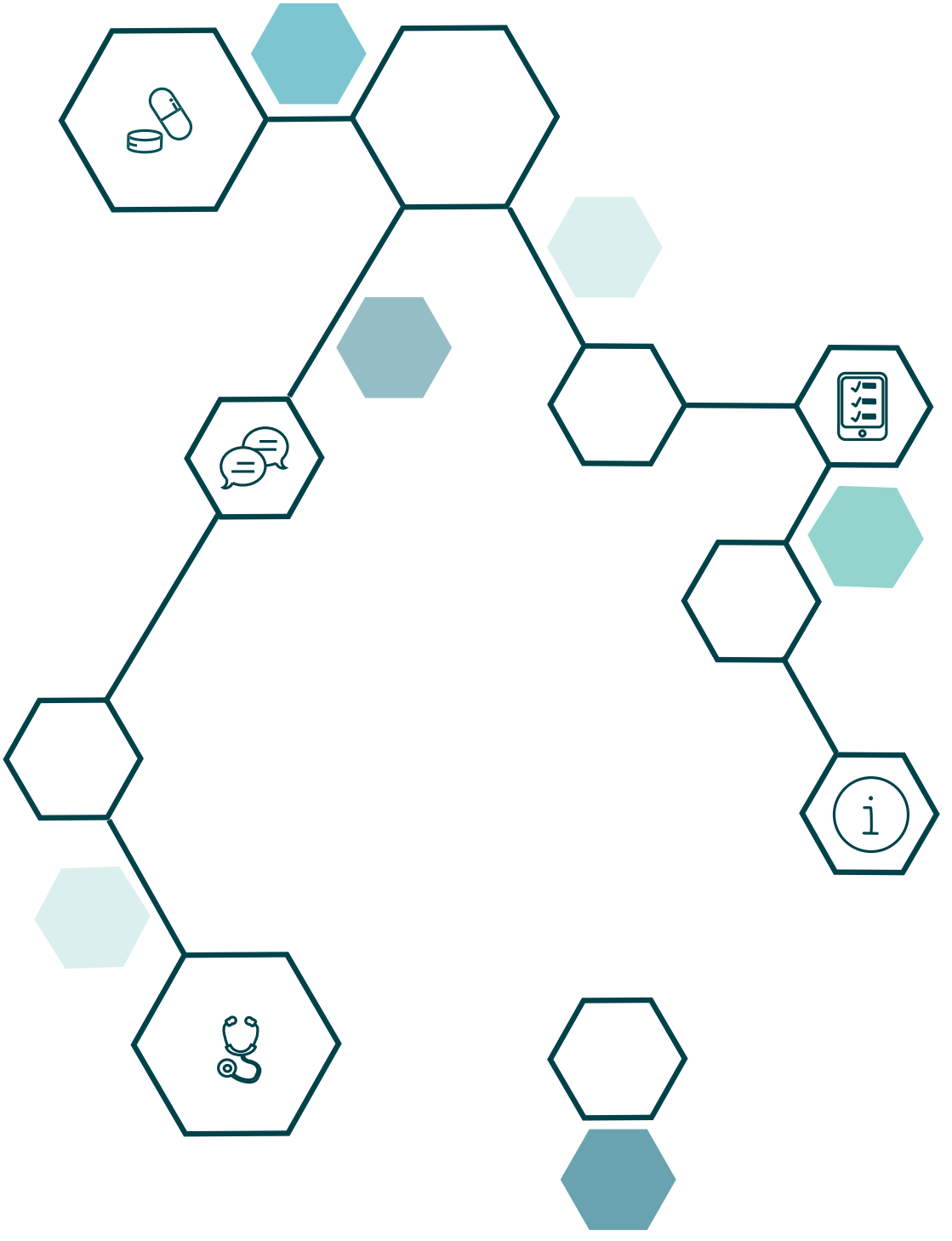

Chapter 5

Patient expectations, experiences and satisfaction with nintedanib and pirfenidone in idiopathic pulmonary fibrosis: a quantitative study

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ABSTRACT

Background

Two antifibrotic drugs, nintedanib and pirfenidone, are available for treatment of idiopathic pulmonary fibrosis (IPF). Although efficacy and adverse events have been well studied, little is known about patient experiences with these drugs. We aimed to systematically and quantitatively evaluate patient expectations, experiences, and satisfaction with nintedanib and pirfenidone. Furthermore, we assessed which factors were associated with overall patient satisfaction with medication in patients with IPF.

Methods

Outpatients with IPF prospectively completed the Patient Experiences and Satisfaction with Medication (PESaM) questionnaire before start, and after three and six months of antifibrotic treatment, as part of a randomized eHealth trial (NCT03420235). The PESaM questionnaire consists of an expectation module, a validated generic module evaluating patient experiences and satisfaction concerning the effectiveness, side-effects, and ease of use of a medication, and a disease-specific module about IPF. Satisfaction was scored on a scale from -5 (very dissatisfied) to +5 (very satisfied).

Results

In total, 90 patients were included, of whom 43% used nintedanib and 57% pirfenidone. After six months, the mean overall score for satisfaction with medication was 2.1 (SD 1.9). No differences were found in experiences and satisfaction with medication, and the number and severity of side-effects between nintedanib and pirfenidone. Perceived effectiveness of medication was rated as significantly more important than side-effects and ease of use (p=0.001). Expectations of patients regarding effectiveness were higher than experiences after six months. Self-reported experience with effectiveness was the main factor associated with overall medication satisfaction.

Conclusions

Patient experiences and satisfaction with antifibrotic treatment in IPF were positive, and similar for nintedanib and pirfenidone. Systematic evaluation of patient expectations, experiences, and satisfaction with medication could enhance shared-decision making and guide drug treatment decisions in the future.

Keywords

Idiopathic pulmonary fibrosis; patient-reported outcomes; patient satisfaction, medication; patient experiences

BACKGROUND

IPF is a rare, progressive interstitial lung disease with a poor prognosis (1). Two antifibrotic drugs, nintedanib and pirfenidone, are available for treatment of idiopathic pulmonary fibrosis (IPF). These drugs slow down disease progression, may reduce the rate of acute exacerbations, and seem to prolong survival (2-4). The decision to prescribe either nintedanib or pirfenidone is usually based on the specific side-effect profiles, co-morbidities, co-medication, and a patient's preferences (5, 6). The prevalence of adverse events with antifibrotic medication has been reported in randomized controlled trials and registries with real-world data. In these studies, around 20-30% of patients permanently discontinued antifibrotic treatment due to adverse events, such as diarrhea or photosensitivity (7, 8). Although efficacy and adverse events have been well studied, little is known about patient experiences and satisfaction with antifibrotic medication. Earlier qualitative studies suggested that experiences and satisfaction with medication were relatively positive in most IPF patients (9-11). Patients with side-effects reported to have lower satisfaction levels and an impaired (health-related) quality of life ((HR)QOL) (10). Studies in other chronic diseases showed that patient satisfaction with medication can influence health-related decisions and compliance with medication (12, 13). Consequently, experiences and satisfaction with medication may also affect long-term treatment outcomes (12). Moreover, expectations before start of treatment are associated with outcomes and satisfaction in patients with other chronic conditions (14). Gaining better insights in patient expectations before start of treatment could help to optimize expectation management and aid shared-decision making (14).

In recent years, it has been increasingly acknowledged that the patient perspective should play a central role in treatment decisions in IPF (6, 15). Shared-decision making is only possible if patients' needs, expectations, experiences, and preferences are regularly (re)assessed during the disease course. To allow for structured collection and evaluation of patient expectations and experiences with pharmacological treatment, the patient experiences and satisfaction with medication (PESaM) questionnaire has recently been developed and validated in IPF (11, 15).

In this study, we aimed to evaluate patient expectations, experiences, and satisfaction with antifibrotic treatment using the PESaM questionnaire. Furthermore, we compared PESaM scores between patients using nintedanib and pirfenidone, evaluated the relationship between (health-related) quality of life and satisfaction with medication, and assessed which factors were associated with overall medication satisfaction.

METHODS

Study design and participants

Outpatients with IPF prospectively completed the PESaM questionnaire before start, and after three and six months of antifibrotic treatment, as part of a multi-center randomized home monitoring trial at four sites in the Netherlands (16). The trial is registered on www.clinicaltrials.gov (NCT03420235). Eligible to participate were adults (>18 years) with a diagnosis of IPF confirmed in a multidisciplinary team meeting, according to the ATS/ERS/JRS/ALAT guideline, who were about to start on antifibrotic treatment (1). This study was approved by the institutional review board of all participating centers. All patients provided written informed consent prior to study entry. Patients also completed the King's Brief Interstitial Lung Disease questionnaire (K-BILD), EQ-5D-5L, Hospital Anxiety and Depression Scale (HADS), and a visual analogue scale (VAS) on symptoms (17-19). All questionnaires were completed online in a secured application on a tablet, before the doctor's visit. Forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) were performed at all hospital visits.

Outcome measures

The PESaM questionnaire evaluates patient expectations (only before start of drug treatment), experiences, and satisfaction regarding effectiveness, side-effects, and ease of use of medication, and its impact on a patient's health and daily activities. The PESaM consists of three modules; an expectation module, a generic module applicable to any medication, and a disease-specific module, especially for IPF. The expectation module consists of 11 questions reported on a 5-point Likert scale from 0 to 4. Questions concern the expected effectiveness, bothersomeness of side-effects, and ease of use of a medication; higher scores indicate more positive expectations. The generic module includes 18 items in three domains (effectiveness, side-effects, ease of use). Patient experiences are scored similar to expectations on a Likert scale from 0-4, with higher scores representing more positive experiences. Satisfaction is scored on a horizontal thermometer with scores ranging from -5 (very dissatisfied) to 5 (very satisfied). Finally, patients scored how important they considered effectiveness, side-effects, and ease of use of their medication (0=not important at all, 4=very important). The disease-specific module contains 10 items, and evaluates experiences with disease-specific symptoms and side-effects. Information on generic and disease-specific topics in the PESaM questionnaire can be found in supplementary table 1. More detailed information regarding the development, scoring and validation of the PESaM questionnaire has previously been described (11, 15).

The K-BILD consists of 15 items in four different domains (total score, psychological domain, breathlessness and activities, and chest domain). Scores range from 0 to 100 with higher scores indicating a better HRQOL (17). The EQ-5D-5L comprises 5 questions and a visual analogue scale on general wellbeing from 0 to 100; higher scores represent a better QOL (18). The HADS is divided in a 7-item anxiety and 7-item depression scale, with scores ranging from 0 to 21. A score of 8 or higher indicates anxiety or depressive symptoms (19). Symptoms (cough, dyspnea, and general complaints) were scored on a VAS from 0 to 10.

Statistical analysis

Analyses were conducted in patients who completed the PESaM questionnaire at ≥1 time point. Differences between nintedanib and pirfenidone were analyzed with independent students t-tests at three and six months. Paired students t-tests were used to analyze differences between scores at three and six months in the overall group. Expectations before start of treatment and experiences after six months were analyzed on item level with Wilcoxon Signed Ranks tests. Correlations between health-related quality of life and satisfaction at six months were analyzed with Pearson correlation coefficients. Differences in patient-reported importance of effectiveness, side-effects and ease of use were analyzed using repeated measures ANOVA with post-hoc tests (Bonferroni correction). A linear regression model was used to analyze factors predictive for satisfaction with medication after six months. Variables included in the univariable analysis were age, gender, and patient expectations at baseline, and lung function, type of antifibrotic drug, symptoms, HADS scores, and self-reported experiences with effectiveness, side-effects, ease of use, and severity of side-effects at six months. Variables with a p-value <0.10 on the univariable analysis were included in the multivariable analysis (enter method). A p-value <0.05 was considered statistically significant. All statistical analyses were performed in SPSS Statistics version 25.

RESULTS

A total of 90 patients were included, of whom 43% used nintedanib and 57% pirfenidone. Of these patients, 83 completed the PESaM at baseline, 83 after three months, and 78 after six months. Baseline characteristics were comparable between both groups, except for FVC (**Table 1**). During the study, two patients died, five patients discontinued antifibrotic treatment, and seven patients switched medication.

Table 1. Baseline characteristics of study patients (n=90)

	Nintedanib (n=39)	Pirfenidone (n=51)
Age, years	70 (7)	72 (7)
Male sex – no. (%)	35 (90)	47 (92)
FVC % predicted	86 (16)	76 (16)
FVC (L)	3.4 (0.9)	2.9 (0.6)
DLCO % predicted	48 (14)	49 (14)
K-BILD total score	56.5 (9)	56.7 (10)
EQ5D-Index value	0.78 (0.15)	0.77 (0.19)
EQ5D-VAS scale	65 (24)	63 (23)
VAS – cough*	4.8 (2.6)	4.6 (2.5)
VAS – dyspnea*	5.1 (2.3)	5.6 (2.4)
VAS – general complaints**	5.6 (2.4)	5.5 (2.4)
HADS – depression score	3.0 (3.1)	3.9 (3.5)
HADS – anxiety score	4.7 (2.3)	4.6 (2.3)

Data are presented as mean (SD). FVC = forced vital capacity, DLCO = diffusion capacity of the lung for carbon monoxide, K-BILD = King's Brief Interstitial Lung Disease questionnaire, VAS = visual analogue scale, HADS = Hospital Anxiety and Depression Scale. * a higher score represent worse symptoms, ** a higher score represents fewer symptoms.

Expectations, experiences, and satisfaction in the overall group

In the overall group, there were no significant differences in experiences and satisfaction after three and after six months (**Table 2**). Expectations of patients regarding effectiveness (mean score 2.8, SD 0.8) and side-effects (mean score 2.5, SD 0.8) were positive. At six months, the mean score for experiences with effectiveness (score 2.0, SD 1.0) was lower than the expectation score (difference 0.8, p=0.001). Experiences with side-effects (mean score 2.9, SD 1.1) were comparable with expectations (difference 0.4, p=0.07). Many patients chose the answer option "don't know" for questions in the expectation module. Hence, expectations and experiences could only be compared in a relatively small number of patients (n=26 for effectiveness, n=39 for side-effects). Expectations, experiences and satisfaction were similar across treatment centers.

After six months, patients rated how important they considered the effectiveness, side-effects and ease of use of their antifibrotic medication. Effectiveness (mean score 3.5, SD 0.8) was rated as significantly more important than side-effects (mean score 2.2, SD 1.3), and ease of use (mean score 1.8, SD 1.3), p=0.001. Self-reported adherence with antifibrotic medication after six months was high: 88% of patients reported 100% adherence, 10% reported that they missed one or a few pills, and 2% reported that they often skipped their medication in the past four weeks.

Table 2. Patient experiences and satisfaction with antifibrotic treatment after three and six months in the overall group (n=75)

	Month 3	Month 6	Difference (95% CI)	p value
Satisfaction with effectiveness	1.6 (1.6)	1.6 (1.8)	0.0 (-0.3-0.5)	0.70
Satisfaction with side-effects	1.8 (2.0)	1.6 (2.1)	0.2 (-0.4-0.6)	0.57
Satisfaction with ease of use	2.9 (1.6)	2.7 (1.7)	0.2 (-0.1-0.6)	0.18
Overall satisfaction with medication	2.1 (1.8)	2.1 (1.9)	0.0 (-0.4-0.5)	0.90
Experiences with effectiveness	2.0 (0.9)	2.0 (1.1)	0.0 (-0.4-0.5)	0.84
Experiences with side-effects	3.1 (1.1)	2.9 (1.2)	0.2 (-0.3-0.5)	0.44
Experiences with ease of use	3.9 (0.5)	3.8 (0.5)	0.1 (-0.1-0.2)	0.38
Number of reported side-effects per patient	6.4 (4.2)	5.8 (4.7)	0.6 (-0.2-1.4)	0.14
Severity score side-effects	9.5 (11.1)	8.7 (9.3)	0.8 (-1.6-3.2)	0.51

Data are presented as mean (SD). Experiences are scored on a scale from 0-4; a higher score corresponds with more positive experiences Satisfaction is scored on a scale from -5 to 5.

Comparison between nintedanib and pirfenidone

Expectations before start of treatment were similar for nintedanib and pirfenidone. No differences were found in experiences and satisfaction between nintedanib and pirfenidone after three and six months of antifibrotic treatment (**Table 3**). Moreover, the reported number and severity of side-effects were similar in patients using nintedanib and pirfenidone. For nintedanib, the most frequently reported side-effects were diarrhea (70.3%), fatigue (56.8%), and abdominal pain (45.9%). For pirfenidone, the most frequently reported side-effects were fatigue (68.3%), skin-related events (58.5%), and decreased appetite (53.7%).

Relation between satisfaction with medication and (HR)QOL

Scores of K-BILD and EQ-5D-5L did not change over six months. Overall, moderate correlations were found between (HR)QOL and satisfaction with medication at six months. The total K-BILD score was moderately correlated with satisfaction regarding effectiveness ($r=0.57$, $p=<0.001$), side-effects ($r=0.51$, $p<0.001$), ease of use ($r=0.42$, $p<0.001$), and overall medication satisfaction ($r=0.46$, $p<0.001$). The EQ5D-VAS score also showed a moderate correlation with overall satisfaction ($r=0.59$, $p<0.001$), satisfaction with side-effects ($r=0.48$, $p<0.001$), ease of use ($r=0.53$, $p<0.001$) and effectiveness ($r=0.58$, $p<0.001$).

Factors associated with overall satisfaction with medication

Experiences with effectiveness, side-effects and ease of use, severity of side-effects, anxiety and depression scores, cough, dyspnea and general complaints were significantly associated with overall satisfaction after six months on univariable linear regression analysis (**Table 4**). Patients' expectations before start of treatment, lung function pa-

Table 3. Experiences and satisfaction with nintedanib and pirfenidone after three and six months of antifibrotic treatment

	Month 3				Month 6			
	Nintedanib (n=37)	**Pirfenidone (n=46)**	**Difference (95% CI)**	**p-value**	**Nintedanib (n=37)**	**Pirfenidone (n=41)**	**Difference (95% CI)**	**p-value**
Satisfaction with effectiveness	1.7 (1.6)	1.5 (1.6)	0.2 (-0.5-0.9)	0.58	1.4 (1.7)	1.7 (1.9)	0.3 (-1.1-0.6)	0.54
Satisfaction with side-effects	1.7 (2.0)	1.8 (2.2)	0.1 (-1-0.9)	0.9	1.3 (1.9)	1.8 (2.2)	0.4 (-1.4-0.5)	0.37
Satisfaction with ease of use	3.2 (1.6)	2.6 (1.6)	0.6 (-0.1-1.3)	0.08	2.9 (1.4)	2.5 (1.9)	0.4 (-0.4-1.1)	0.3
Overall satisfaction with medication	2.2 (1.7)	1.9 (1.8)	0.2 (-0.5-1)	0.53	1.9 (1.7)	2.2 (2.0)	0.2 (-1.1-0.6)	0.58
Experiences with effectiveness	1.7 (1.0)	1.7 (0.9)	0.09 (-0.7-0.5)	0.75	2 (1.1)	1.8 (1.0)	0.2 (-0.6-1)	0.55
Experiences with side-effects	3.1 (1.2)	2.9 (1.2)	0.3 (-0.3-0.8)	0.41	2.8 (1.2)	3.1 (1.1)	0.3 (-0.8-0.2)	0.25
Experiences with ease of use	3.9 (0.3)	3.8 (0.5)	0.1 (-0.05-0.3)	0.14	3.9 (0.3)	03.7 (0.6)	0.1 (-0.07-0.4)	0.18
Number of reported side-effects per patient	6.0 (3.5)	6.6 (4.6)	0.6 (-2.4-1.3)	0.55	5.7 (4.2)	5.7 (5.1)	0.05 (-2-2.1)	0.96
Severity score side-effects	9.9 (13.2)	9.8 (9.3)	0.1 (-4.8-5.1)	0.96	8.9 (9.5)	8.3 (9.0)	0.6 (-3.3-4.5)	0.75

Data are presented as mean (SD). Experiences are scored on a scale from 0-4; a higher score corresponds with more positive experiences Satisfaction is scored on a scale from -5 to 5

rameters, the type of antifibrotic drug, age and gender were not associated with patient satisfaction. Because of the strong relation between cough and dyspnea, we chose to include general complaints in the multivariable model, as a proxy for cough and dyspnea. In the multivariable model, only experiences with effectiveness was significantly associated with satisfaction with medication (**Table 4**).

Table 4. Univariable and multivariable linear regression analyses of factors associated with overall satisfaction with medication (n=78)

	Univariable analysis		Multivariable analysis	
	B (95% CI)	P-value	B (95% CI)	P-value
Age	0.019 (-0.04;0.08)	0.55	-	-
Gender	-0.97 (-2.6;0.6)	0.25	-	-
Expectations effectiveness	0.54 (-0.15;1.2)	0.12	-	-
Expectations side-effects	-0.10 (-0.85;0.65)	0.79	-	-
FVC % predicted	0.004 (-0.02;0.03)	0.76	-	-
DLCO % predicted	0.008 (-0.02;0.04)	0.60		
Antifibrotic drug	0.24 (-0.62;1.1)	0.58	-	-
VAS - cough	-0.23 (-0.39;-0.07)	0.005		
VAS – dyspnea	-0.41 (-0.56;-0.26)	<0.001		
VAS - general complaints	0.36 (0.15;0.57)	0.001	0.07 (-0.28;0.42)	0.69
HADS – anxiety score	-0.30 (-0.47;-0.14)	0.001	-0.32 (-0.70;0.07)	0.11
HADS – depression score	-0.24 (-0.35;-0.13)	<0.001	0.008 (-0.27;0.29)	0.95
Experiences effectiveness	1.2 (0.6;1.75)	<0.001	1.0 (0.28;1.71)	0.008
Experiences side-effects	-0.53 (-0.87;-0.18)	0.003	0.15 (-0.55;0.85)	0.66
Experiences ease of use	-0.99 (-1.8;-0.17)	0.019	-0.20 (-1.38;0.98)	0.73
Severity score side-effects	-0.07 (-0.11;-0.03)	0.001	-0.03 (-0.11;0.048)	0.43

FVC = forced vital capacity, DLCO = diffusion capacity of the lung for carbon monoxide, HADS = hospital anxiety and depression scale, VAS = visual analogue scale

DISCUSSION

In this study, we evaluated patient expectations, experiences and satisfaction with antifibrotic medication in patients with IPF, as this could aid future shared-decision making. To our knowledge, this was the first study in IPF which systematically assessed patient experiences with medication, using the validated PESaM questionnaire (15). Patient experiences and satisfaction after three and six months of antifibrotic treatment were fairly positive, and similar in nintedanib and pirfenidone. Satisfaction with medication had a moderate positive correlation with (HR)QOL. Self-reported experiences with the effectiveness of the medication (e.g. positive impact on physical health, daily activities) was the main factor associated with overall medication satisfaction. Patient expecta-

tions before start of treatment, anxiety, depression, and symptom scores, experiences with side-effects, and perceived severity of side-effects were not associated with overall medication satisfaction after six months.

Interestingly, patients considered effectiveness of their medication more important than side-effects and ease of use. This is in line with findings from a recent study, which found that IPF patients were more concerned about slowing down disease progression than about side-effects. In contrast, almost a quarter of the surveyed healthcare providers in that study considered side-effects more important than the risk of disease progression (9). Our results highlight the importance of shared-decision making, taking into account patients' expectations, experiences and preferences in all treatment decisions, as patients' opinions and considerations may be different than healthcare providers assume.

Overall, expectations regarding effectiveness were slightly higher than consecutive experiences, which emphasizes the need for realistic patient education and expectation management during the disease course (14). Expectations and consecutive experiences with side-effects were comparable. There were no differences in reported expectations and experiences across participating centers. Expectation management may be complex in IPF, due to the heterogeneous disease course and the fact that antifibrotic medication does not halt or reverse lung function decline. Hence, it may be difficult for patients and their healthcare providers to judge the effectiveness of these drugs. This was reflected in the fact that a substantial number of patients answered that they did not know what to expect, and were uncertain whether treatment was effective or not. Nevertheless, the perceived effectiveness of medication was the only factor which was associated with overall medication satisfaction in a multivariable model. Patients' beliefs and opinions regarding the effectiveness of their medication are factors known to impact medication adherence in other diseases (20). In the present study, (self-reported) adherence with medication was very high, showing that uncertainty about effectiveness seemed to have no influence on adherence. Moreover, only a small minority of patient discontinued treatment (5.5%). The high adherence and low discontinuation rate could possibly be due to the relative short study duration. Longer prospective studies are needed to assess whether perceived effectiveness and satisfaction with medication affects long-term compliance and treatment outcomes (12, 15).

Previous studies have shown that nintedanib and pirfenidone have a similar effect on lung function decline. Furthermore, no significant differences in all-cause mortality and frequency of side-effects were found between the two drugs (2, 3, 5, 21). However, these studies did not compare patient experiences and satisfaction between both antifibrotic drugs. Results of our study showed that self-reported experiences and satisfaction were

similar in patients using nintedanib and pirfenidone. One could have speculated that the perceived ease of use would be different between nintedanib and pirfenidone, because of the differences in dosing schedule. However, experiences and satisfaction with ease of use were very high in both groups, showing that patients considered it relatively easy to integrate the use of antifibrotic medication in their daily life. Although the side-effect profile was different for both drugs (e.g. more diarrhea in patients using nintedanib, more skin problems in patients using pirfenidone), the number and perceived severity of side-effects were similar. Use of structured tools like PESaM could facilitate insights into expectations, experiences and satisfaction in individual patients, and thereby guide decisions on treatment choices and adjustments throughout the disease course.

A strength of this study was that data were prospectively collected in a multi-center population of newly treated IPF patients. Due to this multi-center design with multiple healthcare providers, potential differences in patient education about medication have been taken into account. This study has also limitations. The PESaM questionnaire has been developed and validated in IPF, but no minimal important difference and responsiveness has been established yet. However, as no differences were found between timepoints and use of nintedanib versus pirfenidone, this has not impacted our results and conclusions.

CONCLUSIONS

Patient experiences and satisfaction with medication after three and six months of antifibrotic treatment were relatively positive, and comparable between nintedanib and pirfenidone. Patient expectations before start of treatment were high, emphasizing the need for realistic expectation management. Perceived effectiveness of medication was associated with overall medication satisfaction. The PESaM questionnaire is a novel, simple tool to evaluate patient satisfaction and experiences with medication, and can be used both in clinical trials and in daily practice. We believe that systematic evaluation of patient experiences could enhance shared-decision making and guide treatment decisions in the future.

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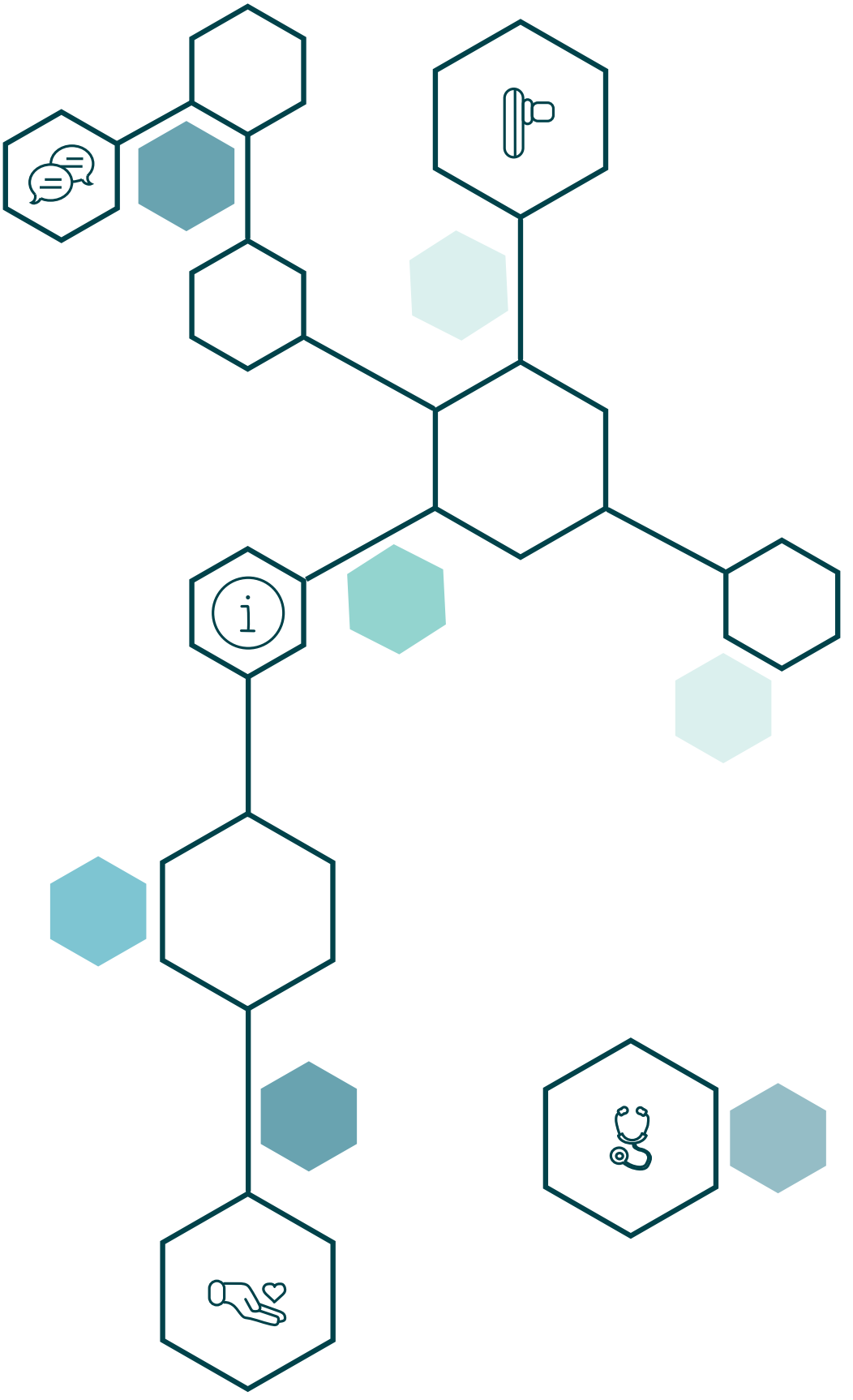
Supplementary table 1. Overview of topics included in PESaM questionnaires in different modules

Domain	PESaM-module		
	Disease-specific (IPF)	Generic experiences	Generic expectations
Effectiveness	- Coughing - Shortness of breath - Fatigue - Disease stabilisation	- Perceived effectiveness - Impact on physical health - Impact on feelings and emotions - Impact on social and daily activities - Satisfaction	- Expected effectiveness - Impact on physical health - Impact on feelings and emotions - Impact on social and daily activities
Side-effects	- Headache - Insomnia - Fatigue - Dizziness - Weight loss - Decreased appetite - Photosensitivity - Other skin problems - Diarrhoea - Nausea - Vomiting - Flatulence - Stomach pain - Abdominal pain - Coughing - Other - Bothersomeness of each experienced side-effect - Non-adherence due to side-effects	- Bothersomeness experienced side-effects (any) - Impact on physical health - Impact on feelings and emotions - Impact on social and daily activities - Satisfaction	- Bothersomeness side-effects (any) - Impact on physical health - Impact on feelings and emotions - Impact on social and daily activities
Ease of use	- Intake capsules - Timing - Non-adherence due to inconvenience	- Administration mode - Time schedule or frequency - Incorporate into daily life - Satisfaction	- Administration mode - Time schedule or frequency - Incorporate into daily life
Other	N/A	- Overall satisfaction - Importance of effectiveness vs side-effects vs ease of use	N/A



Chapter 6

Needs, perceptions and education in sarcoidosis: a live interactive survey of patients and partners

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ABSTRACT

Objectives

Sarcoidosis is a chronic, multisystem disease with often a major impact on quality of life. Information on unmet needs of patients and their partners is lacking. We assessed needs and perceptions of sarcoidosis patients and their partners.

Methods

During patient information meetings in 2015 and 2017 in the Erasmus University Medical Center we interviewed patients and partners using interactive voting boxes. Patients responded anonymously to 17 questions. Answers were projected directly on the screen in the room.

Results

210 patients and 132 partners participated. Sarcoidosis has a subjective significant impact on lives of both patients and partners. The vast majority of patients and partners feel regularly misunderstood because of the general unawareness of sarcoidosis. Many patients and partners experience anxiety. Three-quarters of patients would like to see more attention and support for their psychological problems. Additionally, more supportive care for partners of sarcoidosis patients is warranted. Interactive interviewing was considered educational (91%) and pleasant (84%).

Discussion

This study improves awareness of needs and perceptions of patients with sarcoidosis and their partners. Sarcoidosis leads to anxiety and psychological distress and impairs wellbeing of patients and their partners. Attention for psychological support, better disease education and more supportive care for partners is warranted.

BACKGROUND

Sarcoidosis is a heterogeneous, granulomatous disorder of unknown cause, most often localized in the lungs and lymphatic system. However, sarcoidosis can affect almost every organ. Therefore, disease presentation and behavior vary and can be unpredictable (1, 2). Sarcoidosis often occurs in relatively young adults, between 20 and 50 years of age (2, 3). Quality of life (QOL) is often impaired due to burden of symptoms such as fatigue, pain, dyspnea, persistent cough and reduced exercise intolerance. These symptoms can lead to stress, anxiety and depression, and social and physical limitations (4-7). Side-effects of treatment and complications of disease can also negatively impact QOL (6-8). Only a few studies aimed to improve QOL in patients with sarcoidosis; these studies were mainly focused on pulmonary rehabilitation (9, 10). Although it is well-known that sarcoidosis is a disabling disease (7, 11), studies on patients' needs and preferences in care are lacking. Also, to our knowledge, no currently available studies assessed whether sarcoidosis also influences wellbeing of partners or other close relatives.

Every year a multidisciplinary sarcoidosis patient meeting takes place in the Erasmus University Medical Center Rotterdam in the Netherlands, aiming to provide up-to-date information and new insights on sarcoidosis to patients and their partners. All patients with confirmed sarcoidosis from the Erasmus University Medical Center are invited to visit these patient meetings. Several medical specialties involved in sarcoidosis care, and the Dutch sarcoidosis patient organization (sarcoidose.nl), organize and attend these meetings. These meetings allow us to ask patients and partners multiple questions with the use of an interactive voting system. This system enables the attendants to directly see the aggregated results, thereby providing live information about experiences and needs of other patients and partners. A study in pulmonary fibrosis showed that the use of an interactive voting system is considered informative and appreciated by participants, and that it could be an efficient way to inform and educate patients and partners (12).

The aim of this study was to evaluate the needs and perceptions of patients with sarcoidosis and their partners. Moreover, we assessed whether interactive interviewing could be used to enhance education in patients with sarcoidosis.

METHODS

In 2015 and 2017 patients were interviewed during patient information meetings in the Erasmus University Medical Center, one of the two recognized sarcoidosis expert centers in the Netherlands. Patients and partners received voting boxes (TurningPoint

2008; Keepad Interactive, Sydney, Australia) at the start of the information meeting and voted anonymously. Participants were asked permission to use the data before the meeting started. Medical Ethical Committee approval was granted. In accordance with the study of van Manen et al. (12) the term "partners" comprised also other nearest and dearest. Fifteen questions were asked during the meetings in 2015 and 2017. Three questions, about organ involvement and the value of interactive voting were added in 2017. Literature search, input from patients, physicians and specialist nurses were used to compose the questions. Moreover, the validated Generalized Anxiety Disorder-Single Item (GAD-SI) was administered (13). Questions were shown on a big screen and read out loud by one of the speakers. Subsequently, a ten second countdown was projected on the screen to provide enough time for participants to vote. Afterwards, answers of participants were shown on the screen and directly discussed with the audience. Data were exported and analyzed in Microsoft Excel 2010 afterwards. All data are presented as % (n).

RESULTS

A total of 210 sarcoidosis patients and 132 partners participated in the interactive voting during the two information meetings. Of the 342 participants, 40 people attended both meetings. In 2017, patients (n=104) were asked to report which organs were involved in their sarcoidosis; 47% of patients reported multi-organ involvement, 34% reported only pulmonary involvement, and a small minority of patients reported respectively only neurological involvement (7%), eye involvement (6%), joint/muscle involvement (3%), cardiac involvement (3%) and skin involvement (1%).

The symptoms that affected sarcoidosis patients most, were fatigue, painful joints and/or muscles and breathlessness. Furthermore, cough, skin manifestations, ocular complaints and depressive symptoms were reported by a minority of patients as their most disabling symptom (**Figure 1**).

Sarcoidosis had a huge impact on the lives of the majority of patients and their partners in a similar manner; almost three-quarters of patients reported (very) much influence on their daily life (**Figure 2**).

In the vast majority of patients and partners the GAD-SI score was elevated, which indicates high levels of anxiety (**Figure 3**). The answers "more than half of the days" (19%, n=50) and "almost every day" (29%, n=74) based on the GAD-SI questionnaire are considered suggestive of having a generalized anxiety disorder (GAD) (13). Almost

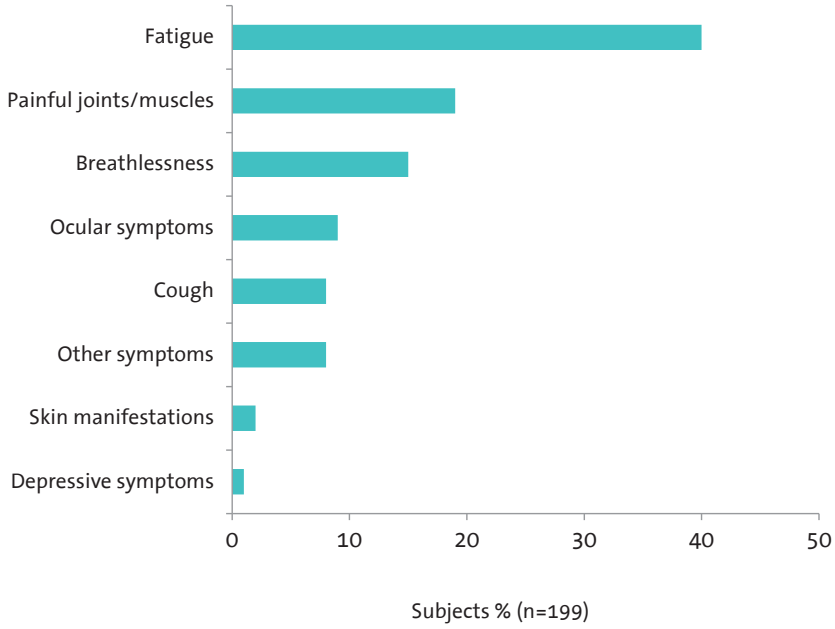

Figure 1. Patients' response to the question "What symptom of sarcoidosis affects you the most?"

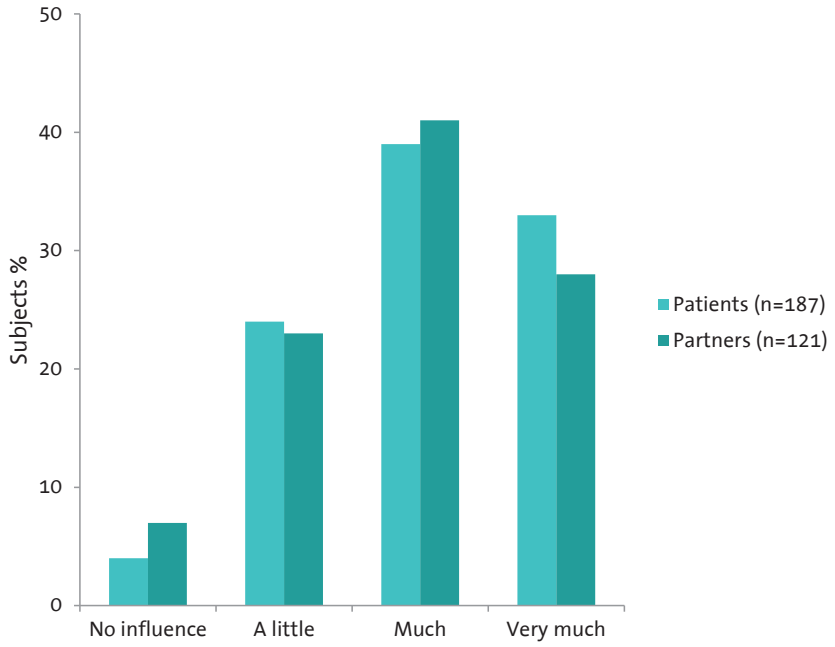

Figure 2. Subject responses to the questions "What is the influence of sarcoidosis on your life at this moment?" and "What is the influence of having a partner with sarcoidosis on your life at this moment?"

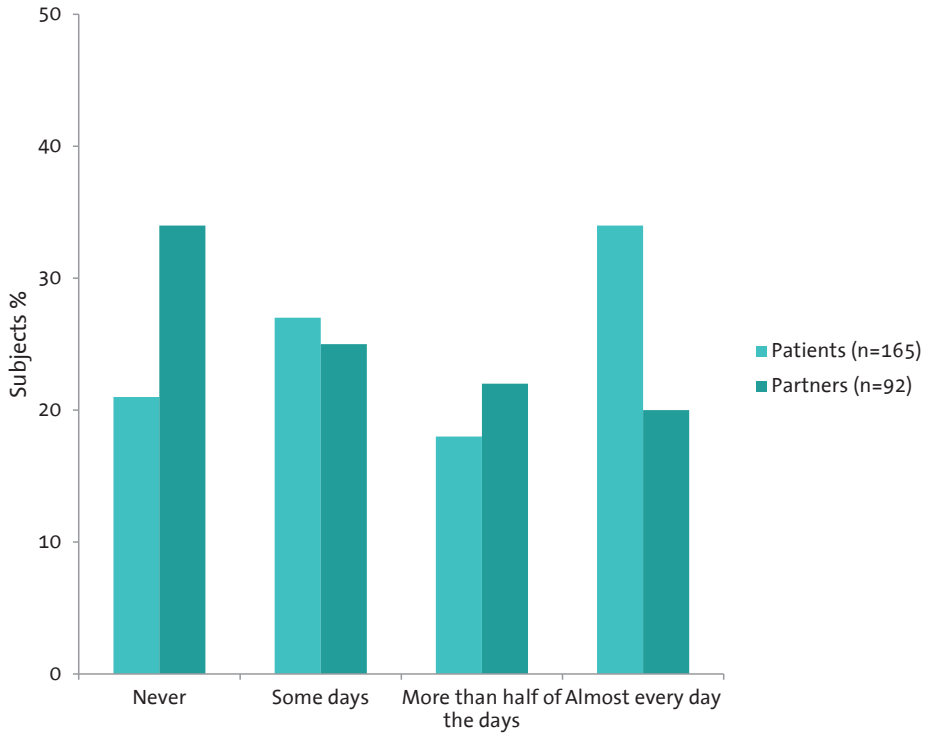

Figure 3. Experience of anxiety of both patients and partners based on the Generalized Anxiety Disorder-single item questionnaire (13) "How often in the past two weeks did you have trouble relaxing?"

three-quarters of patients (74%, n=132) would like to see more attention and support for their psychological problems. One third of patients (33%, n=59) stated that they missed psychological support in standard care, whereas 41% (n=73) of patients would only like to receive psychological care when they specifically ask for it. A minority of patients reported no psychological issues (18%, n=32).

In addition, many participants experienced some degree of misunderstanding, because of the general unawareness of sarcoidosis . **Figure 4** shows that partners seem to experience even more misunderstanding than patients.

The main needs in care of patients with sarcoidosis were easy access to an expert center for sarcoidosis (36%, n=67) and receiving adequate information about the disease (41%, n=78). Additionally, the importance of practical and emotional support, and contact with peers were mentioned by patients. Also, 41% (n=53) of partners thought that there should be more support for the partners of sarcoidosis patients. Furthermore, we asked patients questions about their opinion on eHealth. The majority of participants (70%,

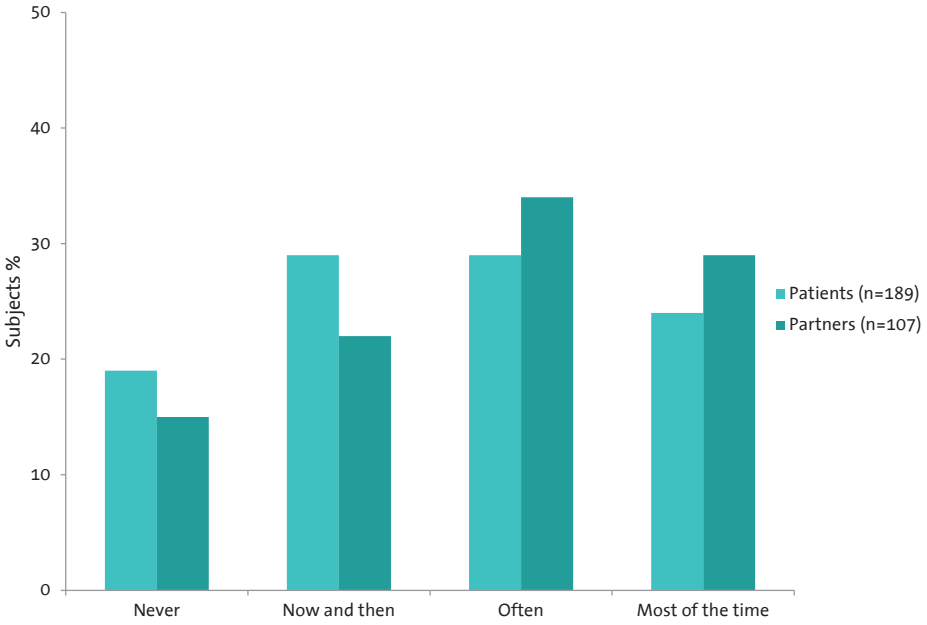

Figure 4. Participants' responses to the question "How often do you experience misunderstanding because people do not know what sarcoidosis is?"

n=132) would like to keep track of their data and symptoms on the internet. Almost all patients (92%, n=170) would be willing to measure lung function at home to optimize treatment. Most patients and partners rated the information meeting as very useful (86%, n=237). About one third of participants felt more confident after the meeting (**Figure 5**). In 2017, 84% (n=128) of participants appreciated seeing the answers of other participants immediately after each question, and 91% (n=136) considered the interactive interviewing educational.

DISCUSSION

This study shows the major psychological and social impact of sarcoidosis, not only on patients but also on their partners. Education and psychological support are reported as important unmet needs. Furthermore, the study shows that patients and partners appreciate the interactive voting system and consider it informative. Interactive voting might be a suitable method to facilitate discussion with patients and to educate and support them at the same time.

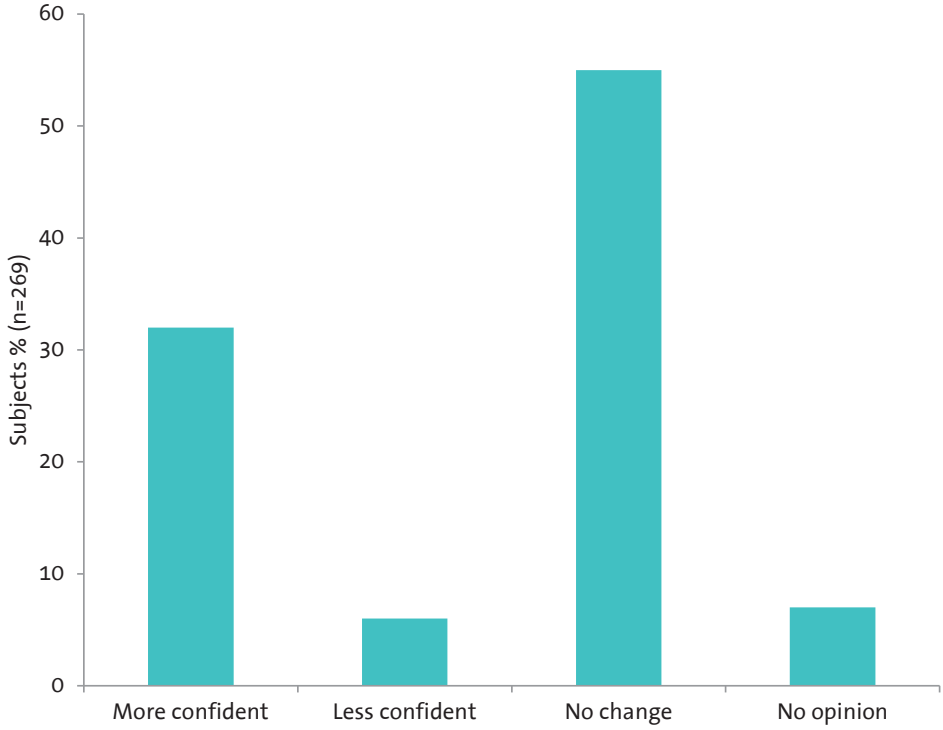

Figure 5. Feelings of patients and partners at the end of the meeting

The patient voice in care

The importance of patient participation and shared decision making in healthcare has been increasingly acknowledged during the last years (14). Although studies on patient participation in sarcoidosis are scarce, it is appreciated that engaging patients in care could lead to better clinical outcomes and treatment adherence, especially because sarcoidosis is such a multidimensional disease (11). Recently, the Netherlands institute for health services research showed that 75% of sarcoidosis patients considers shared decision making important (15). However, to allow for shared decision making, patients must be well informed and physicians should have better insights into patients' perception of disease and preferences in care. The data of this study can be used to better address the needs of patients with sarcoidosis and their partners, and to improve daily care.

Fatigue

Most patients in our study report fatigue as the symptom which affects them most. This is in accordance with previous studies, in which fatigue was the most burdensome and frequent symptom in sarcoidosis (16, 17), with a negative impact on QOL (8, 11, 18).

Fatigue often persists, even if sarcoidosis is treated well and no other sarcoidosis disease activity can be found (11). A few small studies showed effect of neurostimulants or pulmonary rehabilitation on fatigue (9, 10, 19, 20); however, larger randomized trials with specific fatigue interventions are lacking. Design of such trials is complicated, because sarcoidosis-associated fatigue is a multidimensional, complex problem with unknown etiology (17, 21). Besides, fatigue in sarcoidosis is related to depressive symptoms and sleep disturbance (17, 18, 22, 23). As also illustrated by the results of this study, fatigue remains a major problem for patients. A multidisciplinary approach towards sarcoidosis-associated fatigue is needed and should be subject for future research.

Influence of sarcoidosis on daily life

Our study shows that sarcoidosis has a major influence on patients' daily lives. It is well established that sarcoidosis has a huge impact on patients; health status and QOL are lower than in the normal population (4, 7, 24). This study is the first to show that sarcoidosis also has a major impact on the daily lives of partners of sarcoidosis patients. Many patients feel that they are not taken serious by relatives and friends. The reason for this might be that sarcoidosis is often not visible (11). In our study, many patients and partners experience misunderstanding because of the general unawareness of sarcoidosis in society. Patients often have non-specific symptoms, such as fatigue, depression, reduced exercise capacity or pain, which are difficult to quantify. This could contribute to incomprehension of the impact of sarcoidosis, and lead to reduced labor force participation, social isolation, and disturbed relationships (4, 11, 25). Improving general awareness about sarcoidosis and acknowledging the impact of sarcoidosis on many aspects of life, could possibly help sarcoidosis patients and partners to feel better understood.

Psychological problems

Anxiety, stress and depressive symptoms are common problems in sarcoidosis. In our study, the vast majority of patients experience some level of anxiety (13). In literature, prevalence of depressive symptoms in sarcoidosis ranges from 27-66% and prevalence of anxiety ranges from 5-32% (5, 6, 23, 26, 27). Severe disease, multi-organ involvement and dyspnea are associated with more depressive symptoms (26, 27). However, the design of our study does not permit looking at such a correlation. Patients' perception of disease, independent of disease status, might lead to anxiety and depression (27). Disease chronicity, unpredictable course and uncertain future perspectives can also impair emotional wellbeing (23). In daily practice, these aspects are often neglected, and more recognition and tailored interventions should be stimulated. Examples of possible interventions include cognitive behavioral therapy or psychological counselling (11, 24).

Anxiety in partners

Strikingly, not only patients but also two-thirds of partners experience anxiety, 20% of them almost every day. In other chronic diseases, such as cancer, dementia and rheumatoid arthritis, it has been acknowledged that many partners encounter psychological distress and have a decreased QOL (28). Some studies showed that caregivers are even more distressed than patients, and that depression of patients was significantly associated with depression of their partners (28-30). Partners of sarcoidosis patients in our study report more anxiety and misunderstanding than partners of idiopathic pulmonary fibrosis (IPF) patients as reported previously (12). This is remarkable when considering the progressive nature of disease and associated severely reduced life expectancy in IPF. Currently, there are different questionnaires available which evaluate wellbeing, anxiety and depressive symptoms of (informal) caregivers (31, 32). In the light of the results of our study, it should be considered to incorporate such questionnaires in future care and studies, to gain more insight in QOL of partners of patients with sarcoidosis, and its effect on wellbeing of the patient.

Preferences in care

Many partners of sarcoidosis patients in our study think that partners should receive more care. This is in line with studies assessing needs in partners of patients with other chronic illnesses (28, 30). One of the options mentioned in literature is to invite partners more actively for outpatient clinic visits, encouraging them to ask questions or express concerns, and involve partners in decision making (28). Clinicians tend to have more attention for physical parameters than psychological issues in patients with sarcoidosis (23). This is in accordance with findings from our study, in which the majority of patients would appreciate more attention for psychological care. Furthermore, patients reported the importance of access to an expert center, practical support and contact with other patients. Patient organizations can also play an important role in facilitating contact with expert centers, information and peer support.

Home monitoring

Use of eHealth technologies has been increasing in recent years, and eHealth studies show promising results for improving quality of care (33). The majority of patients in our study wish to keep track of their symptoms and manage their personal data at home using an internet tool. Furthermore, most patients in the current study are also willing to measure lung function at home. These are encouraging results for future care and trials, because a recent study in patients with newly diagnosed sarcoidosis showed that home spirometry was feasible and allowed for early detection of steroid treatment effects (34). Home monitoring of lung function, symptoms and side-effects, can help physicians to

enhance individually tailored treatment by minimizing side-effects, maximizing effects and engaging patients in care (34).

Education

One of the main unmet needs in sarcoidosis care revealed in this study, is the need for more information about the disease. In a recent government survey about chronic lung diseases, more than half of Dutch sarcoidosis patients reported that they cannot find sufficient information about their disease and its prospects (15). This is one of the reasons that sarcoidosis patient information meetings are organized every year. However, literature about the best method to provide information to patients with sarcoidosis is scarce. Drent and colleagues (11) state that the complex etiology of sarcoidosis and its variability make it complicated to provide adequate information, and that "affective communication" probably makes it easier for patients to remember medical information. In the current study, one third of patients felt more secure after the information meeting and the vast majority of patients appreciated live interactive interviewing, showing that this may be a promising method to enhance education of patients and partners.

Limitations

This study has of course limitations. Because of the interactive voting system, no specific patient characteristics are available, such as age, gender and disease duration. Organ involvement was self-reported by patients and could not be verified. Furthermore, this was a single center study. Despite these limitations, we believe that the results are relevant for a broader group of sarcoidosis patients. We invited all patients with confirmed sarcoidosis of the Erasmus Medical Center, including patients with a wide spectrum of disease manifestations and severity. A small minority of patients attended both the 2015 and 2017 meeting. However, because the total group of participants is large, the estimated effect of overlap in data is only small. Furthermore, not all patients answered all questions. Reasons for not answering could be preference not to answer certain questions or being too late to respond. Therefore, we expressed all results as n (%), since the response rate might differ per question.

CONCLUSION

This study improves awareness of needs and perceptions of both patients and their partners in sarcoidosis. Sarcoidosis not only leads to anxiety and psychological distress and impaired wellbeing in patients, but also in their partners. Therefore, attention for psychological support, better disease education, and more care for partners is warranted. Besides the ongoing need for improvement of disease modifying agents, future

research should also focus on patient-centered programs to relieve distress and improve QOL for both sarcoidosis patients and their partners.

Acknowledgements

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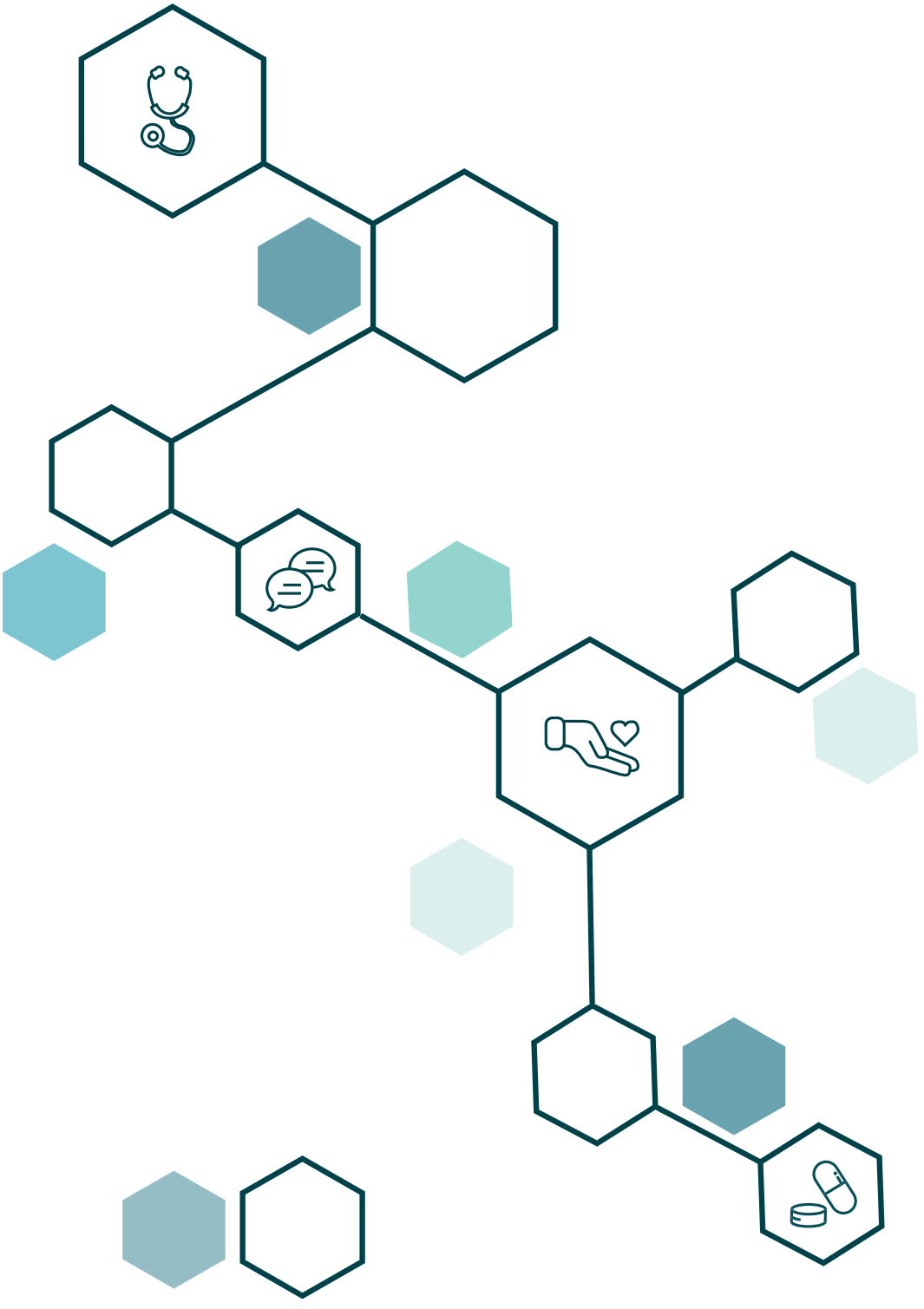

Chapter 7

Managing fatigue in patients with interstitial lung disease

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ABSTRACT

Fatigue is one of the most burdensome symptoms in interstitial lung disease (ILD), and can have a major impact on quality of life of patients, social interactions and work capacity. The etiology of fatigue is complex, and it is caused or aggravated by a combination of different predisposing, precipitating and perpetuating factors. There is no uniform definition of fatigue, but it is often divided in a physical and mental component. Several validated questionnaires can be used for structural assessment of fatigue in daily care. Although the high burden of fatigue in ILD is increasingly recognized, studies investigating pharmacological and non-pharmacological treatment options are scarce. As fatigue in ILD is often a multifactorial problem, therapeutic interventions should ideally be aimed at different domains. One of the first steps is to optimize treatment of the underlying disease. Subsequently, treatable causes of fatigue should be identified and treated. Recently, an increasing number of studies showed that supportive measures have the potential to improve fatigue. However, evidence-based treatment guidelines are lacking, and more research is highly needed in this field. In clinical practice, a comprehensive, multidisciplinary, and individually-tailored approach seems best fit to optimize treatment of fatigue in ILDs.

INTRODUCTION

Interstitial lung disease (ILD) is a broad term for a group of more than 200 rare lung diseases. Some of these diseases are mainly inflammatory, while others are more fibrotic from the start and many are a combination of both. This diversity in underlying pathobiology is also reflected in the variable clinical disease behavior: some ILDs are reversible, some have the potential to stabilize, and some have a progressive fatal course (1). ILDs often have a major impact on patients' quality of life (QOL), daily living, work capacity, and social interactions (2). Most frequently reported symptoms are cough, dyspnea, and fatigue (3-5). Although the impact of fatigue is widely acknowledged, there is limited information about the etiology and management of fatigue in ILDs. Most studies are conducted in patients with sarcoidosis, and, more recently, some small studies have been published in other ILDs. In this review, we will give an overview of the most recent insights of fatigue in ILD.

Case report

A 37-year old man presented at our outpatient clinic with sarcoidosis. His most burdensome symptoms were a dry cough and fatigue. The x-ray showed bilateral lymphadenopathy, and discrete nodular abnormalities in the upper lobes. Pulmonary function tests were normal. Blood testing showed normal blood count, liver and kidney tests. Calcium and thyroid-stimulating hormone levels were also normal, while the soluble interleukin 2 receptor (sIL-2R) level was slightly elevated. Additional examination revealed obstructive sleep apnea (OSA), for which he was successfully treated with continuous positive airway pressure (CPAP), resulting in his apnea-hypopnea index (AHI) becoming normalized. However, fatigue did not improve. On follow up, his x-ray spontaneously improved, pulmonary function tests remained normal, and his sIL-2R normalized. Consultation at the cardiologist revealed no abnormalities. Subsequently, treatment with methylphenidate was initiated without success. Considering the major negative impact of fatigue on his quality of life, we referred him to a psychologist for cognitive behavioral therapy.

Prevalence of fatigue in ILD

In the general population, fatigue is reported in 5-20% (6). Although fatigue is often reported as a common symptom in ILD, data about prevalence in different ILDs are scarce (**Figure 1**). In idiopathic pulmonary fibrosis (IPF), fatigue is reported in up to 95% of patients (4, 7). In the European IPF registry, prevalence of fatigue was similar for IPF patients (69.2%) compared with non-IPF ILDs (70.6%). In systemic sclerosis studies, fatigue was present in up to 89% of the patients (8). In chronic hypersensitivity pneumonitis, fatigue has been reported in up to 87% of patients (9). A recent multinational survey

showed that fatigue was present in 90% of patients with sarcoidosis, with up to 48% of patients mentioning extreme fatigue (5). Fatigue mostly occurs at disease onset and during the active phase of sarcoidosis. Nevertheless, even up to 56% of the patients with complete remission report fatigue (10). The prevalence of fatigue in different ILDs is difficult to compare, because different questionnaires were used. It also depends on whether fatigue is patient- or physician-reported. For instance, in a sarcoidosis registry study physicians only reported fatigue in 30% of the patients, which is much lower than patient-reported fatigue in other studies (5, 11). This emphasizes the importance of regularly asking patients whether fatigue is present.

Etiology of fatigue in ILD

One of the complicating factors in studying fatigue is that there is no uniform definition of fatigue, although it is often divided into a physical and a mental component (6, 12). Mental fatigue (perceived fatigability) can be described as a subjective symptom of malaise, tiredness, lack of energy, and aversion to activity (6, 12, 13). Physical fatigue (performance fatigability) refers to impaired physical performance (6, 12). The etiology of fatigue is poorly understood; however, physiological, psychological, and behavioral factors seem to play a role in the onset and persistence of fatigue (6, 13). In most sarcoidosis studies fatigue is poorly correlated with clinical parameters. However, in IPF and systemic sclerosis, there seems to be an association with disease severity (7, 14-16). Many uncertainties still exist about the etiology of fatigue, which is likely not ILD specific.

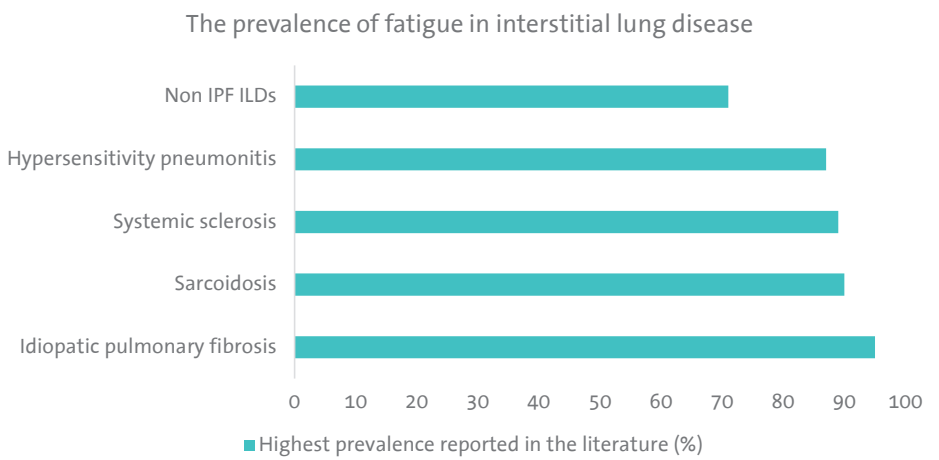

Figure 1. Reported prevalence of fatigue in interstitial lung diseases.

Fatigue is a prevalent symptom in many chronic disorders (17). A recent study demonstrated that only 11% of the variation in fatigue could be explained by the specific diagnosis. In this study, fatigue was mainly explained by transdiagnostic factors, such as reduced motivation, pain, limitations in physical functioning, concentration problems, reduced activity levels, poor sleep quality, and the ability to cope with fatigue (17).

From other areas outside ILD, we have learned that factors influencing fatigue can be divided into predisposing factors, precipitating factors, and perpetuating factors (6, 13). For a large part, many of these factors also hold true for ILD (**Figure 2**). Patients with predisposing factors such as biological vulnerability, vulnerable personality, and

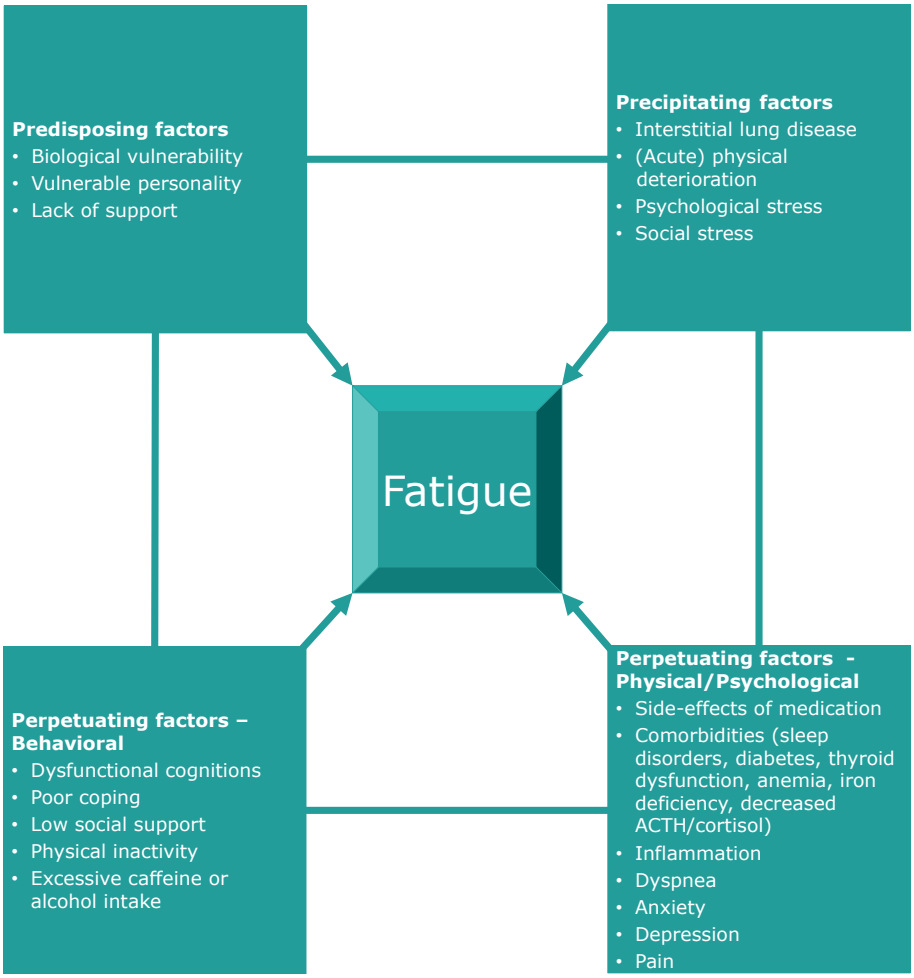

Figure 2. Predisposing, precipitating and perpetuating factors that can cause or aggravate fatigue in ILDs. Most of these factors are interrelated, and some are related in a bidirectional way.

lack of support are at increased risk of developing fatigue (6, 18). In different forms of ILD, physical deterioration, psychological stress, and social stress have been described as precipitating factors that can cause fatigue (2, 7, 8, 16). Furthermore, there is a wide range of physical, psychological, and behavioral factors that may further perpetuate fatigue and are described in more detail below.

Perpetuating factors - physical and psychological factors

Poor sleep quality is reported more frequently in ILD patients as in the general population (16, 19, 20). Sleep architecture is often disrupted, with a decrease of rapid eye movement sleep, increase of sleep fragmentation, and more nocturnal desaturations compared with the general population (20, 21). In a study on sleep quality in 15 IPF patients, a significant correlation was found between nocturnal saturation and fatigue scores (22). Whether nocturnal oxygen suppletion has an effect on sleep quality and fatigue has not yet been studied. Other ILD-related factors that may alter the sleep architecture are cough, periodic limb movement, restless legs syndrome and the side-effects of medication such as corticosteroids (19, 20). Another reason for fatigue may be OSA, with a reported prevalence of up to 88% in ILD (20, 21). The high prevalence of OSA could be partly explained by comorbidities, such as obesity or upper airway pathologies. However, one study showed that even when these comorbidities were excluded, OSA was found in 68% of the ILD patients (82.3% in IPF, 66.6% in sarcoidosis, and 55.5% in systemic sclerosis). Another explanation proposed for the high prevalence of OSA, is the upper airway collapse caused by the restrictive lung disease (20).

It has been suggested that low-grade inflammation may play a role in fatigue; however, not much data for this exist in ILD. A study in patients with sarcoidosis in clinical remission demonstrated that a decrease in Th2 cytokine production was associated with fatigue (23). However, most studies have not found a relation between serological markers, such as angiotensin-converting enzyme, sIL-2R and C-reactive protein, and fatigue (24). Furthermore, fatigue often persists in sarcoidosis patients who are in clinical remission and have no signs of active inflammatory response (10).

Medication is another factor that may cause or aggravate fatigue. Different studies have shown that corticosteroids are associated with fatigue and impaired QoL in sarcoidosis (25). As fatigue is a registered common side-effect of corticosteroids, this may also play a role in other ILDs. Overall, corticosteroids often lead to side-effects such as weight gain, sleep disturbance, psychological disturbance and diabetes mellitus, which are also independently associated with fatigue (20, 24). Current treatment of IPF consists of the anti-fibrotic drugs nintedanib and pirfenidone (26). Fatigue is one of the registered side-effects of pirfenidone (26). Pooled data of the pirfenidone trials showed fatigue occurred

as an adverse event in 26% of the pirfenidone group and 19% of the placebo group (27). In an observational study on the long-term safety of pirfenidone in IPF, fatigue was reported as one of the most common adverse drug reactions in 18.5% of patients (28).

Other comorbidities that are associated with fatigue are diabetes mellitus, thyroid dysfunction, anemia, iron deficiency, and decreased ACTH/cortisol levels (2, 24, 29). Evaluation of the presence of these comorbidities is important, as many are found to be more prevalent in ILDs and may not only impact fatigue but also influence the disease course. For instance, in patients with IPF, hypothyroidism and diabetes mellitus are more prevalent and are also associated with worse prognosis (16, 29-31). Some small observational studies have found an association between physical activity, measured with wrist worn activity trackers, and fatigue in patients with ILD (10, 32, 33). Patients who were less active seemed to be more tired. The association between activity and fatigue seemed stronger in patients with IPF, than in patients with sarcoidosis(32, 33). Most patients with IPF report fatigue as physical exhaustion, while patients with sarcoidosis mainly report mental fatigue (7). This may explain why fatigue is more strongly correlated with physical activity in IPF than in sarcoidosis. Other physical factors associated with fatigue in ILD are dyspnea, muscle strength, and pain (10, 13, 15).

Anxiety, depressive symptoms, memory loss and concentration problems (cognitive failure) are related to fatigue in a bidirectional way (34). Psychological symptoms are not only more prevalent in ILDs but also in other chronic diseases (7, 8, 16, 17). Uncertainty about prognosis, and a decrease in social and work participation are some of the factors that lead to increased stress and anxiety in ILD (2, 35). In patients with (self-reported) cognitive impairment, normal daily tasks require more cognitive effort, which in turn might lead to higher fatigue levels (34). In sarcoidosis, small fiber neuropathy is frequently reported and strongly associated with fatigue (5, 34).

Perpetuating factors - Behavioral

In general, behavioral factors, such as dysfunctional cognitions, poor coping, inactivity, excessive caffeine or alcohol intake, and low social support, can perpetuate fatigue (13). These factors have not been specifically evaluated in ILD in relation to fatigue. However, some of the abovementioned factors could potentially be managed by simple interventions and support from a social worker or psychologist. Therefore, we believe that behavioral factors should not be overlooked in the assessment and treatment of fatigue in ILD.

The impact of fatigue

Fatigue has a huge impact on many aspects of the lives of patients including social relationships, work participation, and quality of life. Many patients consider fatigue as a very burdensome symptom (5, 16). The impact of fatigue may be difficult to understand for family, friends, employers and healthcare professionals because it is a nonspecific symptom and patients often look completely healthy. Consequently, some patients feel that they are not taken seriously, which may lead to further social isolation (2, 6, 34). Fatigue has been reported as an important negative predictor of QOL in ILD patients and was found to be associated with depression and anxiety, both in patients with sarcoidosis as well as with other ILDs (16, 34). Furthermore, fatigue is associated with decreased work participation, loss of income, and social isolation (36-38). In turn, a low income has also been associated with the development of sarcoidosis-related comorbidities, such as fatigue (39). In a study on work performance in sarcoidosis, 43% of 755 patients underwent disability evaluation. In these patients, fatigue levels were significantly higher than in the group who had not undergone work capacity assessments.

Measurement of fatigue

Although highly prevalent, fatigue is often not structurally assessed in patients with ILD. Evaluating fatigue can be challenging due to the different determinants of fatigue and the lack of a uniform approach(12). Obviously, active evaluation of fatigue, and other burdensome symptoms, should take place during every visit. Extensive history taking is needed to assess the severity and impact of fatigue on patients' lives, and to identify possible perpetuating factors. In addition to this, different questionnaires can be used for a more structured evaluation of fatigue. The fatigue assessment scale (FAS) and Sarcoidosis Assessment Tool (SAT) fatigue subscale are developed to asses fatigue in sarcoidosis patients. The FAS is most commonly used, also in other ILDs. It consists of ten questions on a 5-point response scale; five questions about physical fatigue and five questions about mental fatigue. The total score ranges from 10-50 points; a score of ≥ 22 points indicates fatigue and ≥ 34 points severe fatigue. The minimal clinical importance difference is 4 points (40). The SAT fatigue subscale consist of five questions and is incorporated in a QOL questionnaire. Other questionnaires that have been used to measure fatigue in ILD are the Functional assessment of chronic illness Therapy-Fatigue (FACIT-F) and the Patient Reported Outcomes Measurement Information Systems (PROMIS) Fatigue Instrument (PFI) (41). These questionnaires may be used to quantify fatigue in clinical trials, but also to assess the effect of treatment for individual patients in clinical practice.

Treatment of fatigue in ILD

Even though the high burden of fatigue in ILD is well recognized, studies investigating treatment options are limited. As fatigue in ILD is often a multidimensional problem, therapeutic interventions should ideally be aimed at the different domains involved. **Figure 3** shows a decision making flowchart on how to handle fatigue in ILD. One of the first steps is to optimize treatment of the underlying disease, and to exclude that fatigue is a side-effect of prescribed medication. The side-effects of corticosteroid use, especially, should be thoroughly monitored, and the prescribed dosage should be regularly re-assessed and down-titrated if possible. Subsequently, treatable causes of fatigue should be excluded. As mentioned before, one of the treatable causes of fatigue in ILD is OSA. Two studies in IPF concluded that effective CPAP treatment improved daily living activities, quality of sleep, QOL, and daytime fatigue (21, 42). Currently, a trial is ongoing to assess the prevalence and the effect of CPAP treatment in sarcoidosis patients with OSA (NCT03926832). Comorbidities, such as hypothyroidism, should be optimally treated, although no studies have reported on the effect of treatment of comorbidities on fatigue (30). In patients with depression, anxiety or stress referral to a psychologist could be considered. As a high symptom burden of the underlying disease may also directly or indirectly lead to fatigue, treatment should also be directed at symptom relief. At the moment, a randomized controlled trial is assessing the effect of advancing symptom alleviation with palliative treatment (ADAPT) in ILD. In this study, the intervention group is supported by a nurse and social worker with the aim of relieving burdensome symptoms, such as fatigue (NCT02713347).

When all systemic treatable causes have been excluded, the focus should be on the other domains. As far as possible, behavioral, precipitating, and perpetuating factors should be identified and, where possible, targeted. There is increasing evidence that exercise therapy or pulmonary rehabilitation (PR) could be beneficial in ILD patients with fatigue. PR is a comprehensive intervention consisting of exercise training, education and self-management strategies (43). One study showed a positive effect of a 6-week PR program on fatigue in IPF (43). The treatment guideline of IPF also recommends PR to alleviate symptoms (26). A randomized trial in patients with different ILDs demonstrated that an 8-week supervised exercise program improved fatigue scores, exercise capacity and QOL (44). Similar positive results were found in sarcoidosis studies (45). Next to pulmonary rehabilitation, cognitive behavioral therapy has been proposed as a potential treatment option for patients with sarcoidosis-associated fatigue (2). A pilot study in sarcoidosis showed that a 45-minute mindfulness-based workshop improved fatigue and other symptom scores directly after the intervention (46). Long-term effects of this mindfulness workshop have not yet been evaluated. At the moment, a randomized controlled study to evaluate the effects of a 12-week online cognitive behavioral therapy in

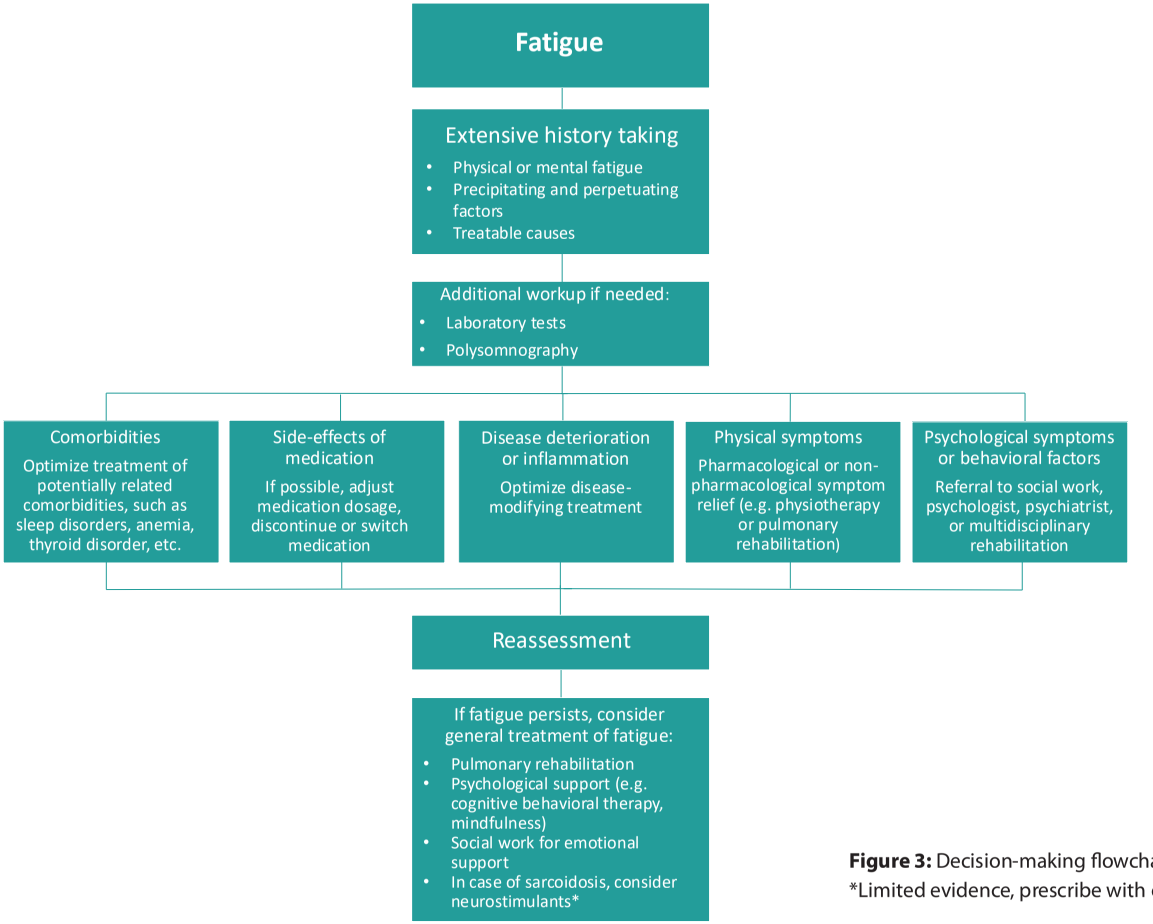

Figure 3: Decision-making flowchart on how to manage fatigue in ILD.
*Limited evidence, prescribe with caution

patients with sarcoidosis-associated fatigue (FAS score ≥22 points) is ongoing (https://www.trialregister.nl/trial/7816). Although cognitive behavioral therapy has also been suggested in IPF, no studies have been conducted to date. As fatigue is also perpetuated by inactivity, low social support and psychological wellbeing, tailored interventions by physiotherapists, psychologists or social workers may sometimes improve symptoms.

Neurostimulants have been suggested as potential treatment options for fatigue in sarcoidosis. The effect of dexmethylphenidate hydrochloride (d-MPH) and armodafinil on sarcoidosis-associated fatigue was first described in 2008 (47, 48). D-MPH, which inhibits dopamine and noradrenaline in the brain, was studied in 10 patients. Armodafinil, which increases extracellular dopamine levels in the brain and is mainly used in narcolepsy, was studied in 15 patients. Both of these neurostimulants led to a significant improvement in fatigue scores and appeared to be safe. While the results of these studies were promising, only a small number of patients were included. Currently, a new study on the effect and side-effects of methylphenidate in sarcoidosis-associated fatigue is being conducted. This trial was mainly initiated to determine the feasibility and design of a future large-scale RCT. Hopefully, these results will enable larger scale future studies to provide better evidence for the use of neurostimulants for fatigue in sarcoidosis (49). The use of these agents has not been investigated and their use cannot be recommended in other ILDs. It has been suggested that anti-TNF-alpha treatment may have positive effects on sarcoidosis-associated fatigue; however, this finding has not been replicated in a randomized trial (50). At present, no studies have evaluated the effects of pharmacological interventions in other ILDs.

Most of the data on how to deal with fatigue in ILD currently stem from sarcoidosis (41). Although we believe that there are many similarities between fatigue in chronic diseases and ILD, and between sarcoidosis and other ILDs, also important differences exist (2, 7, 16). Stable chronic diseases may have more general approaches, while in progressive fatal diseases as IPF, disease course and prognosis will also dictate treatment choices (51). In diseases with more rapid disease progression and worse prognosis, treatment of fatigue should be a part of integrated palliative care programs. To further advance insights into fatigue and develop better treatment strategies, more research is obviously needed. On one hand, the multifactorial etiology in often heterogeneous populations increases the complexity of the research, on the other hand, collaboration with partners outside the ILD research area could help to generate progress in the field, as fatigue is a universal problem in many chronic diseases.

CONCLUSION

Fatigue is a major problem for both patients with ILD and for treating physicians. The etiology of fatigue in ILD is likely multifactorial, but many aspects are still unknown. Different predisposing, precipitating and perpetuating factors contribute to fatigue, of which many also play a role in other chronic diseases. Unfortunately, specific guidelines and evidence-based treatment recommendations for fatigue are still lacking. In clinical practice, a comprehensive, multidisciplinary, and individually-tailored approach seems the best fit to optimize treatment of fatigue in ILDs. Hopefully, new studies will lead to better treatment options for fatigue and ultimately improve quality of life for patients with ILD.

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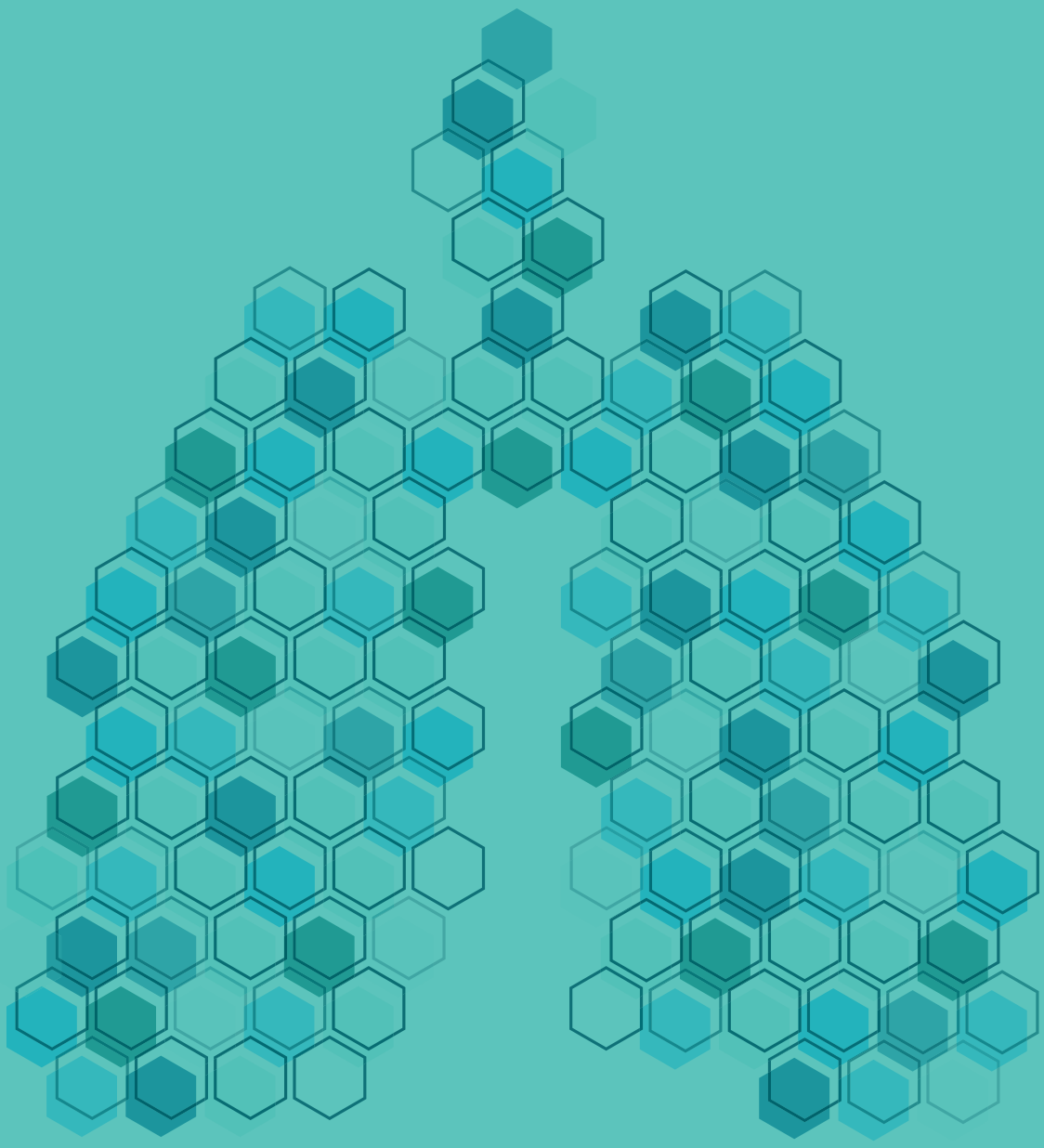
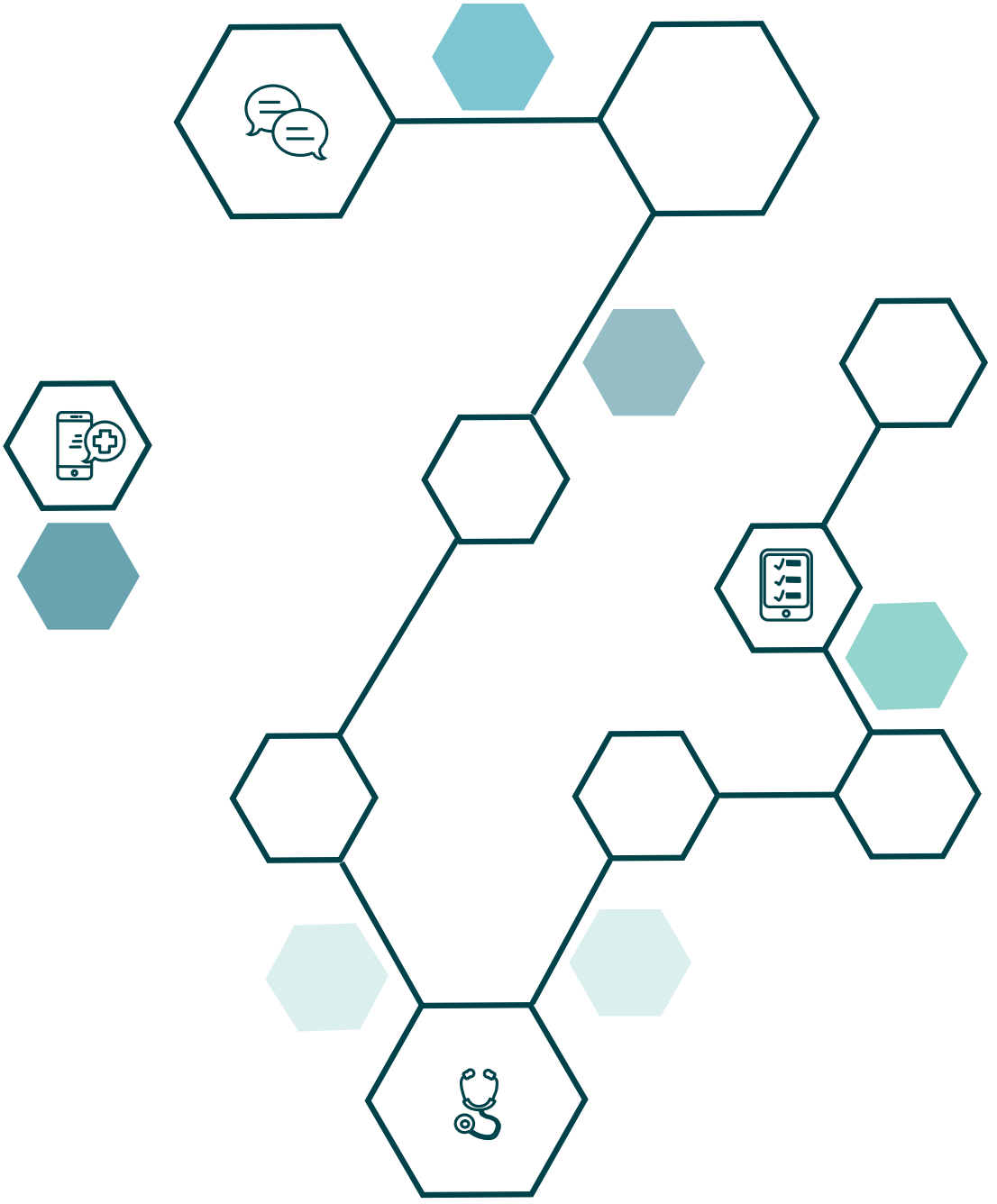


PART 3

Development and evaluation of eHealth solutions in interstitial lung disease



Chapter 8

Development and feasibility of an eHealth tool for idiopathic pulmonary fibrosis

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To the editor:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease with a poor prognosis. The quality of life (QOL) of patients is often impaired (1, 2). In other chronic lung diseases, the use of eHealth to improve clinical outcomes have been increasingly investigated (3-5). eHealth is defined as "the use of information and communication technologies for health" (6). Use of eHealth may improve understanding of disease, promote self-management and facilitate longitudinal data collection for both care and research (3, 7). Experience with eHealth tools in IPF is scarce and people are often hesitant to start online initiatives in this mostly elderly population. However, collecting data at home and facilitating consultations at a distance, could hold great benefits for these patients as they often struggle to come to the hospital because of reduced mobility, dyspnoea and extra oxygen needs. Together with patients we developed IPF-online, an eHealth tool for patients with IPF, and evaluated the feasibility and user satisfaction of this tool.

During two pulmonary fibrosis information meetings in 2014 and 2015 at our hospital, patients were asked whether they would like to keep track of their disease online; 82% of patients (n=67) responded with "yes". In response to this, we developed an eHealth tool, based on available information from literature, experiences in other fields and individual patient suggestions. This resulted in IPF-online (www.ipfonline.nl), a secured personal platform which contains information about IPF, patient-reported outcome measures (PROMs), medication use and an eConsult possibility. Results of hospital-based lung function measurements are imported by the healthcare provider. Patients remain owner of their data, and give digital informed consent for clinical or research purposes. Data is stored in high-end ISO 27001 certified data centers. Patients access IPF-online *via* personal codes, in compliance with European safety regulations.

The prototype of IPF-online was submitted to the Medical Ethical committee and approval was granted to further develop and evaluate the tool together with patients in a hands-on approach. Two consecutive groups of outpatients, with a diagnosis of IPF (1), were invited to participate. Patients were given access to their personal platform and were asked to report medication use and PROMs at baseline and after 14 days in IPF-online. Symptoms as cough, fatigue and breathlessness were assessed with visual analogue scales (VAS). Patients also completed different questionnaires, such as the King's Brief Interstitial Lung Disease health status questionnaire and the Euroqol 5D-5L (8, 9). An evaluation questionnaire was sent afterwards to assess patient experiences. We used suggestions of patients to further develop and improve IPF-online. Subsequently, a second group of patients was asked to test and evaluate the adapted version of IPF-online.

In total, 27 patients participated; 18 patients in the first group, and 9 patients in the second group. The mean age was 67 years (range 56-86 years); most patients were male (85%); median forced vital capacity (FVC) was 78% of predicted (range 46-131%) and median diffusion capacity of the lung for carbon monoxide corrected for haemoglobin (DLCOc) was 50% (range 16-79%).

All patients managed to use IPF-online and complete electronic PROMs without help from healthcare providers. Patients provided constructive feedback on IPF-online and suggested different features that could be added to improve the tool, such as the choice of tables and graphs to display longitudinal data. The first group suggested adding educational movies about IPF and information about medication and side-effects. These patient recommendations were used to adapt IPF-online. The second group additionally mentioned the need for a better explanation about PROM scores and video consultation with the healthcare provider, which will be implemented.

In both groups, many patients used the information platform (on average twice a week per patient) and the eConsult option (**Table 1**). More than two-thirds of patients considered IPF-online easy to use, which increased after the adaptations made according to the suggestions of the first group. The vast majority had positive experiences (table 1). Some patients mentioned the advantages of the interactive part of IPF-online: "I like it because you can have easier communication with doctors and nurses", "clear questions and useful interaction with health carers", "the eConsult option is very useful", and "I am immediately updated".

Table 1. Patient experiences and use of IPF-online during 14 days pilot study

	Group 1 (n =18)	Group 2 (n = 9)
Use of IPF-online		
Completion of PROMs	100%	100%
Information platform	100%	100%
eConsult	33%	44%
Patient experiences		
Easy to use	78%	89%
Useful	89%	89%
Would recommend it to others	89%	89%
Wish to continue	94%	100%
Spontaneously continued use of IPF-online after pilot	72%	100%

PROMs; patient-reported outcome measures

Other patients commented on the information platform: "IPF-online makes it possible to absorb information at my own pace", and "all useful information is gathered in one place". Almost all patients wished to continue using IPF-online: "the more contact you have, the better it is", "I like having my own follow-up data", and "it gives a good overview". A few patients (3/27) were less satisfied: "completing online questionnaires is too time consuming", "an internet tool does not have added value for me", and "I can't find all available information".

This pilot study shows that the use of an eHealth tool is feasible in patients with IPF. Patient satisfaction was high and most patients continued the use of IPF-online. One of the factors that may account for the high patient satisfaction is the multi-step co-development approach we took to create IPF-online. Previous research has shown that perspectives of healthcare providers and patients regarding eHealth might differ (3). In our project ease of use improved after patients recommended changes, underlining the importance of patient contribution.

The age range of our cohort was 56-86 years. As IPF occurs mostly in an elderly population, internet access and experience with online tools may be questioned. However, European data show that internet use is steadily increasing among people aged over 65 years (10). Furthermore, studies in COPD with a similar age range, showed that eHealth technologies were feasible in this population (5, 11).

eHealth solutions have the potential to improve care and facilitate research for patients with IPF. We believe that eHealth may enable earlier identification of inter-current problems and disease deterioration. Need for more and adequate information, and shared decision-making is repeatedly reported in IPF (12, 13). IPF-online provides patients with more insight into their own disease, can guide personalized treatment decisions and can be used as outcome parameter for both research and clinical practice. Expansion with home spirometry is currently being investigated.

In the current study, we obtained 100% PROMs completion rate, which may have definite benefits for research, avoiding missing data. This is in line with the opinion of the ePRO task force of the International Society for Pharmacoeconomics and Outcomes Research, stating that electronic PROMs have advantages over paper-based questionnaires and provide equivalent, reliable outcomes (14, 15). The questionnaires incorporated in IPF-online were not validated for online use. However, current evidence shows that full psychometric validation of ePROMs is not necessary when only minor modifications are made to the original PROMs (14). Testing usability of ePROMs in a small group, as done

in the current study, to evaluate whether participants are able to use the device and software to complete the questionnaires is sufficient (14).

A limitation of this study is that it was a short pilot study in a relatively small and possibly more motivated patient group. This may be a reason for the 100% PROM completion rate. Nonetheless, 82% of the overall patient population was motivated to use the eHealth tool. Furthermore, the group included a broad range in age and severity of disease and the majority of patients continued using the tool.

All together, we believe that the use of IPF-online is feasible and highly valued by patient with IPF. Whether its long-term use improves QOL, medication use and end-point assessment for trials is a field for further studies.

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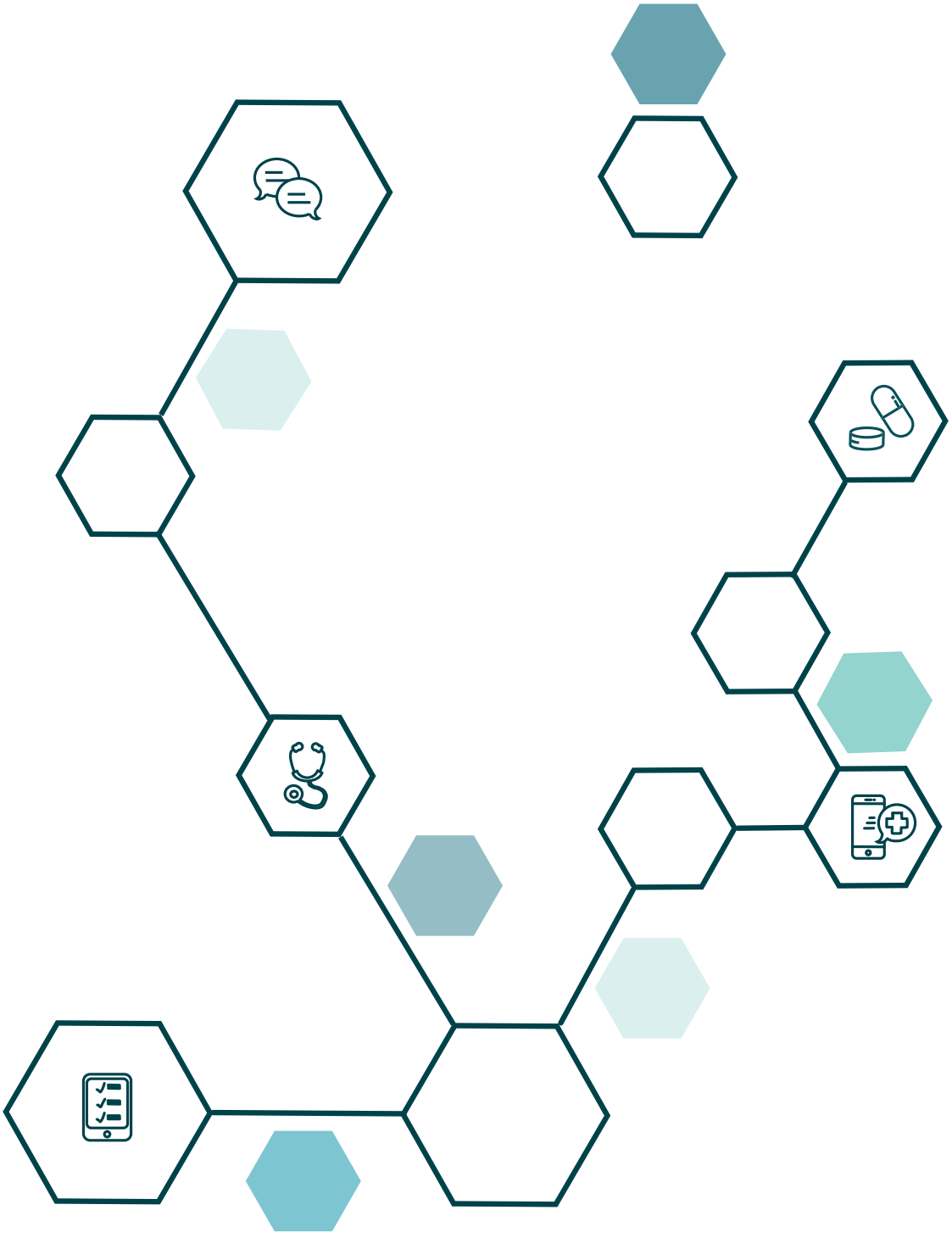

Chapter 9

A home monitoring program including real-time wireless home spirometry in idiopathic pulmonary fibrosis: a pilot study on experiences and barriers

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ABSTRACT

In idiopathic pulmonary fibrosis (IPF), home monitoring experiences are limited, not yet real-time available nor implemented in daily care. We evaluated feasibility and potential barriers of a new home monitoring program with real-time wireless home spirometry in IPF. Ten patients with IPF were asked to test this home monitoring program, including daily home spirometry, for four weeks. Measurements of home and hospital spirometry showed good agreement. All patients considered real-time wireless spirometry useful and highly feasible. Both patients and researchers suggested relatively easy solutions for the identified potential barriers regarding real-time home monitoring in IPF.

Keywords

Idiopathic Pulmonary Fibrosis; eHealth; home monitoring; spirometry

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, devastating disease with a poor prognosis (1). Symptoms as increasing shortness of breath and immobility make regular hospital visits a challenge for many patients. New eHealth technologies hold great potential for research and care by facilitating real-time, frequent data collection at home. In IPF, home monitoring experiences are limited and not yet implemented in daily care. Few studies using daily handheld spirometry have been performed in patients with IPF (2, 3). These studies showed that home spirometry in IPF is feasible, may allow for better disease prediction and decrease sample size for future trials (2, 3). However, earlier studies using home spirometry in interstitial lung diseases used paper-based collection or central read-out of Forced Vital Capacity (FVC) results (2-4). This limits possibilities to control quality of measurements, or respond directly to FVC decline or non-adherence.

We assessed feasibility of a pre-developed home monitoring program in IPF (5), integrated with real-time, wireless home spirometry. Furthermore, we evaluated potential barriers and solutions for implementation of wireless home spirometry in this mostly elderly patient population.

METHODS

This was a prospective pilot study at the Erasmus Medical Center in 2017. Consecutive outpatients with IPF were invited to participate. Approval of the Medical ethics committee was obtained, and participants provided written informed consent. Patients were asked to test the home monitoring program "IPF-online" (www.ipfonline.nl) for four weeks on a tablet. IPF-online is a secured online personal platform, following European safety regulations. The program consists of daily home spirometry, online patient-reported outcomes (PROs) at baseline and after four weeks, weekly reporting of side-effects and symptoms on visual analogue scales, an information library, medication coach and eConsultations. The bluetooth-enabled spirometer (MIR Spirobank Smart, Italy) transmits data real-time via a secure encrypted connection, enabling patients and healthcare providers to access data directly **(Figure 1)**. The system generates email alerts when patients report bothersome side-effects or FVC declines >10% for three consecutive days. If patients fail to perform spirometry or record symptoms, they receive a reminder. Incorporated PROMs are King's Brief Interstitial Lung Disease health status questionnaire, Hospital Anxiety and Depression Scale, Euroqol 5D-5L and an evaluation questionnaire (6-8). At start, patients received standardized instructions about the correct use of home spirometry and the different components of the online tool. Patients

were considered trained when they were able to perform three good, reproducible FVC measurements, with less than 150 ml difference in the two highest FVCs. Before start of the study, potential barriers of the system were identified based on literature and own experiences. At baseline, potential barriers were discussed with patients. After four weeks, their experiences and suggestions were evaluated. Furthermore, patients performed hospital spirometry at baseline and after four weeks. Pearson correlation and Bland-Altman plots were used to compare home with hospital spirometry, Wilcoxon signed ranked test was used to compare baseline with follow-up scores. Data are presented as mean (SD) or median (range).

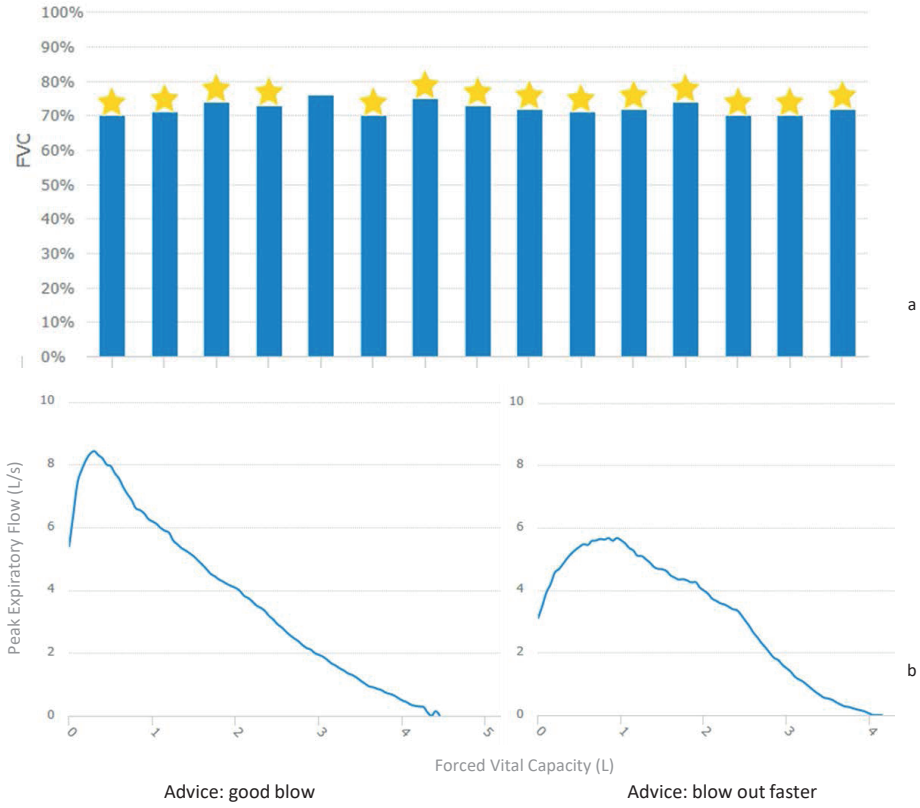

Figure 1. a) Daily FVC in % predicted of one patient during two weeks. A star on top of the bar corresponds with a forced expiration > 6 seconds, and is intended as extra motivation for patients.
b) Two examples of flow volume loops including daily remarks/advices.

RESULTS

Of 12 patients invited to participate, 10 patients were included (9 men), with a mean age of 71 years (5). All patients were on disease-modifying medication (60% nintedanib, 40% pirfenidone). The mean FVC was 3.28L (1.04) or 79% of predicted (16).

Reliability of home spirometry

Measurements of home and hospital spirometry for FVC (r=0.94 (p<0.001)) and FEV1 (r=0.97 (p<0.001)) were highly correlated, and a Bland-Altman plot showed good agreement (**Figure 2**). Median difference between hospital and home spirometry was 0.22L (0.01-0.69L) with overall lower readings for home spirometry. To evaluate within-subject reproducibility, the median SD for 28 measurements was calculated (0.13L (0.05 -0.39L)). The median coefficient of variation was 3.76% (3-12%).

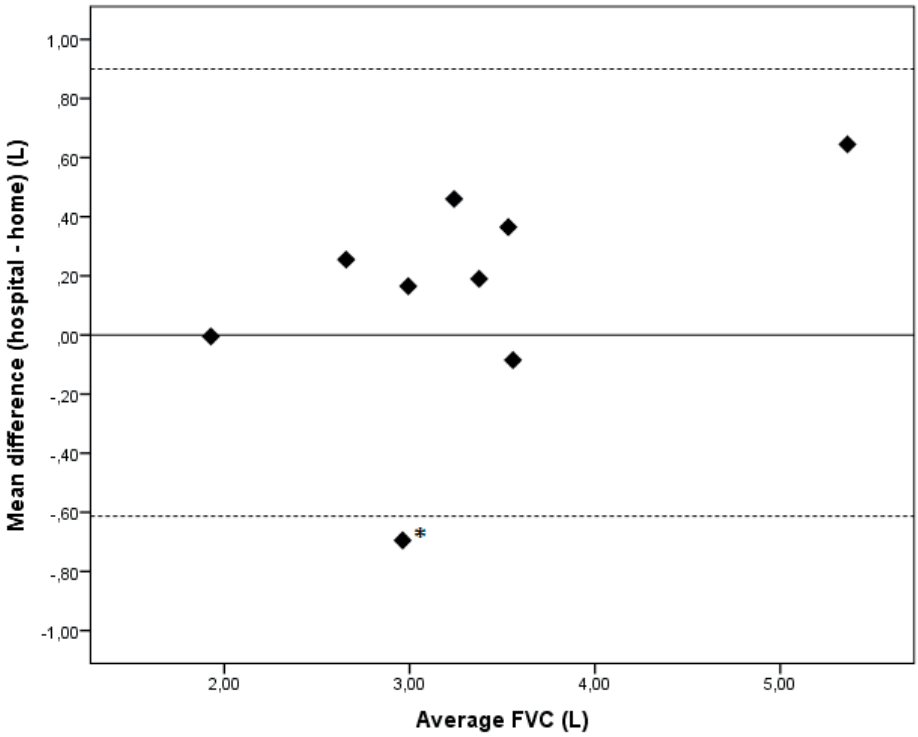

Figure 2: Bland-Altman plot comparing hospital and home spirometry . The value for hospital FVC is the mean of the hospital-based FVC at baseline and after four weeks. The value for home spirometry is the mean of 28 home FVC readings. The solid line represents the mean difference and the dashed lines 95% limits of agreement (-0.61 to 0.90L). Data of 9 patients shown, as hospital-based FVC at 4 weeks was missing in 1 patient.* This patient did not use the mouthpiece correctly leading to more variable and higher readings compared to hospital spirometry.

Feasibility and potential barriers of home spirometry in patients with IPF

The vast majority of patients considered daily spirometry easy (80%) and not burdensome at all (90%), the other patients were neutral. The mean adherence to home spirometry was 98.8% (SD 2.5). Most patients (80%) found it pleasant to see their FVC results, 20% was neutral. All patients considered real-time spirometry useful and would recommend it to others, 90% wished to continue home monitoring after the pilot: "It helps me feel more in control", "I like to monitor my own disease and be monitored" and "I hope this program can replace outpatient clinic visits in the future". Daily home monitoring did not lead to higher anxiety levels (HADS anxiety score at baseline 4.5, score after 4 weeks 4.3, p=0.57), and quality of life remained stable (K-BILD total score at baseline 59.2, score after 4 weeks 60.3, p=0.65). **Table 1** provides a comprehensive overview of potential barriers, experiences and solutions for use of the home monitoring system.

DISCUSSION

This pilot study shows that a home monitoring program integrated with real-time wireless home spirometry is feasible in patients with IPF. In line with other studies, home-based measurements were slightly lower than hospital-based FVC, which may partly be equipment-related, but also effort-related (2, 4). We tried to minimize the risk for 'underperforming' at home by motivating patients through graphically displaying their personal target value and prior results, a six seconds countdown and advices to technically improve the measurements. However, home and hospital readings are highly correlated and the relative variability of home-based FVC is low, indicating that home spirometry is a reliable tool to monitor patients at a distance. In a patient population with progressive breathlessness and decreasing mobility this enables close monitoring, while lowering the burden of hospital visits, especially in countries with long distances to the hospital. Moreover, real-time uploading of results and automated email alerts not only allow quality review of measurements, it also enables real-time detection of FVC decline. For example, we already observed a decrease in FVC two days before a patient reported symptoms of a respiratory tract infection. Early detection may potentially improve efficiency and quality of care for patients. Besides spirometry, patients also recorded symptoms and validated questionnaires online, which could be important additional features for future studies.

All patients in our study supported the usefulness of home monitoring, and appreciated being actively involved in monitoring their disease. One patient experienced technical problems with spirometry, highlighting the importance of good instruction. No effects on anxiety or quality of life were observed, however, we believe that the duration of

Table 1. A comprehensive overview of the identified potential barriers for use of the home monitoring system (wireless and real-time), experiences from the pilot study, and possible solutions as suggested by patients and staff.

Potential barriers for the use of real-time home spirometry	Findings in our pilot experiment	Possible solutions
No internet access	Patient who never used internet before had no problems using the tablet and perform spirometry because of the simple design.	- Provide patients with a smartphone or tablet with 4G SIM card during study to guarantee internet access - Use a simple application without too much information
Quality of measurements is difficult to control	All patients performed mostly good quality flow volume loops, which could be checked real-time.	- New wireless spirometers have automated quality control and provide advice to patients - Use a device that shows a flow volume loop accessible to patient and researchers to review quality
A handheld spirometer may be difficult to use	A few patients had to get used to handheld spirometry the first days. Only one patient had variable results, due to technical difficulties with the standard mouthpiece. After providing an additional mouthpiece the readings were comparable to hospital readings.	- Provide a clear instruction manual and good training at start of the study. Patients should be able to perform 3 good quality measurements with ≤ 150 ml difference in the 2 highest FVCs. - Assess individual patients' needs - Consider using an extra/other mouthpiece - Use a video consultation or clinic visit for refreshment training
Motivation	A 6 seconds countdown and FVC target value is always shown during a forced expiration. This motivated patients to blow as good and long as possible.	- Do not use an FVC of 100% predicted as target value as this might demotivate patients - Provide an individual target value for each patient and adjust target value during study if necessary
Home spirometry might induce coughing	Some patients mentioned more urge to cough compared to hospital spirometry, but one measurement a day was not a problem.	- Advise patients to perform spirometry after a period of rest - Advise patients to try again later that day when a measurement failed because of coughing
Patients might get worried seeing their own results	Anxiety and depression scores were not higher after this short pilot. Almost all patients considered it pleasant to see their daily results.	- Incorporate automated email alerts to the researchers and explain to patients that they will be contacted if FVC declines significantly - Provide an extra option that blinds patients from their results
Daily home spirometry can be bothersome to patients	None of the patients in the pilot considered once daily spirometry bothersome, because it was not time consuming and became part of their routine.	- Advise patients to perform spirometry at almost the same time every day to create a routine - Explain that the whole process takes less than two minutes
Compliance	Patients got motivated by keeping track of their own results and almost all patients continued home spirometry after the pilot.	- Send patients email reminders when they do not perform spirometry or report their symptoms

the study is too short to draw definite conclusions on this. We found no major barriers regarding use of real-time wireless home spirometry; relatively easy solutions were suggested by patients and investigators for potential issues.

A limitation of this study is that it is a single center study, with 10 out of 12 consecutive patients willing to participate. In the Netherlands, use of internet amongst elderly people is rather high, however, also in other countries internet use among people over the age of 65 is steadily growing (9). With worldwide increasing internet use and technological advances, we envision that relatively simple and low-cost systems like this, will facilitate access to care and research for a wider group of patients, also in remote areas and lower socio-economic settings. Further limitations of this pilot are the small sample size and short duration. Although this was sufficient to evaluate reliability and potential barriers of a home monitoring program with real-time wireless home spirometry, larger studies are required to assess whether it improves care, allows for earlier detection of exacerbations, and enhances data collection in clinical trials.

CONCLUSION

A home monitoring program including wireless home spirometry, is highly feasible and appreciated by patients with IPF, and enables real-time detection of change in FVC and PROs facilitating personalized care.

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Chapter 10

Feasibility of a comprehensive home monitoring program for sarcoidosis

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ABSTRACT

Sarcoidosis is a chronic, heterogeneous disease which most commonly affects the lungs. Currently, evidence-based and individually-tailored treatment options in sarcoidosis are lacking. We aimed to evaluate patient experiences with a home monitoring program for sarcoidosis and assess whether home monitoring is a feasible tool to enhance personalized treatment. Outpatients with pulmonary sarcoidosis tested the home monitoring program "Sarconline" for one month. This is a secured personal platform which consists of online patient-reported outcomes, real-time wireless home spirometry, an activity tracker, information library and eContact option. Patients wore an activity tracker, performed daily home spirometry, and completed patient-reported outcomes at baseline and after one month. Patient experiences were evaluated during a phone interview. Ten patients were included in the study. Experiences with the home monitoring program were positive; 90% of patients considered the application easy to use, none of the patients found daily measurements burdensome and all patients wished to continue the home monitoring program after the study. Mean adherence to daily spirometry and activity tracking was respectively 94.6% and 91.3%. In conclusion, a comprehensive home monitoring program for sarcoidosis is feasible and can be used in future research and clinical practice.

Keywords

Lung; sarcoidosis; eHealth; home monitoring; wearable devices; feasibility; patient experiences

INTRODUCTION

Sarcoidosis is a chronic, granulomatous disorder of unknown etiology with a heterogeneous presentation and disease course. This multisystem disease can be localized in almost any organ, but most commonly affects the lungs and lymphatic system (1). Symptoms as dyspnea, persistent cough, fatigue and physical limitations negatively affect quality of life (QOL) of patients and often lead to stress, and even anxiety, depression and social isolation (2-4). Oral corticosteroids are the mainstay of treatment for patients with significant symptoms or impaired organ function. However, there is a lack of evidence-based treatment regimens for sarcoidosis, and little data is available regarding long-term effects, optimal duration and dosage of medication (1, 5). In practice this may result in under and over treatment, with often unnecessary side-effects. In approximately 70% of patients, sarcoidosis resolves spontaneously or after treatment; in about one third of patients, sarcoidosis becomes chronic and progressive (1).

Recently, much research effort has been put into new 'omic' techniques and the identification of biomarkers to predict disease progression in sarcoidosis, to determine who is likely to have spontaneous resolution, who should be treated, and who will respond to therapy. However, there is still a long way to go before this could possibly be used to enable personalized treatment (6, 7). Personalized medicine should not only take these biological factors into account, but also patient factors, such as preferences, lifestyle, comorbidities and response to treatment (8, 9). New eHealth technologies could play an important role in facilitating personalized care, by frequent monitoring of lung function, activity, symptoms, side-effects and QOL at home at a low burden for patients (10-12). In that way not only more insights are gained in disease course, but therapies can also be better tailored. In an interactive survey on needs and preferences in sarcoidosis, the majority of patients supported the idea of managing their personal health-related data online. Almost all patients reported that they would be willing to measure lung function at home to enhance personalized treatment (13).

An observational study showed that home spirometry was feasible and allowed for early detection of steroid treatment effects in sarcoidosis (14). However, patients recorded their lung function and symptoms in a paper diary, which makes it impossible to respond directly to changes in lung function or symptoms. Recently, we have developed a home monitoring program together with idiopathic pulmonary fibrosis (IPF) patients, including real-time wireless home spirometry and online recording of symptoms and side-effects (15). Development of eHealth tools in close collaboration with patients may result in better outcomes, because the final 'product' will be customized to patients' needs and wishes (11, 16). We have adapted this home monitoring program for sarcoid-

osis. In the current study, we aimed to evaluate patient satisfaction and feasibility of this home monitoring program, and assess its possible role for future clinical trials and daily practice (**Figure 1**).

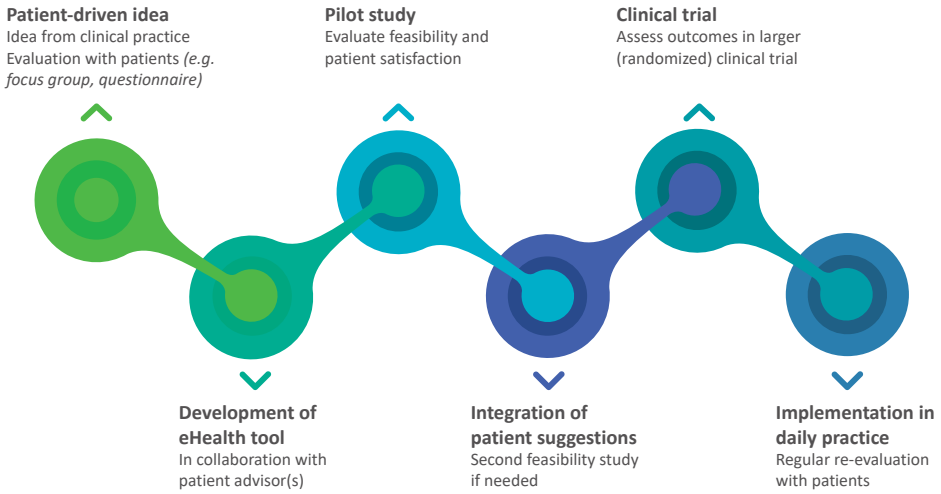

Figure 1. Framework for development of eHealth tools in close collaboration with patients. The current project falls within the pilot study phase.

MATERIALS AND METHODS

Study design and population

This was a prospective observational study at the pulmonary department of the Erasmus Medical Center, Rotterdam, the Netherlands, a tertiary referral center for sarcoidosis. Consecutive outpatients with sarcoidosis were recruited prospectively at the outpatient clinic. Inclusion criteria were a diagnosis of sarcoidosis according to the ATS/ERS/WASOG criteria with pulmonary involvement, and age above 18 years (1). Patients were excluded if they were not able to speak, write and read in Dutch, had no internet access at home, or no compatible smartphone/tablet. This study was approved by the local ethics committee (MEC-2018-1536). All patients gave online informed consent.

Study procedures

Patients were invited to test the home monitoring program Sarconline (www.sarconline.nl) for one month. The test period consisted of daily home spirometry, activity tracking and recording of symptoms and patient-reported outcomes (PROMs) at baseline and after one month. After one month, the test period was evaluated with patients during a phone interview.

Home monitoring program

Sarconline is an online eHealth application developed for patients with sarcoidosis (Curavista, the Netherlands). It consists of a secured personal platform, in which patients can keep track of their own health-related data, such as pulmonary function tests, activity, quality of life questionnaires, symptoms and medication (**Figure 2**). Patients directly see a graphical overview of their data. There is a possibility to communicate with the healthcare team by using the email functionality (eContact). Sarconline also contains news and information about sarcoidosis and links to useful websites. The patient is owner of the data and determines which healthcare providers can access his or her data. Data is stored on a secured and approved datacenter with ISO27001 certification, following European safety legislations.

Figure 2. Overview of home monitoring program Sarconline with different components

Home spirometry

Patients received a Bluetooth-enabled handheld spirometer (MIR, Spirobank Smart, Italy) to measure pulmonary function at home. This spirometer measures forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF). Patients were requested to send their daily results directly to Sarconline via a secured encrypted connection, using a five-digit personal code. If FVC declines for three consecutive days (relative decline ≥10%) an automated email alert is sent to the research team. At baseline, patients were trained on how to use the home monitoring program, including the handheld spirometer, for approximately 20 minutes. Patients were considered adequately trained if they could perform three measurements with less than 150 ml difference in the two best FVCs, and difference with hospital-based spirometry was less than 10 percent.

Activity tracking

Steps per day, activity level and calories were measured with a Bluetooth-enabled wrist-worn activity tracker (Fitbit Flex 2, FitBit, Inc., San Francisco, USA). Patients were instructed to wear the activity tracker at daytime. Patients who wished to track their sleep, could also wear the activity tracker at night time. The Fitbit activity tracker has incorporated behavior change techniques for activity and sleep, intended to stimulate long-term behavior change (i.e. goal-setting, alerts and rewards) (17). Activity tracker data were imported in Sarconline.

Patient-reported outcome measures (PROMs)

Patients were asked to complete a number of quality of life-related questionnaires and symptom scores at baseline and after one month. The King's Sarcoidosis Questionnaire (KSQ) assesses health status in patients with sarcoidosis. It comprises 29 items in 5 sub-domains: general health status, lung, medication, skin and eyes (18). The Euroqol-5D-5L (EQ5D-5L) comprises five questions on the domains mobility, self-care, daily activities, pain and mood, and a Visual Analogue Scale on general health-status (19). The Hospital Anxiety and Depression Scale (HADS) comprises a 7-item depression scale and a 7-item anxiety scale. The scores range from 0-21 for either anxiety or depression. The cut-off point of 8/21 is identified for either anxiety or depression (20). The fatigue assessment scale (FAS) is a 10-item self-administered questionnaire about fatigue in patients with sarcoidosis. The score ranges from 5-50 points, with a score of ≥ 22 points as cut-off for fatigue (21). Patients were asked to complete weekly visual analogue scales (VAS) on fatigue, dyspnea, cough and general wellbeing, with scores ranging from 0-10.

Phone interview

During a phone interview, patients were questioned about their opinion towards the home monitoring program. Satisfaction, feasibility of the program, and ease of use of the application and different devices were evaluated with patients. Furthermore, patients were asked whether they encountered (technical) problems, wished to continue home monitoring after the pilot and had any suggestions or advices to improve the system.

Statistical analysis

Data are presented as median (range) or mean (SD). Adherence to home spirometry and activity tracking was assessed by dividing the total number of measurements by the total number of days, and expressed in percentage (%). Correlations between lung function (hospital and home), activity level and symptoms were analyzed with Pearson's correlation coefficients. Differences between results of patient-reported outcomes at baseline and after one month were evaluated with the Wilcoxon signed rank test. Patient experiences, satisfaction and use of the home monitoring program are qualitatively described. Statistical analyses were performed with SPSS version 24. A p-value <0.05 is considered statistically significant. Because this was a pilot study, no formal power calculation could be performed. We aimed to include ten patients, based on a previous pilot study in IPF (15).

RESULTS

Of 11 consecutive outpatients invited to participate, ten patients with a broad range in age, time since diagnosis and disease severity were enrolled for this study. One patient was excluded because she did not bring a compatible smartphone. Baseline characteristics of patients are described in **table 1**.

Home-based assessments

All patients managed to complete online PROMs, perform daily home spirometry and track their activity at home. Mean adherence to daily spirometry was 94.6% (SD 9). Home spirometry measurements highly correlated with in-hospital measurements of FVC ($r=0.97$, $p<0.001$) and FEV1 ($r=0.96$, $p<0.001$). One subject with severe airflow obstruction (FEV1/FVC of 27%) had consistently much lower home FVC results compared with hospital FVC (difference 0.65 L or 18%). When leaving this subject out, median difference between hospital and home spirometry was 0.26L (0.08-0.55L) with overall lower readings for home spirometry in 78% of patients. Within-subject reproducibility was assessed; median SD of 28 FVC measurements was 0.17L (0.09-0.38L) and the median coefficient of variation was 5.78% (2-8%).

Table 1. Baseline characteristics of study patients (n=10)

Age	53 (31-68)
Women	4 (40)
Ethnicity	
Caucasian	9 (90)
Surinamese Hindi	1 (10)
Time since diagnosis, y	5 (0-15)
Multi-organ involvement	6 (60)
BMI, kg/m^2	27 (19-35)
Medication	
Prednisolone	9 (90)
Methotrexate	6 (60)
Other	3 (30)
Lung function	
FVC % predicted	86 (69-105)
FVC (L)	3.50 (2.53-6.47)
FEV1 % predicted	81 (25-97)
FEV1 (L)	2.60 (0.96-3.68)
FEV1/FVC (%)	72 (27-89)
DLCO (%)	74 (44-96)

Data are presented as median (range) or n (%). BMI = Body Mass Index, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusion capacity of the lung for carbon monoxide

Results of PROMs, lung function and activity are summarized in **table 2.** In one patient, daily activity could not be analyzed because there were technical difficulties with sending the Fitbit results to the secured platform. For the other patients, mean adherence to daily activity tracking was 91.3% (SD 19); 7 patients had 100% adherence. One patient measured activity on only 43% of days, because he was not allowed to wear the wrist-worn tracker at work.

Symptoms measured by HADS, FAS and VAS, and QOL measured by KSQ and EQ5D-5L were not significantly different at baseline compared to month one. Moreover, no changes in daily step count and home-based FVC were observed during the study period. There was no correlation between lung function and mean daily step count for FVC (r=-0.38, p=0.31) and a trend toward significance for DLCO (r=0.66, p=0.08). Furthermore, no correlations were found between activity level and PROM scores, and lung function and PROM scores.

Table 2. Home-based assessment of study patients (n=10)

Daily step count	9781 (4355-17274)
Active, minutes/day	309 (146-484)
Light activity, minutes/ day	263 (124-401)
Home-based FVC (L)	3.3 (2.4-6.2)
Home-based FEV1 (L)	2.5 (0.8-3.4)
EQ5D-5L index value	0.81 (0.1-0.92)
EQ5D-5L VAS	76 (14-93)
KSQ General health	62 (36-77)
KSQ Lung	61 (37-72)
HADS anxiety	7 (2-12)
HADS depression	6 (1-11)
FAS	25 (17-37)

Data are presented as median (range). Activity and lung function data are mean results for one month, results of patient-reported outcomes are measured at baseline. EQ5D-5L = Euroqol-5D-5L, VAS = visual analogue scale, KSQ = King's sarcoidosis questionnaire, HADS = hospital anxiety and depression scale, FAS = fatigue assessment scale

Patient experiences

Overall, patient experiences of the home monitoring program were positive. Almost all patients (90%) considered the application easy to use. None of the patients considered daily spirometry, activity tracking and reporting of PROMs burdensome. All patients wished to continue the use of the home monitoring program after the test period. The vast majority of patients (90%) answered that they would we willing to measure daily lung function for a prolonged period of time to enhance individually-tailored treatment, to evaluate response to therapy, or for study purposes. One patient mentioned that it could possibly be distressing to be confronted with your disease every day; this patient would prefer home spirometry at a weekly interval. Patients responded that it was very useful for them to see a daily overview of their lung function; this gave better insights into the effects of medication and the progression of their disease (**Figure 3**). The direct feedback on the quality of the measurement was perceived as useful guidance. All patients endorsed the usefulness of activity tracking, as this stimulated them to be more active. Two patients mentioned that their activity level corresponded better with their overall functioning than lung function alone. All patients used the Fitbit to track sleep; 70% of patients found that this provided good insights in their fatigue and sleep patterns.

At baseline, patients were asked to fill in their personal goal for the upcoming period and their plan to reach this goal. Five patients wished to improve their dyspnea, four patients fatigue and one patient general wellbeing. A few examples of how patients

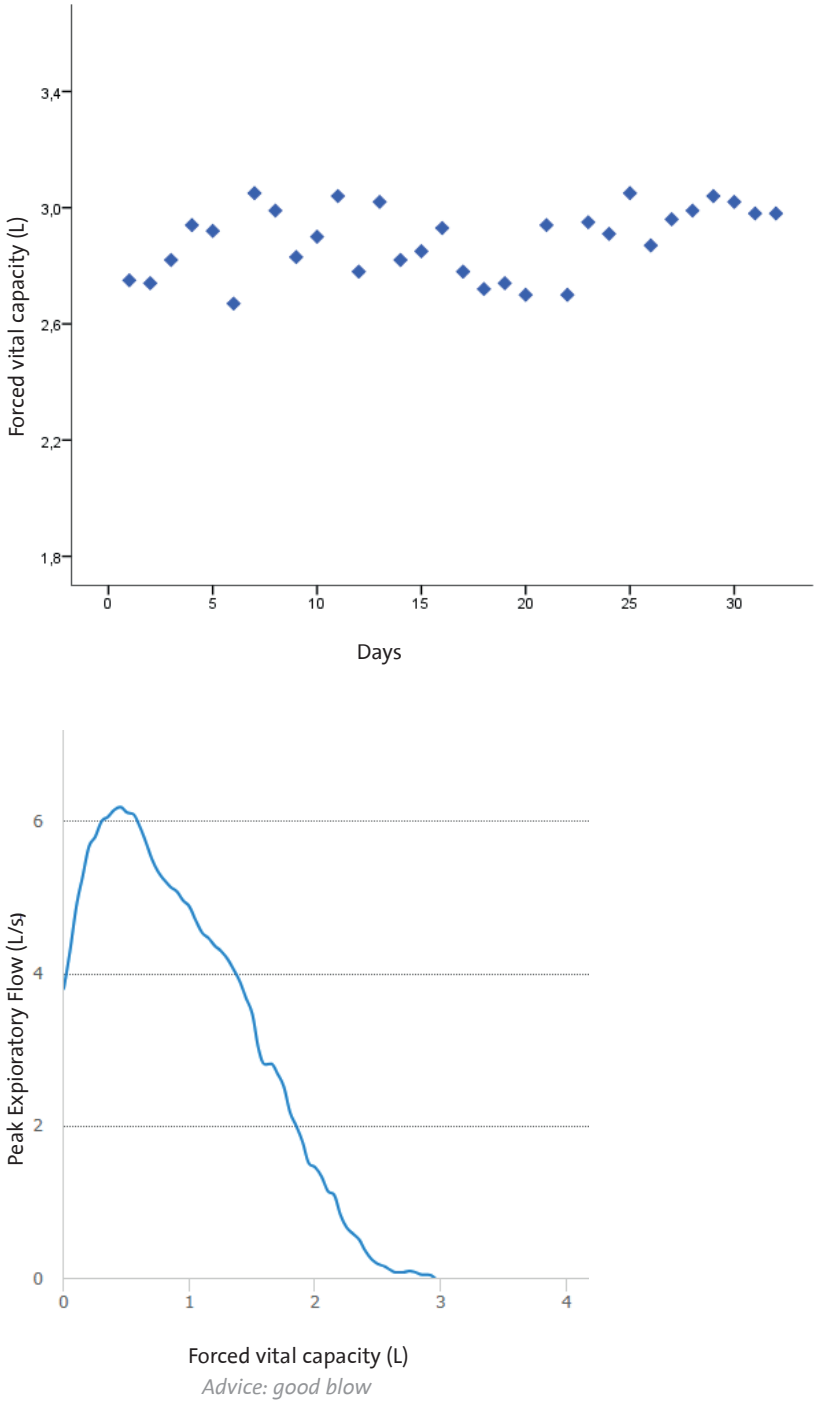

Figure 3. Measurements of FVC of an individual patient during one month, including one example of a flow volume loop

planned to reach these goals were to sport once a week, live a more regular life and good adherence to medication. In the home monitoring program, patients could track their personal goal over time. One patient mentioned that this was an extra incentive to change her behavior. Most patients believed that establishing a personal goal cabe of added value, especially when treatment is changed, or when symptoms get worse.

During the test period, 50% of patients used the eContact option; 16 eConsultations were sent in total. Patients appreciated the short lines of communication: "if I have a problem and send a message, I get a really quick response". Patients provided various suggestions for improvement and feedback on what they felt was missing in the home monitoring program. More disease-specific information and information about lung function was desired by three patients. Some patients would like more wearable devices integrated in the app; four patients mentioned that it could be interesting to measure oxygen saturation at home and two patients would like to monitor their heartrate more closely. Some minor technical problems occurred during the test period, such as problems with sending activity results via the app, difficulties with completing a questionnaire, and a bad Bluetooth connection between spirometer and app. A selection of more detailed patient quotes from the evaluation interviews is given in **table 3**.

DISCUSSION

To our knowledge, this is the first study evaluating feasibility and patient experiences with a comprehensive online home monitoring program for sarcoidosis. Patient satisfaction and adherence to daily spirometry and activity tracking were high. All patients wished to continue the use of the home monitoring program after the study. Only a small number of technical problems occurred, and patients had useful suggestions for improvement of the system. These suggestions, such as the possibility to report side-effects, explanation about lung function testing and adjustable reminders, will be implemented in the program. The high patient satisfaction and compliance with home-based assessments is in line with pilot studies on home monitoring in other chronic diseases (15, 22-25). Previous studies also showed that evaluation with patients yields valuable insights in how to enhance personalized medicine through eHealth solutions, with key elements described in **table 4** (11, 15, 16, 22-24).

Other studies using home spirometry in sarcoidosis and pulmonary fibrosis showed comparable results regarding correlation with hospital FVC, reproducibility and overall lower results for home spirometry (14, 15, 26). The current study showed a slightly higher variability between daily FVC measurements, possibly because patients measured

Table 3. Selection of patient quotes from the evaluation interview

" It is very difficult to tell exactly how you felt four weeks ago. By completing the questionnaires, my personal goal, and symptoms on a regularly basis, I get a better overview of my disease over time."
"I think this app gives much more details about my health than the regular outpatient clinic visit every three months. This information could also be very helpful for my doctor and nurses."
"For me, the app contains enough information and devices at the moment. Otherwise I might become too much focused on my disease."
"I use inhaled medication; this had a direct positive effect on my lung function. I appreciated it very much that I was able see this directly at home. Now I really know why I have to use it."
"I have quite some side-effects from my medication. It would appreciate if I also could monitor my side-effects in the app."
"It is a reassuring idea that the healthcare team monitors you at a distance, and that they directly see it if your lung function declines."
"Reminders on my email to perform my measurements would be very helpful for me, otherwise I forget it sometimes. But I understand that other patients probably won't need those reminders."
"When I did not reach my step goal at the end of the day, I went outside to walk around some more. Seeing my activity worked very motivating."
"Sometimes, it was frustrating to see my step count, especially on the days that I was very tired and not feeling well. I wished I could walk more, but on some days that was just not possible."
"Everything together, the questionnaires, overview of symptoms, lung function and activity gave a good total picture of my health."
"It would be helpful to receive some more information or education about lung function. What do the different tests measure exactly and how should I interpret the results? Maybe it is an idea to make an information movie about this. For me, that is easier to understand than text."
"My sarcoidosis is very stable at the moment. I think home monitoring would be more useful if your disease is getting worse, or if you start with new medication."
"I have had some technical difficulties with the connection between spirometer and the app, but when I called the helpdesk, they could help me out."
"If possible, I would also like to track my heart rate. If I don't feel good, my heart rate goes up very fast. I think this would give extra information about my physical condition."

Table 4. Key factors for integrating personalized care in eHealth

Application customized to patient' needs and wishes
Low threshold communication (e.g. eContact or video contact)
Patient education
Real-time availability of data for patients and healthcare providers
Adjustable email reminders for patients and healthcare providers
Integration of personal goal
Low burden for patients and healthcare providers

their lung function at different times during the day. Besides, the patients who used inhaled bronchodilators not always performed spirometry consequently before or after their medication. Hence, patients should be instructed to perform home spirometry at the same time every day, also taking into account medication use. Whether home measurements of FVC are reliable in patients with severe airflow obstruction and low exhaled flow, should be studied further. It could be speculated that equipment-related factors can play a role in these patients, as the turbine flow sensors of home spirometers are probably less capable in detecting very low flow rates. Patients considered home monitoring easy and not burdensome at all, which are promising results for future applications. Real-time home spirometry in sarcoidosis can potentially be used in upcoming clinical trials evaluating the efficacy of (new) sarcoidosis treatments. If future and larger studies also show positive experiences with the use of a home spirometer, this could pave the way for use in clinical care. Home spirometry could be an attractive method to evaluate pulmonary improvement after starting or switching treatment, allowing for early tapering of medication in individual patients and facilitating timely detection of disease deterioration.

A few observational studies evaluated activity levels in patients with sarcoidosis using an activity tracker for a short period of time (5-7 days) (27-29). The current study shows that sarcoidosis patients find it feasible and not burdensome to collect activity data for a sustained period. The range in daily step count in previous studies in sarcoidosis was between 4566 and 7490 steps. Daily step count in our study was somewhat higher; patients walked on average 9780 steps per day over a one-month period. This could be partly due to differences in sarcoidosis severity, as one previous study only included patients with chronic stage IV sarcoidosis (28). Moreover, patients in our study mentioned that they were more motivated to walk because of the activity tracker. In contrast to previous studies in sarcoidosis, the activity tracker used in the current study is connected to a mobile application, with integrated reminders and alerts to stimulate activity. A recent survey amongst users of activity trackers showed that wearing an activity tracker increases activity levels for a prolonged period of time (30). Studies concerning physical activity and rehabilitation in sarcoidosis are scarce, nonetheless, current evidence suggests that increased physical activity leads to better health outcomes (31). Thus, activity trackers with incorporated behavior change techniques could potentially be of added value in future interventional studies in sarcoidosis to enhance physical activity, as part of a comprehensive home monitoring or rehabilitation program. For this purpose, integration of other data, such as heart rate measurements, should also be studied in sarcoidosis patients.

The main limitation of this study is the inclusion of a limited number of patients from one tertiary referral center. Nevertheless, the number of participants was sufficient for evaluating feasibility and patient experiences with the home monitoring program. During the last evaluation interview no new information emerged, meaning that data saturation was established. Moreover, a mixed group of patients with a broad range of age, disease severity and treatment were included. The fact that all consecutive patients were willing to participate, highlights the clinical applicability of home monitoring in sarcoidosis.

In conclusion, a comprehensive home monitoring program is feasible and can be used in sarcoidosis research. Home monitoring could also be attractive for use in daily care, though studies are needed to evaluate its role and additive value. Potentially, home monitoring may enable timely recognition and response to changes in symptoms, lung function and activity. Especially in a heterogeneous disease as sarcoidosis, home monitoring may pave the way for better individually-tailored treatment, enhanced self-management and improved quality of life.

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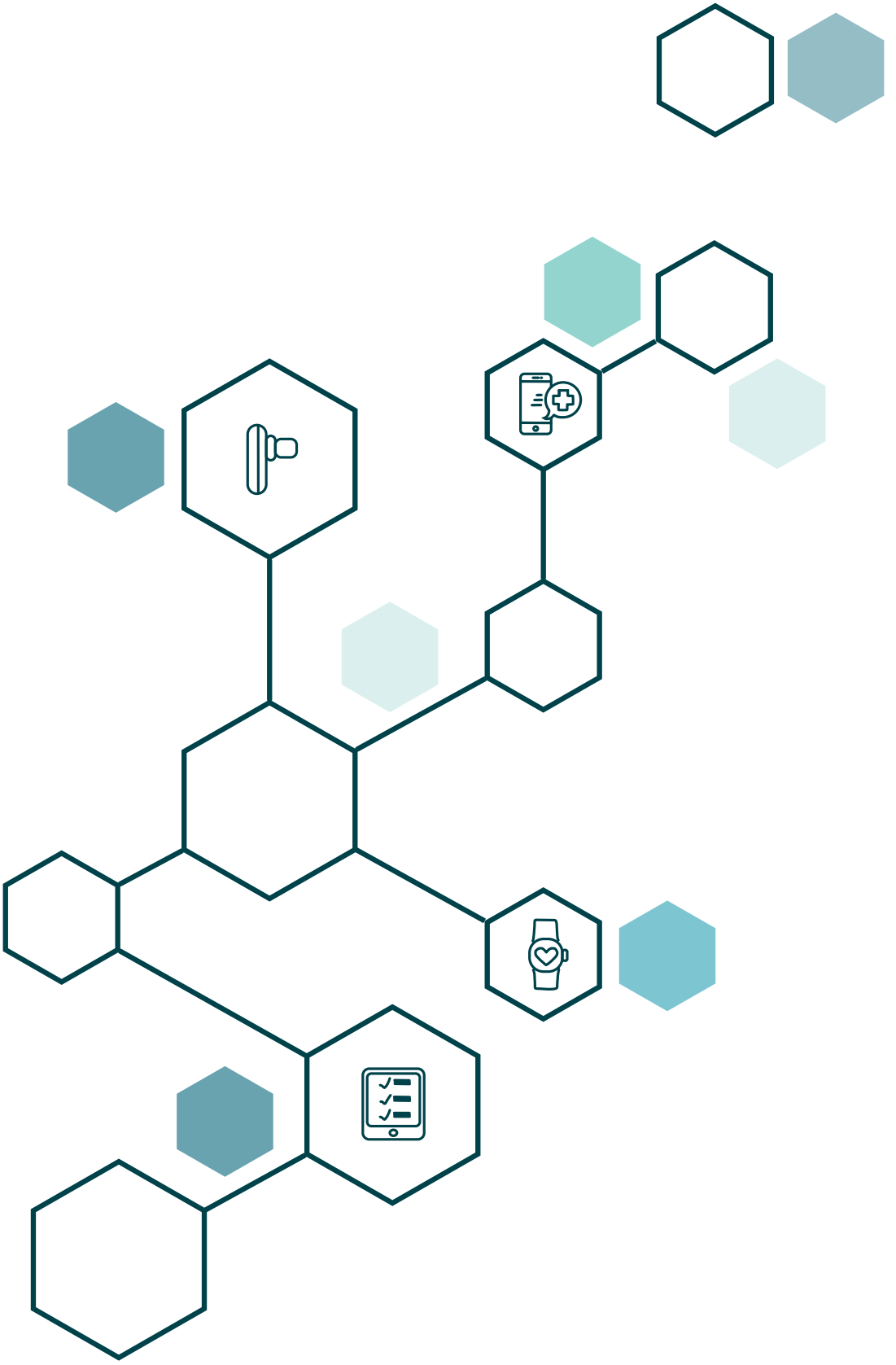

Chapter 11

Diurnal variation in forced vital capacity in patients with fibrotic interstitial lung disease using home spirometry

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INTRODUCTION

Forced vital capacity (FVC) is used as the routine physiological measure to assess disease progression in fibrotic interstitial lung diseases (f-ILDs) (1). New drugs are currently being investigated on top of "standard care" with anti-fibrotic drugs in idiopathic pulmonary fibrosis (IPF) and other f-ILD, resulting in small margins of change in FVC (2, 3). Recently, the first trial with antifibrotic medication in patients with systemic-sclerosis associated ILD has shown a numerically small but significant lower annualized rate of FVC decline (41 mL) in patients treated with nintedanib compared with placebo (3).

Data regarding a possible circadian rhythm in pulmonary function are contradictory (4-6). Diurnal variation has never been investigated in f-ILD, but could have implications for the interpretation and design of clinical trials and for monitoring in daily practice. Taking advantage of new eHealth technologies (7, 8), we aimed to assess whether there is a diurnal variation in FVC in patients with f-ILD using home spirometry. Furthermore, we evaluated whether there was a relation between FVC and activity as we hypothesized that exercise just before the measurement may affect FVC values.

METHODS

Between December 2018 and May 2019 consecutive outpatients with f-ILD were invited to participate in this prospective single center observational study for six weeks. Medical ethical committee approval was obtained and all patients provided written informed consent. Our previously developed and validated home monitoring program was used for home-based measurements (7). Patients measured FVC twice daily with a handheld spirometer (Spirobank Smart; MIR, Rome, Italy); once in the morning and once in the afternoon. FVC measurements were excluded if only one measurement was available for that day, if the morning FVC measurement was before 6 AM, or if difference from baseline FVC was >20%. In addition, steps were continuously counted using an activity tracker (Flex 2; FitBit, San Francisco, CA, USA) in blocks of 15 minutes, to assess activity during one hour before FVC measurement. At baseline and after six weeks, patients completed the King's Brief Interstitial Lung Disease questionnaire (K-BILD) online (9). In-hospital spirometry was performed at start of the study, and patients received standardized instructions about the home monitoring program. Linear mixed models were used to evaluate differences between morning and afternoon measurements. Pearson correlation coefficient was used to assess correlations between study parameters (R version 3.5.2). We estimated that between 4 and 50 patients would be needed to determine a significant difference between morning and afternoon FVC with a power of 90%, as-

suming a total variance of 0.026L and between-patient standard deviation of 0.006-0.1L, based on pilot data.

RESULTS

Of 57 invited patients, 50 patients consented to participate. Median age of patients was 68 (43-79) years and 68% were male; 50% of patients had IPF, 18% chronic hypersensitivity pneumonitis, and 12% non-specific interstitial pneumonia. Other diagnoses were combined pulmonary fibrosis and emphysema (n=4), fibrotic sarcoidosis (n=3), unclassifiable fibrosis (n=1), pleuroparenchymal fibroelastosis (n=1) and ANCA associated vasculitis with fibrosis (n=1). Median FVC was 3.0 L (range 1.5-5.2) or 76% of predicted (range 46-119), median FEV1 2.4L (range 1.4-4.0) or 82% of predicted (range 50-114), and diffusion capacity of the lung for carbon monoxide (DLCO) 50% (range 16-110). Mean±SD K-BILD total score at baseline was 57.4±11 and breathlessness and activity domain score was 45.3±18.

Home-based FVC measurements were available for 44 patients; 1 patient withdrew consent and 5 patients did not manage to perform consistent measurements due to cough or bad technique. In total, 2842 FVCs were analyzed. Activity measurements of 37 patients were analyzed; three patients did not manage to send their activity data due to technical problems. Additionally, data of patients who did not wear their activity tracker before the morning measurement were excluded.

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. In 33 out of 44 patients, morning FVC was numerically higher than afternoon FVC (**Figure 1a**). Mean±SD difference in FVC% predicted was 1.2±1.0%. Coefficient of variation was higher for afternoon FVC compared with morning FVC (5.1 vs. 4.6%, $p=0.018$). No diurnal variation was found for FEV1 (mean difference 7 ml, $p=0.35$). Home and hospital spirometry were highly correlated ($r=0.98$, $p<0.001$). Total variance in FVC was 0.021L and between-patient standard deviation 0.033L.

Median number of steps per day was 6290 (IQR: 3752-9439). Step count was lower before morning FVC compared with afternoon FVC (**Figure 1b**). Mean difference was 49 steps during 15 minutes before FVC measurement ($p=0.005$) and 219 steps during the hour before FVC measurement ($p<0.001$). Patients were relatively inactive during 15 minutes before spirometry; 87% of patients walked <250 steps. Daily step count correlated with

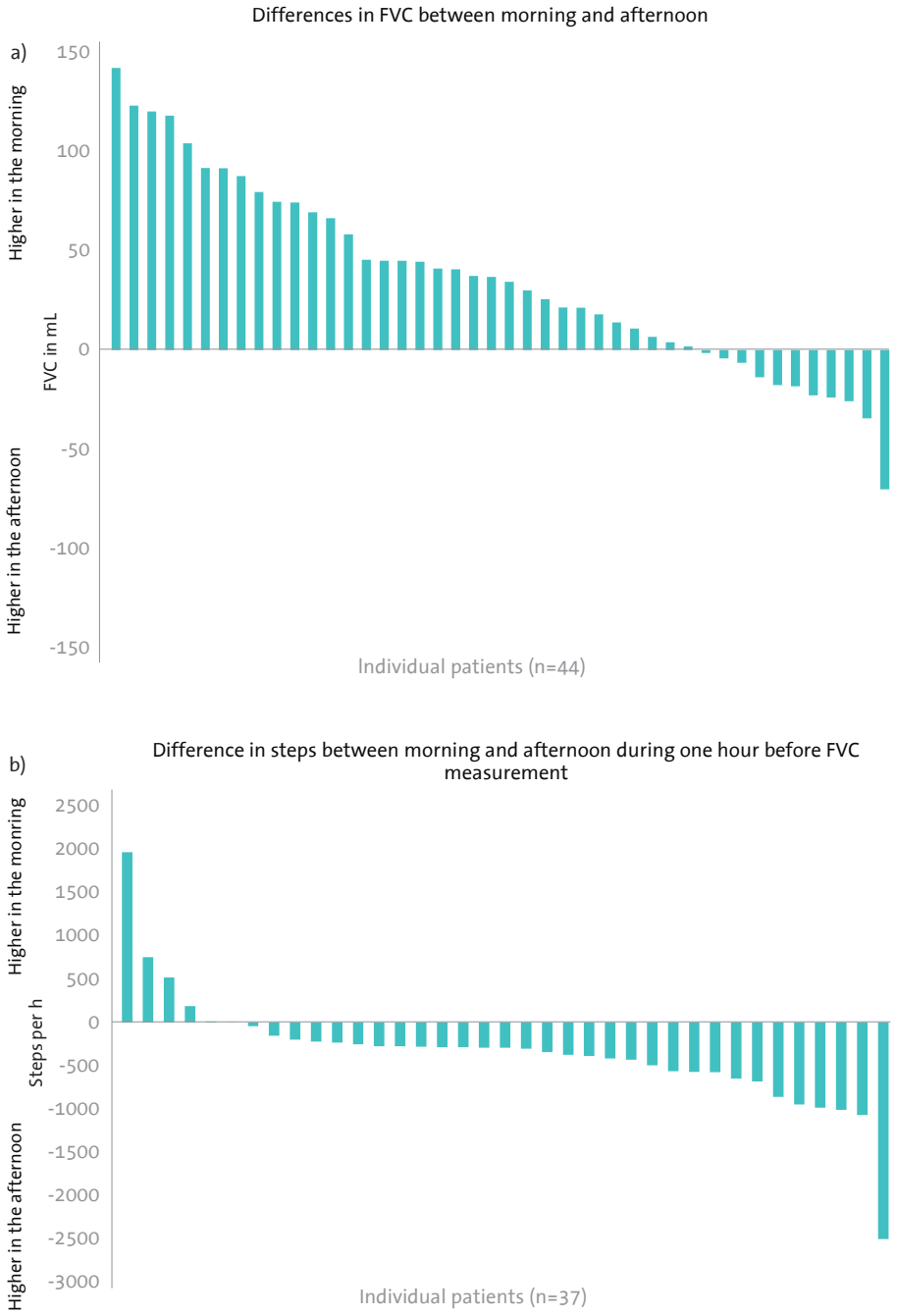

Figure 1 a) Differences in forced vital capacity (FVC) between morning and afternoon for individual patients. b) Differences in steps per hour before morning and afternoon FVC measurement.

FVC (r=0.32, p=0.028), DLCO (r=0.46, p=0.001), K-BILD total score (r=0.5, p<0.001) and K-BILD breathlessness and activities domain (r=0.6, p<0.001).

DISCUSSION

In this study, we observed a diurnal variation in FVC measured with home spirometry in patients with f-ILD, with a higher FVC in the morning than in the afternoon. In contrast, patients had a lower step count before the measurement in the morning compared to the afternoon. However, most patients were relatively inactive before both measurements, and hence activity just before measurement cannot fully explain the diurnal variation in FVC. Most patients reported that they were more tired in the afternoon and attributed differences in FVC to fatigue.

Previous studies, mainly in asthmatics or healthy subjects, suggested that diurnal variation in lung function could be due to varying airway resistance. Proposed mechanisms are a variation in plasma cortisol level, catecholamine levels, parasympathetic tone, mucociliary clearance, and activity (4-6). We did not observe a diurnal variation in FEV1 in our study, making variation in airway resistance less likely. Thus, the exact mechanism causing diurnal variation in FVC in patients with f-ILD remains to be elucidated.

Interestingly, steps per day had a stronger correlation with quality of life than with lung function, especially with the K-BILD breathlessness and activity domain. This finding suggests that activity better reflects how a patient feels and functions than pulmonary function alone. Home-based activity tracking could be a useful tool for future research, as our study showed that wearing an activity tracker for a relatively long period of time is feasible in patients with f-ILD.

A limitation of this study is that it was a single-center study, hence, these findings need validation in a larger multicenter cohort. Furthermore, some patients had technique issues leading to missing data. However, in view of the large number of recordings, we believe that the impact on study outcome is limited. Compared with a recently published study using home spirometry that reported multiple technical problems, our study had very few technical issues (10). In most previous trials with home spirometry in IPF, patients were blinded for their results. In the current study, we used an online application with direct feedback to patients and researchers, low-threshold communication with the study team and thorough instruction of patients at baseline and during the study. Hence, home-based FVC had an acceptable variability and showed reliable

results compared with hospital-based FVC. These results are encouraging for future home spirometry studies in f-ILD.

Taking into account the small margins in FVC change in current trials in IPF and other f-ILD (3), timing of spirometry should be standardized for research purposes. For daily care, we believe that differences between morning and afternoon FVC are too small to have an impact on serial changes and on treatment decisions.

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Chapter 12

Home monitoring in patients with idiopathic pulmonary fibrosis: a randomized controlled trial

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ABSTRACT

Rationale

Idiopathic pulmonary fibrosis (IPF) is a deadly disease with increasingly impaired health-related quality of life (HRQOL). eHealth technologies facilitate collection of physiological outcomes and patient reported-outcomes (PROMs) at home, but randomized controlled trials (RCTs) on the effects of eHealth are scarce. We investigated whether a home monitoring program improved HRQOL and medication use for IPF patients.

Methods

We performed a multicenter RCT in newly treated patients with IPF. Patients were randomly assigned to standard care or a home monitoring program on top of standard care for 24 weeks. The home monitoring program included home spirometry, reporting of symptoms and side-effects, PROMs, information, a medication coach and eConsultations. The primary endpoint was between-group difference in change in Kings Brief Interstitial Lung disease (K-BILD) questionnaire score at 24 weeks.

Results

90 patients were randomized (46 patients home monitoring, 44 standard care). After 24 weeks, no statistically significant difference was found in K-BILD total score, with 2.70 points increase in the home monitoring group (SD 9.5) and 0.03 points increase in the standard care group (SD 10.4); between-group difference was 2.67 points (95% confidence interval -1.85;7.17, p=0.24). Between-group difference in psychological domain score was 5.6 points (95% confidence interval -1.13;12.3, p=0.10), with an increase of 5.12 points in the home monitoring group (SD 15.8) and decline of 0.48 points in the standard care group (SD 13.3). In the home monitoring group medication was more often adjusted (1 vs 0.3 adjustments per patient, 95% confidence interval 0.2-1.3, p=0.027). Patient satisfaction with the home monitoring program was high. Home-based spirometry was highly correlated with hospital-based spirometry over time.

Conclusions

The results of this first-ever eHealth RCT in IPF showed that a comprehensive home monitoring program did not improve overall HRQOL measured with K-BILD, but tended to improve psychological wellbeing. Home monitoring was greatly appreciated by patients and allowed for individually-tailored medication adjustments.

Key words

Idiopathic pulmonary fibrosis; quality of life; eHealth; home spirometry; interstitial lung disease

Clinical trial registered on www.clinicaltrials.gov (NCT03420235)

Scientific knowledge on the subject: Previous studies on home spirometry in IPF yielded mixed results regarding reliability and adherence. However, these studies did not allow for real-time data sharing with the hospital nor with the patient, which limits quality and compliance control and the possibility to react to changes. eHealth tools have been increasingly investigated in chronic diseases, but studies in IPF are scarce. Until now, no randomized controlled trials evaluating the effect of eHealth interventions in IPF have been published.

What this study adds to the field: This is the first-ever randomized controlled trial of an eHealth intervention in IPF. A comprehensive online home monitoring program, including home spirometry, did not improve health-related quality of life in IPF, but tended to improve psychological wellbeing. Home monitoring was highly appreciated by patients and allowed for individually-tailored treatment adjustments. Moreover, home spirometry correlated well with hospital spirometry over time. Thus, home monitoring could be a reliable tool for close monitoring and follow-up of patients both for research and in daily practice.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, deadly disease resulting in an increasingly impaired health-related quality of life (HRQOL) (1). Currently, two antifibrotic drugs are available that slow down disease decline and improve survival (2-4). IPF patients are regularly followed up at the outpatient clinic with pulmonary function testing. At each visit, potential effects of antifibrotic drugs versus potential side-effects are balanced together with the patient. Furthermore, intercurrent events, such as infections or acute exacerbations, may require extra hospital visits. For an optimal, individually-tailored treatment of patients, frequent hospital visits would be desirable. However, hospital visits can be burdensome for patients because of dyspnea, extra oxygen needs and often considerable travel distances. Consequently, home monitoring could hold great benefits in this patient population.

New eHealth technologies can facilitate collection of physiological outcomes and patient reported-outcomes (PROMs) at home. Earlier studies in other lung diseases showed that eHealth interventions can improve health outcomes (5, 6). Furthermore, eHealth tools focusing on symptoms and side-effects could stimulate self-management, reduce symptom burden and enhance medication use (7, 8). To date, a few studies have investigated the feasibility of home monitoring in IPF, in particular home spirometry (9-11). These studies demonstrated that home spirometry was feasible, reliable and informative in this elderly patient population. However, none of these studies allowed for direct data sharing with the hospital.

Together with IPF patients, we have developed a home monitoring program that integrates real-time home spirometry with collection of PROMs, symptom scores, side-effects, an information library and eConsultations. Pilot studies showed that this home monitoring program was feasible and highly appreciated by patients (12, 13). We hypothesized that a comprehensive home monitoring program could optimize HRQOL for IPF patients by supporting self-management, better tailoring of medication, and allowing for low-threshold communication. To our knowledge, no randomized controlled trials evaluating the effect of eHealth interventions in IPF have been published.

The aim of the current study was to investigate whether a comprehensive home monitoring program improved HRQOL and medication use for patients with IPF. Furthermore, we aimed to assess patient satisfaction with home monitoring and compare home-based with hospital-based spirometry. Some of the results of these studies have been previously reported in the form of an abstract (ATS 2020).

METHODS

Study design and participants

This was a non-blinded, multicenter randomized controlled trial at four sites in the Netherlands. Ethics approval was obtained in the Erasmus Medical Center (MEC-2017-501) and local ethics committees. This trial was registered on www.clinicaltrials.gov (NCT03420235). All patients provided written informed consent before study entry. Eligible patients were adults (≥18 years) with a diagnosis of IPF according to the ATS/ERS/JRS/ALAT 2018 guideline, and about to start on antifibrotic treatment (nintedanib or pirfenidone)(14). Patients were excluded if they were not able to speak, read or write Dutch or if they received prior treatment for IPF.

Study procedures

Allocation of each subject was done with a centralized electronic system using varying block sizes. Participants were randomly assigned in a 1:1 ratio to a home monitoring program as add-on to standard care or standard care alone for 24 weeks. Randomization was stratified per site, and for use of nintedanib or pirfenidone.

The intervention consisted of the home monitoring program IPF-online, which includes daily home spirometry, weekly reporting of symptoms and side-effects, and PROMs at baseline, 12 and 24 weeks. The program contains information about IPF, a medication coach, and eConsultation possibility (figure S2). A flowchart about study procedures and more information about the content of the program is provided in the supplementary material (figure S1). IPF-online is a CE-marked secured personal platform, compliant with the General Data Protection Regulation (Curavista, the Netherlands). At baseline, patients received a password-protected tablet with a pre-installed application, and a Bluetooth-enabled handheld spirometer (Spirobank Smart, MIR, Italy). Standardized instructions were provided for use of the application, including home spirometry. Patients were considered adequately trained if they performed three reproducible FVC measurements, with less than 150 ml difference in the highest FVCs and <10% difference with hospital FVC. Patients were instructed to perform one spirometry each day at approximately the same time. All results were directly transferred via an encrypted connection, and were real-time available to the research team. An automated email reminder was sent to patients when spirometry was not performed for two consecutive days. Patients were able to see their own daily spirometry values, an overview of FVC over time, a flow volume loop, and a quality assessment (supplementary material, figure S3 and S4). The research team received an email alert when no FVC results were sent or FVC declined more than 10% on three consecutive days, and when patients reported bothersome side-effects. In case of a reported side-effect, a pop-up with advice to handle the side-

effect was automatically generated. A flowchart of the alert system is provided in the supplementary material (figure S5).

Standard care comprised of three-monthly outpatient clinic visits with pulmonary function testing. Participants completed PROMs online on a tablet at baseline, 12 week and 24 weeks, but did not have access to the home monitoring program (figure S1).

Outcome measures

The primary outcome measure was between group-difference in change of the King's brief interstitial lung disease health status questionnaire (K-BILD). K-BILD has been developed and validated in interstitial lung diseases and consists of 15 items in three domains: breathlessness and activities, chest symptoms, and a psychological domain (15). The minimal clinically important difference (MCID) is 3.9 points for the total score (16). A higher score represents a better HRQOL, with scores ranging from 0 to 100.

Secondary endpoints included between-group differences in Patient Experiences and Satisfaction with Medication Questionnaire (PESaM), EQ-5D-5L questionnaire, Hospital Anxiety and Depression scale (HADS), visual analogue scales (VAS) and Global Rating of Change (GRC) scores at 12 and 24 weeks, number of adjustments in medication and hospitalizations. Adjustments in medication were defined as a dose change, medication switch, or (temporarily) treatment discontinuation. The PESaM has recently been validated in IPF and assesses patient' expectations, experiences and satisfaction with antifibrotic medication (17). Expectations regarding effectiveness, side-effects and ease of use before start of treatment were recorded on a Likert scale from 0 to 4, with higher scores representing more positive expectations. Satisfaction with medication was scored on a scale from -5 (very unsatisfied) to 5 (very satisfied). Side-effects of medication were scored on a Likert scale from 1 (not bothersome at all) to 5 (very bothersome). The EQ-5D-5L is a generic instrument to assess HRQOL; a higher score corresponds with a better HRQOL. General health status is evaluated using the EQ-5D-VAS score ranging between 0 and 100, with a higher score representing a better general health status (18). The HADS is a validated questionnaire with a subscale for anxiety and depression: a score ≥8 is used as cut-off for anxiety or depressive symptoms (19). Symptoms (general wellbeing, dyspnea, fatigue, cough and urge to cough) were reported on a visual analogue scale from 0 to 10. On the GRC scale, patients indicate whether their QOL improved or deteriorated over time, on a scale from -7 to 7. In the intervention group, satisfaction with home monitoring was evaluated with a non-validated 10-item questionnaire with VAS scores from 0 to 10. Other secondary outcomes were FVC change over 24 weeks in ml, correlation between home-based FVC and hospital-based FVC over time and within-patient variability in home-based FVC.

Statistical analysis

Between-group differences in PROMs were analyzed with independent students' t-tests in the intention-to-treat population. We performed complete case analyses, as missing data were considered to be independent of the primary outcome (e.g. missing questionnaires due to technical errors). Descriptive statistics were used to evaluate study variables at baseline. FVC change in ml was analyzed using a linear mixed model accounting for within-patient correlations and allowing for random missing data. As fixed effects we used a linear slope of time (in days), and an indicator for whether the measurement was taken at home or in the hospital. Additionally, an interaction term between the indicator and time was used. For random effects, random intercepts and slopes were used. The interaction term indicates whether the slopes for home-based FVC differ from hospital-based FVC slopes. Correlation between home and hospital spirometry was analyzed with Pearson Correlation coefficient. Measurements of hospital-based FVC at all time points were compared with the mean of seven home-based FVCs from that week. Within-patient variability was evaluated with the coefficient of variation, using "detrended" data points. These were obtained by fitting a linear regression model on each patient and subtracting the residuals of each spirometry measurement. A p-value of <0.05 on a two-tailed test was considered statistically significant. Data were analyzed using R version 3.6.1 and SPSS statistics version 25.

We determined that with a sample size of 72 patients, the study would have 80% power to detect a significant between-group difference in change in total K-BILD score. The expected standard deviation of change in K-BILD score after 24 weeks was 6 points, based on a group untreated IPF patients from our own cohort (unpublished). Sample size was calculated using a MCID of 4 points (16). To allow for 20% drop-out, based on a previous home monitoring study, we aimed to include 90 patients in total (9).

RESULTS

Between January 2018 and January 2019, 90 patients were enrolled; 46 patients were assigned to the home monitoring group and 44 were assigned to standard care (**Figure 1**). Baseline characteristics of patients were evenly distributed between treatment groups (**Table 1**). The percentage of males was numerically higher in the standard care group, but the difference was not statistically significant (p=0.06). Overall mean age was 71 years (SD 6.9) and 91% were male. Mean total K-BILD score was 56.6 (SD 9.3), mean FVC was 80.1% of predicted (SD 17) and mean diffusion capacity of the lung for carbon monoxide (DLCO) was 48.2% (SD 13.5). Pirfenidone was prescribed in 57% and nintedanib in 43% of patients. In total, 38 patients in the home monitoring group (83%) and 39 patients in the standard care group (89%) completed the study.

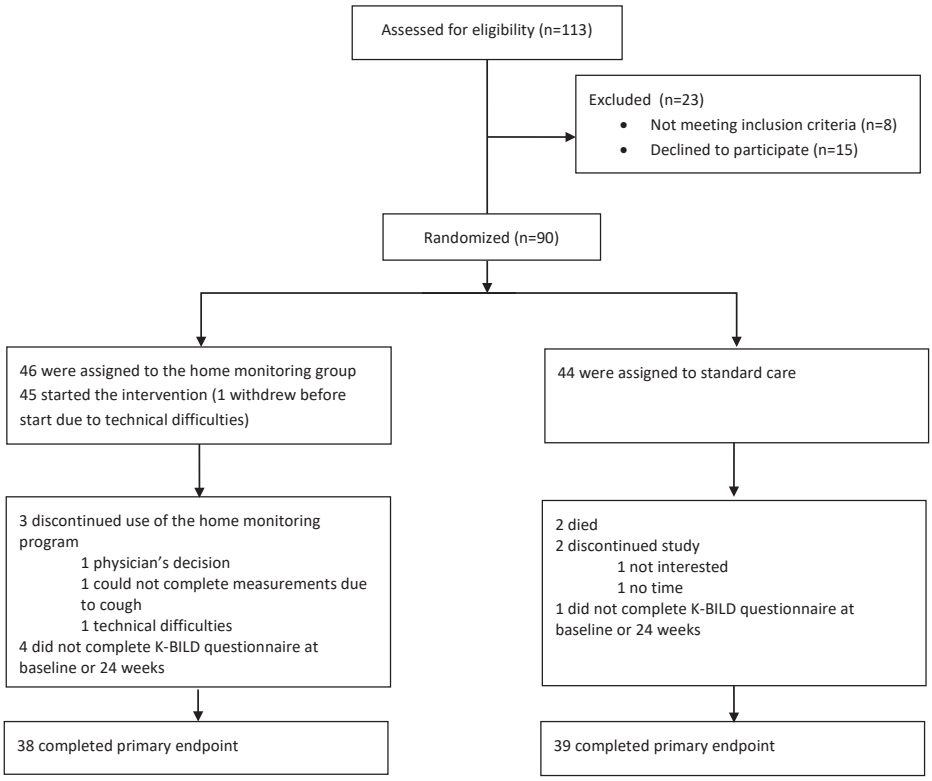

Figure 1. Flowchart of patient inclusion

Patient-reported outcomes

From baseline to 24 weeks, mean total K-BILD score improved with 2.70 points (SD 9.5) in the home monitoring group and 0.03 points (SD 10.4) in the standard care group. Between group-difference was 2.67 points (95% confidence interval (CI) -1.85;7.17, p=0.24) (**Figure 2**). Mean score of the K-BILD psychological domain increased 5.12 points (SD 15.8) in the home monitoring group and declined 0.48 points (SD 13.3) in the standard care group; between-group difference was 5.6 points (95% CI -1.13;12.3, p=0.10). The mean K-BILD breathlessness and activities domain score declined 1.8 points (SD 10.7) in the home monitoring group and 0.93 points in the standard care group (SD 12.8); between-group difference was 0.9 points (95% CI -6.3;-4.4, p=0.73). The mean score of the K-BILD chest domain increased 1.58 points in the home monitoring group (SD 13.3), and declined 2.12 points in the standard care group (SD 20.1); between-group difference was 3.7 points (95% CI -4.5;11.5, p=0.35).

Table 1. Baseline characteristics of study patients (n=90)

	Home monitoring (n=46)	Standard care (n=44)
Age, years (range)	70 (53-83)	72 (58-84)
Male sex – no. (%)	39 (85)	43 (98)
Antifibrotic medication – no. (%)		
Nintedanib	20 (44)	19 (43)
Pirfenidone	26 (57)	25 (57)
Lung function		
FVC % predicted	82 ± 17.7	78 ± 16.0
FVC (L)	3.1 ± 0.8	3.1 ± 0.7
DLCOc % predicted	48 ± 13.8	49 ± 13.0
K-BILD score		
Total	57.2 ± 10.9	56.2 ± 7.7
Breathlessness and activities	48.8 ± 19.3	41.3 ± 15
Chest symptoms	74.3 ± 18.8	73 ± 18.9
Psychological symptoms	54.4 ± 13.9	56.2 ± 11
Hospital anxiety and depression scale		
Anxiety	4.7 ± 2.5	4.6 ± 2.2
Depression	3.4 ± 3.2	3.6 ± 3.6
EuroQol-5D-5L		
Index value	0.77 ± 0.17	0.77 ± 0.17
EQ5D-VAS scale	63.1 ± 24.9	64.4 ± 21.9
VAS score symptoms		
General wellbeing	5.6 ± 0.36	5.5 ± 0.31
Cough	4.6 ± 0.45	4.7 ± 0.33
Dyspnea	4.9 ± 0.38	5.8 ± 0.34
Fatigue	4.8 ± 0.43	5.3 ± 0.38
Stability IPF	6.7 ± 0.31	6.5 ± 0.36

+- standard deviation, FVC = forced vital capacity, DLCOc = carbon monoxide diffusion capacity corrected for hemoglobin, K-BILD = King's Brief Interstitial Lung Disease questionnaire, VAS = visual analogue scale

HADS scores remained stable during the study (**Table 2**); anxiety scores (between-group difference 0.05 points, 95% CI -1.08;0.99, p=0.93) and depression scores (between-group difference 0.4 points, 95% CI -1.61;0.81, p=0.51) were similar in the home monitoring and standard care group. Changes in (HR)QOL and symptom scores did not differ between treatment groups, except for the general wellbeing score (between-group difference 1.04 points, 95% CI 0.09;2.00, p=0.032). Between-group differences in GRC and VAS for stability of disease tended towards statistical significance (**Table 2**).

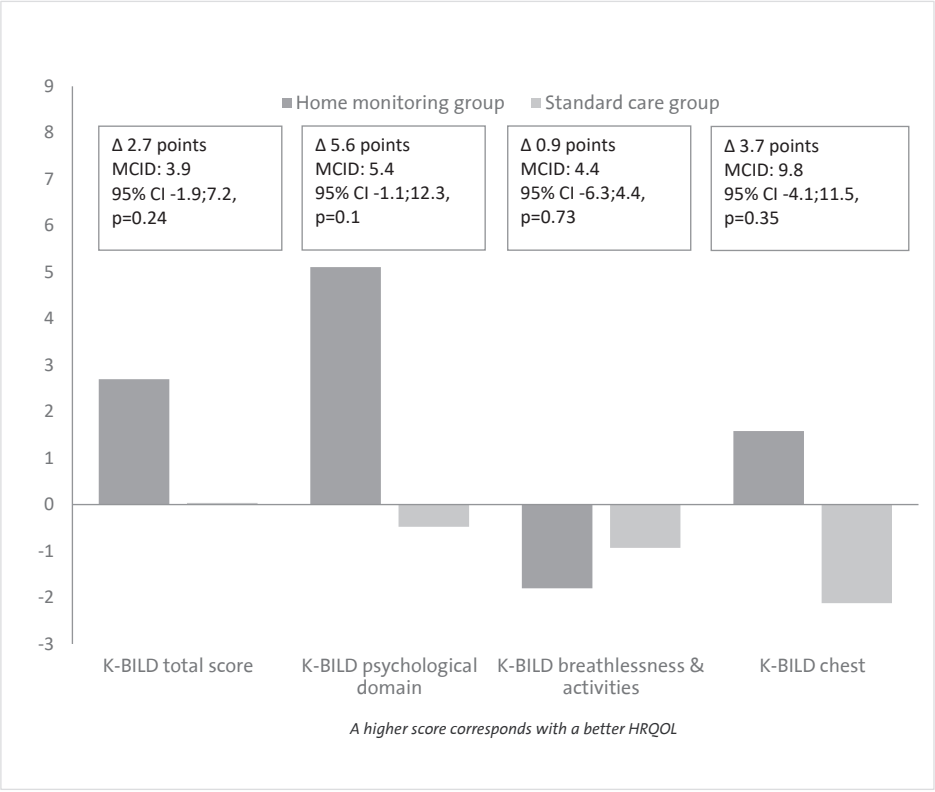

Figure 2. Change in K-BILD score from baseline to 24 weeks. K-BILD = King's Brief Interstitial Lung Disease Questionnaire, HRQOL = Health-related quality of life, MCID = minimal clinically important difference

Medication use and hospital visits

Expectations regarding effectiveness, side-effects and ease of use of antifibrotic medication before start of treatment were relatively high, and similar in both groups (**Table 3**). In the home monitoring group, medication was significantly more often adjusted during the study period (on average 1 vs 0.3 adjustments per patient, between-group difference 0.7, 95% CI 0.2;1.3, p=0.027). All adjustments in medication were due to side-effects. In general, patients were relatively satisfied with their antifibrotic medication, with a mean score of 2.06 (SD 1.89) on a scale of -5 to 5 (Table 3). Satisfaction with medication regarding efficacy, side-effects and ease of use was similar in both groups. The reported number and bothersomeness of side-effects did not differ between groups. Furthermore, the number of side-effects was not significantly correlated with patients' experiences with side-effects (r=0.27, p=0.06) and only weakly correlated with satisfaction with medication (r=0.28, p=0.02). Expectations about effectiveness (r=0.21, p=0.12), side-effects (r=0.05, p=0.79), and ease of use (r=0.09, p=0.47) were not significantly correlated with overall medication satisfaction. Ten hospitalizations occurred during the

Table 2. Secondary endpoints

	Home monitoring (n=38)	Standard care (n=39)	Difference (95% CI)	p value
Number of patients with extra hospital or GP visits	13 (31.7%)	10 (25.6%)		0.55
Hospitalizations*	6	4		0.27
Change from baseline in HADS score at 24 weeks				
Anxiety	0.13 ± 0.35	0.18 ± 0.38	-0.05 (-1.08;0.99)	0.93
Depression	0.34 ± 0.43	0.74 ± 0.43	-0.40 (-1.61;0.81)	0.51
Change from baseline in EQ5D-5L score at 24 weeks				
Index value	0.02 ± 0.02	-0.03 (0.17)	0.05 (-0.01;0.10)	0.11
VAS scale	-0.89 ± 3.6	-4.84 ± 2.8	3.95 (-5.20;13.10)	0.39
Change from baseline in GRC score at 24 weeks	0.34 ± 0.35	-0.70 ± 0.40	1.03 (-0.02;2.09)	0.055
Change from baseline in VAS scores at 24 weeks				
General wellbeing	0.65 ± 0.36	-0.39 ± 0.31	1.04 (0.09;2.00)	0.032
Cough	0.51 ± 0.45	-0.31 ± 0.50	0.82 (-0.52;2.17)	0.23
Dyspnea	0.41 ± 0.32	-0.23 ± 0.30	0.63 (-0.23;1.50)	0.15
Fatigue	0.46 ± 0.40	0.28 ± 0.35	0.18 (-0.88;1.23)	0.74
Stability IPF	0.49 ± 0.31	-0.6 ± 0.52	1.09 (-0.12;2.29)	0.076

+- standard error of the mean, *Mann-Whitney U test, GP = general practitioner, HADS = hospital anxiety and depression scale, VAS = visual analogue scale, GRC = global rating of change

A higher score indicates worse symptoms

A higher score indicates better quality of life or symptoms

study; six in the home monitoring group and four in the control group. Four hospitalizations were respiratory-related (one acute exacerbation). One hospitalization was due to side-effects of medication. Overall, 13 patients in the home monitoring group and 10 patients in the control group had extra appointments with a healthcare provider in between regular visits.

Patient satisfaction and use of the home monitoring program

Median adherence to daily home spirometry was 97% (52-100%), mean adherence was 93% (**Table 4**). Overall, 143 automated FVC alerts were sent to the research team; 33 alerts because patients did not send their FVC results and 110 because of a lower FVC. Most frequent reasons for lower FVC measurements were technique issues and symptoms (cough/dyspnea/chest pain). In one patient, FVC alerts were due to an acute exacerbation. More than half of patients used the information library at least once. During the study, 281 eConsultations were sent, corresponding with an average of one eConsultation per patient per month. In total, 347 automated email alerts about bothersome side-effects were sent to the research team.

Table 3. Medication use

	Home monitoring (n=41)	Standard care (n=39)	Difference (95% CI)	p value
Average number of medication adjustments per patient	1.0	0.3	0.7 (0.2;1.3)	0.027
Number of patients who discontinued medication	2	2	-	-
PESaM questionnaire - baseline				
Expectations - effectiveness	2.90 ± 0.80	2.66 ± 0.77	-0.25 (-0.66;0.17)	0.24
Expectations – side-effects	2.54 ±0.72	2.50 ± 0.83	-0.04 (-0.51;0.43)	0.86
Expectations – ease of use	3.66 ± 0.48	3.64 ± 0.67	-0.02 (-0.28;0.25)	0.90
PESaM questionnaire - 24 weeks				
Satisfaction with medication efficacy	1.52 ± 1.69	1.59 ± 1.97	0.06 (-0.77;0.88)	0.89
Satisfaction with side-effects	1.70 ± 1.90	1.41 ± 2.23	-0.29 (-1.23;0.64)	0.53
Satisfaction with ease of use	2.65 ± 1.59	2.75 ± 1.78	0.10 (-0.66;0.86)	0.80
Overall satisfaction with medication	2.01 ± 1.90	2.11 ± 1.91	0.11 (-0.75;0.97)	0.81
Number of reported side-effects per patient*	6.2 ± 5	4.8 ± 4.5	-1.4 (-3.4;0.6)	0.16
Bothersomeness of side-effects	1.46 ± 0.63	1.47 ± 0.84	0.01 (-0.4;0.3)	0.94

+- standard deviation, PESaM = patient experiences and satisfaction with medication questionnaire. *reported side-effects after 24 weeks

Patient satisfaction with the home monitoring program was high. The vast majority of patients would recommend the home monitoring program to others, mentioned that they gained better insights in their disease course, felt reassured, and that the program enabled low-threshold communication with the hospital (Table 4). Patients considered use of the home monitoring program and spirometer easy and useful, found it pleasant to have an overview of results, and did not consider home monitoring burdensome (**Figure 3**).

Table 4. Patient experiences with home monitoring

Use of home monitoring program	**Home monitoring group (n=42)**
Adherence to daily home spirometry (median)	97%
PROM completion rate	93%
Use of information library (% of patients)	58%
Total eConsultations	281
Patient experiences	**n=38**
Would recommend it to others	95%
Better insights in disease course	89%
Feeling reassured	88%
More accessible communication with hospital	87%

PROM = patient-reported outcome measure

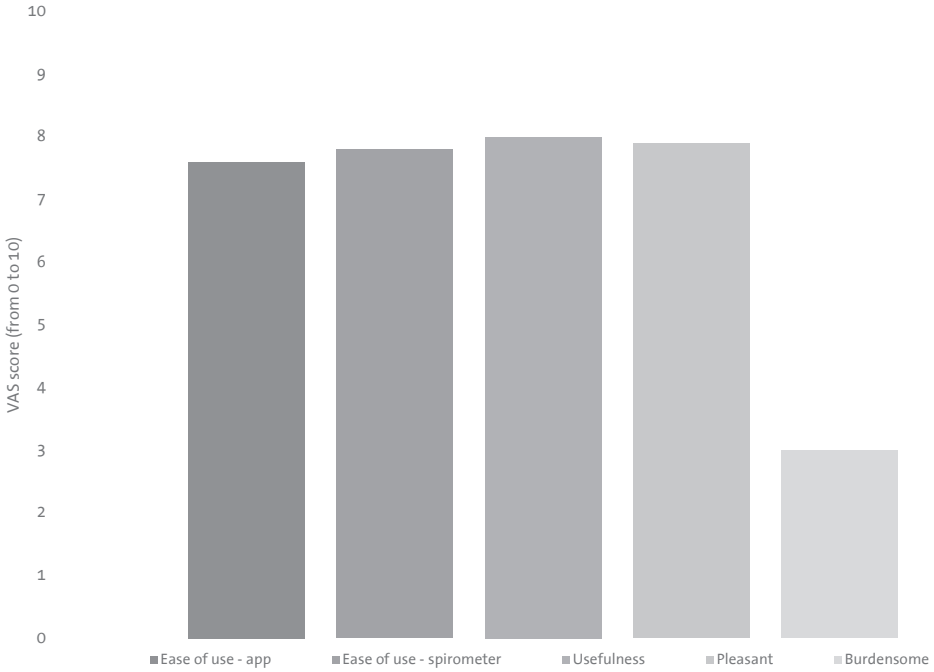

Figure 3. Patient experiences with the home monitoring program, scored on visual analogue scales from 0 to 10 (n=38).

Home and hospital spirometry

Mean change in hospital-based FVC in the standard care group (-87.9 ml, range -209 to 33.2 ml) was not significantly different from FVC change in the home monitoring group (-7.9 ml, range -96 to 69.4 ml, p=0.25). In the home monitoring group, mean change over time in home-based FVC was -16.8 ml (range -124 to 90.9 ml). Correlation between home and hospital spirometry was very strong at all time points; r=0.97 (p<0.001) at baseline and 12 weeks, and r=0.96 (p<0.001) at 24 weeks. Slopes of hospital and home-based FVC over time were comparable (interaction <0.0001, p=0.81) and correlation between slopes was moderately strong (r=0.58, p<0.001). Mean within-patient variability was 5.2% (SD 1.7, range 2.6-9.5%). An example of six individual patients with a wide range in FVC from all trial sites is provided in **figure 4**.

DISCUSSION

This first-ever randomized trial of eHealth in IPF investigated whether a comprehensive home monitoring program on top of standard care improved HRQOL compared with standard care alone. The results of our study show that this home monitoring program

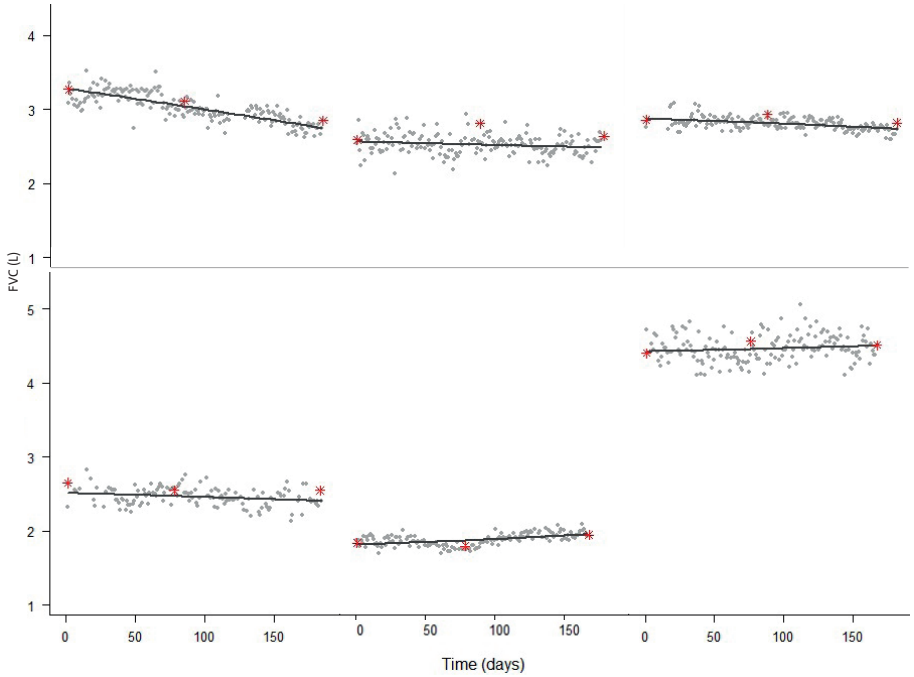

Figure 4. Example of hospital and home-based FVC change (L) over 24 weeks in six individual patients from different trial sites.

did not significantly improve overall HRQOL measured with K-BILD. Despite this, psychological wellbeing tended to improve and general wellbeing was significantly higher in the home monitoring group after 24 weeks. Home monitoring was greatly appreciated by patients, allowed for individually-tailored treatment adjustments and did not increase anxiety levels. Furthermore, daily home spirometry was feasible and provided reliable results similar to hospital-based spirometry.

The main purpose of our home monitoring program was to enhance comprehensive care by targeting multiple domains: stimulating self-management, improving medication use, providing disease-specific information, and enabling low-threshold communication. Capturing these diverse effects in one outcome measure is challenging, as many outcomes are not tangible, nor have validated outcome measures to quantify the effect. In this study, we have chosen the K-BILD as primary endpoint as it seems the most comprehensive HRQOL questionnaire in ILD. Moreover, K-BILD is the only ILD questionnaire to date that has managed to capture improvement in HRQOL in a randomized study evaluating a supportive measure (ambulatory oxygen) (20). However, the K-BILD measures overall health status while our home monitoring program seemed to have

more influence on psychological wellbeing. This was highlighted by the finding that the difference in K-BILD psychological score between both groups after 24 weeks exceeded the MCID. Besides, patients in the home monitoring group reported higher scores for general wellbeing on a VAS scale. Even though these were secondary outcome measures, this suggests that home monitoring could have positive effects on wellbeing and health perception. Our results are comparable with previously published studies using eHealth interventions in COPD and asthma; patient satisfaction with the intervention was generally high, but results regarding HRQOL were mixed (5, 21, 22).

This study was designed to assess the effects of a home monitoring program as add-on to standard care. However, it is important to note that IPF care in the Netherlands is already well-organized. Patients are treated in expert centers and closely monitored by ILD specialist nurses, which reduces differences between standard care and add-on home monitoring. This may also have contributed to the low medication discontinuation rate in the current study (5%), in comparison with previous trials in IPF (2, 3). Future studies are needed to determine whether outpatient clinic visits can be partly replaced by home monitoring including video consultations. This could not only reduce the burden of frequent hospital visits on IPF patients and their families, but potentially lead to more efficient healthcare delivery and cost reduction both for the healthcare system as well as for patients and their families.

Observational studies in IPF and COPD hypothesized that home monitoring could be psychologically distressing, because patients may become more pre-occupied with their disease (9, 23). Our data revealed that home monitoring did not increase anxiety and depression levels after 24 weeks. Patients actually appreciated that they gained more insights in their disease course and felt reassured by the information and feedback they received. It has previously been suggested that daily spirometry could be intrusive for patients if performed for a prolonged period (9, 10, 24). Importantly, patients in our study did not consider daily spirometry burdensome. The vast majority would recommend it to others and wished to continue with home monitoring after the study was completed. The high patient satisfaction was also reflected in the good adherence and completion rate, which was better than in some previous studies (10, 11). Another reason for the high satisfaction and compliance might be that the home monitoring program has been developed together with patients from the beginning; it has been tested and evaluated during two pilot studies, and patient suggestions have been incorporated to improve the program (12, 13). This highlights the importance of active patient participation in the design of eHealth interventions. We previously described that people may be hesitant to use online applications in this elderly patient population (12). However, the high rate of patients willing to participate in the current study (80% of invited patients)

shows that this is not a major concern in patients with IPF. Even a few patients without internet access at home were able to participate, since a tablet and 4G Sim Card were provided. These are encouraging results for future use of eHealth solutions for research and daily care purposes in IPF.

The automated email alerts about burdensome side-effects allowed for an individually-tailored treatment schedule; medication was significantly more often adjusted in the home monitoring group than in the standard care group. Strikingly, medication adjustments did not lead to significant differences in patient satisfaction with medication between both groups. One of the reasons could be that patient satisfaction with medication was relatively high in the whole group. Furthermore, we found that neither expectations before start of treatment, nor the number and perceived severity of side-effects correlated with patient experiences and satisfaction. A systematic review in other chronic diseases also suggested that eHealth tools may enable personalized medication adjustments (7). In line with our data, no evidence was found that medication changes had a positive impact on patient satisfaction (7). Due to the relatively short study duration, it was not possible to assess whether treatment adjustments lead to better long-term outcomes and compliance. Prospective observational studies with a longer duration are needed to answer these important questions.

Recently, there has been quite some debate about the use and reliability of home spirometry in pulmonary fibrosis (24). Our study demonstrated that daily home spirometry was feasible in a multicenter trial. Patient adherence remained high during our study and only a few technical problems were encountered. Home spirometry yielded reliable results similar to hospital-based spirometry, in line with other non-randomized home spirometry studies (9-11, 13). We found that slopes of home- and hospital-based FVC over time were comparable. In contrast, a randomized trial of pirfenidone in progressive unclassifiable interstitial lung disease using home spirometry showed rather conflicting results (24). In that trial, multiple challenges with home spirometry were encountered, mainly due to technical and adherence problems, leading to highly variable FVC results and analytical issues (24). In most previous studies, patients were blinded for their own results, did not receive reminders to perform spirometry, and results were not directly available for the study team. We believe that many of the challenges with home spirometry can be overcome by using an online home monitoring program with real-time feedback and alerts, easy access to a technical helpdesk, and extensive instruction of patients as we did in the current study. Therefore, we believe that we should not discard home spirometry too early as a tool for close monitoring and follow-up of patients in research and potentially also in daily practice.

Home monitoring could potentially allow for early detection of intercurrent events. As only a small number of intercurrent problems and respiratory-related hospitalizations occurred in our study, no conclusions can be drawn regarding the potential of eHealth tools to detect acute exacerbations and prevent hospitalizations in IPF. Presently, an observational study with a longer study duration investigates whether a home monitoring program, including home spirometry, allows for early detection of acute exacerbations (NCT03979430).

This study has some limitations. The healthcare situation and organization of care for IPF in the Netherlands might not be representative for other countries. However, it can be speculated that home monitoring could be even more relevant in countries with other healthcare systems and longer travel distances to the hospital. Furthermore, the study team received on average one eConsultation and less than two email alerts per patient per month; a limitation of this study is that we did not structurally evaluate the time investment and burden on the study team. Finally, no good validated questionnaires exist to evaluate patient satisfaction with eHealth compared to usual care. Consequently, we used a non-validated questionnaire to assess patient satisfaction in the home monitoring group, which was one of the secondary outcomes. Next to patient satisfaction and HRQOL, it could have been useful to measure other patient-reported outcomes such as confidence in self-management and sense of self control. Validated questionnaires to measure these outcomes (e.g. the Patient Activation Measure and Pearlin Mastery Scale) have been used in other diseases and may be of added value in future eHealth studies in IPF (25-27).

In conclusion, a comprehensive home monitoring program for patients with IPF tended to improve psychological wellbeing, but did not improve overall HRQOL measured with K-BILD. Nevertheless, patient satisfaction was high, and home monitoring allowed for individually-tailored medication adjustments. Home spirometry was feasible and provided reliable results over time. Hence, we believe that eHealth tools have the potential to enhance personalized treatment for IPF in the future.

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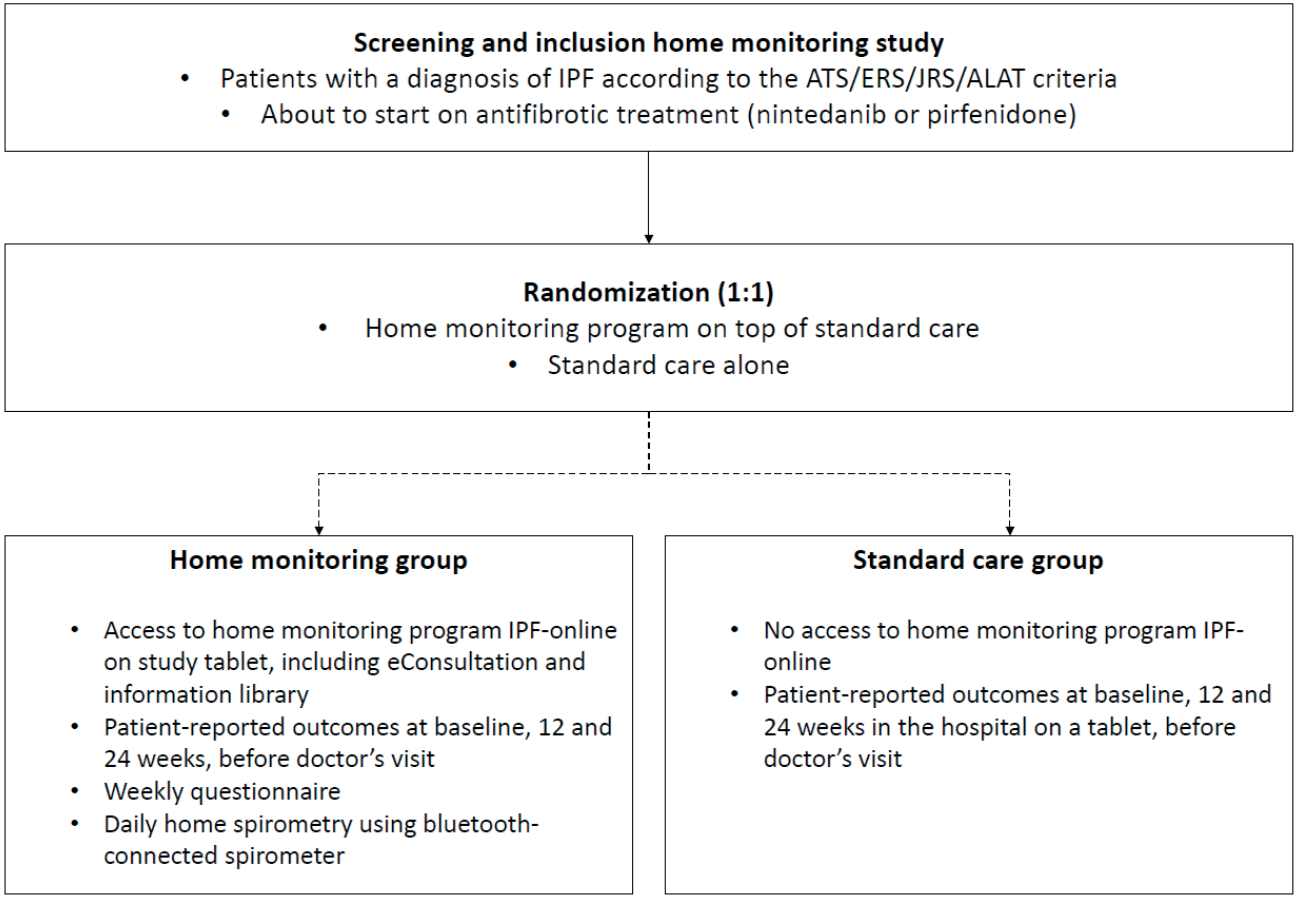


Figure S1. Flowchart of study procedures. Details about the alert system and medication coach are provided in figure S5.

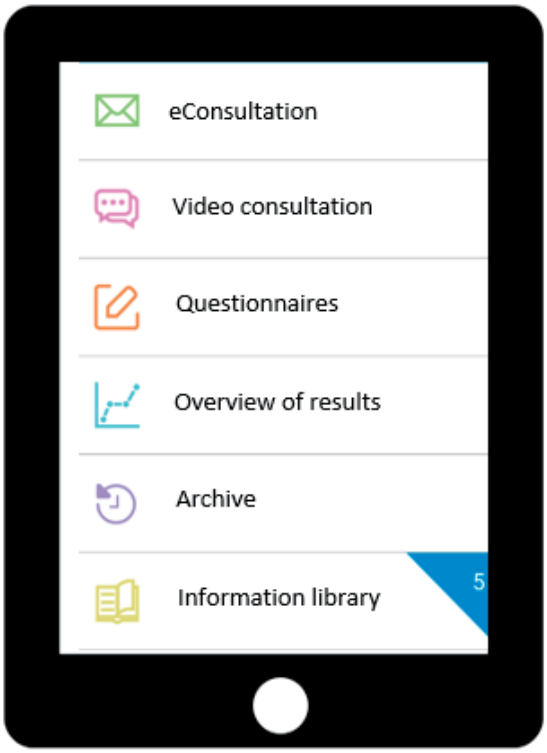


Figure S2. Overview of application IPF-online

SUPPLEMENT

Content of the home monitoring program

eConsultation: An eConsultation is a secured electronic message system in the application. Patients can type a message with a maximum of 1995 characters, which is directly sent to the healthcare providers. Healthcare providers receive an alert via email when a patient sends an eConsultation. Patients can also attach documents, such as lab results or photographs. If patients send an eConsultation they are contacted within 24 hours (during working days).

Video consultation: Not included at the time of the RCT. Incorporated after the RCT based on patient suggestions.

Questionnaires: Here, patients can complete the patient-reported outcome measures (PROMs) at baseline, week 12 and week 14, and their weekly questionnaire about

symptoms and side-effects. Patients receive an email reminder to complete the questionnaires.

Overview of results: Patients can see a graphical overview of their home-based FVC in percentage of predicted (Figure S3), the corresponding flow volume loop including a technical quality assessment (Figure S4), hospital-based FVC at baseline, week 12 and week 24, and an overview of questionnaire scores, symptoms and side-effects over time.

Archive: Overview of completed questionnaires and lung function measurements.

Information library: Information and news about IPF including videos, links to useful websites, and a medication coach. All individual patients have a specific medication coach depending on their prescribed medication (i.e. nintedanib or pirfenidone); it contains the instruction of use, most common side-effects and advices how to manage these side-effects. Advices were composed by ILD physicians and ILD specialist nurses. When a patient reports a side-effect in the weekly questionnaire, the advice how to handle that particular side-effect automatically pops-up on the screen. If a patient reports that a side-effect is bothersome (a score of 4 or 5 on a scale from 1=not bothersome at all to 5=very bothersome) an automatic alert is also send to the healthcare team (figure S5).

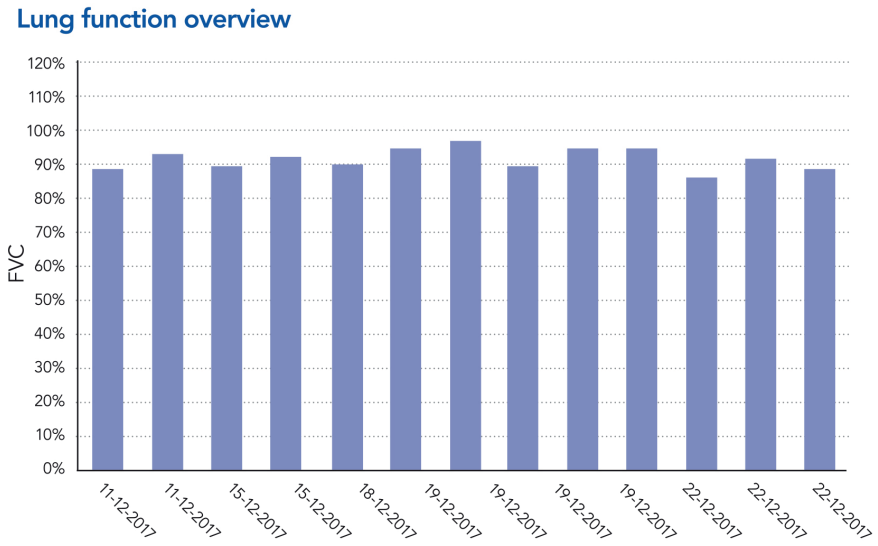


Figure S3. Daily FCV overview in percentage of predicted

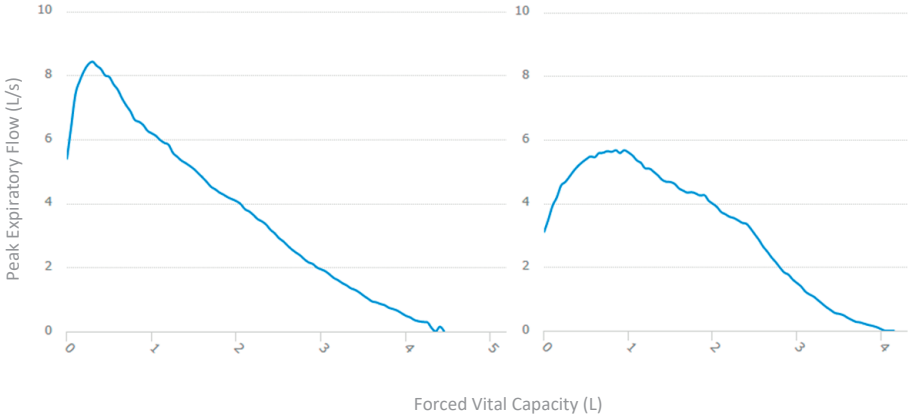


Figure S4. Flow volume loop including quality assessment

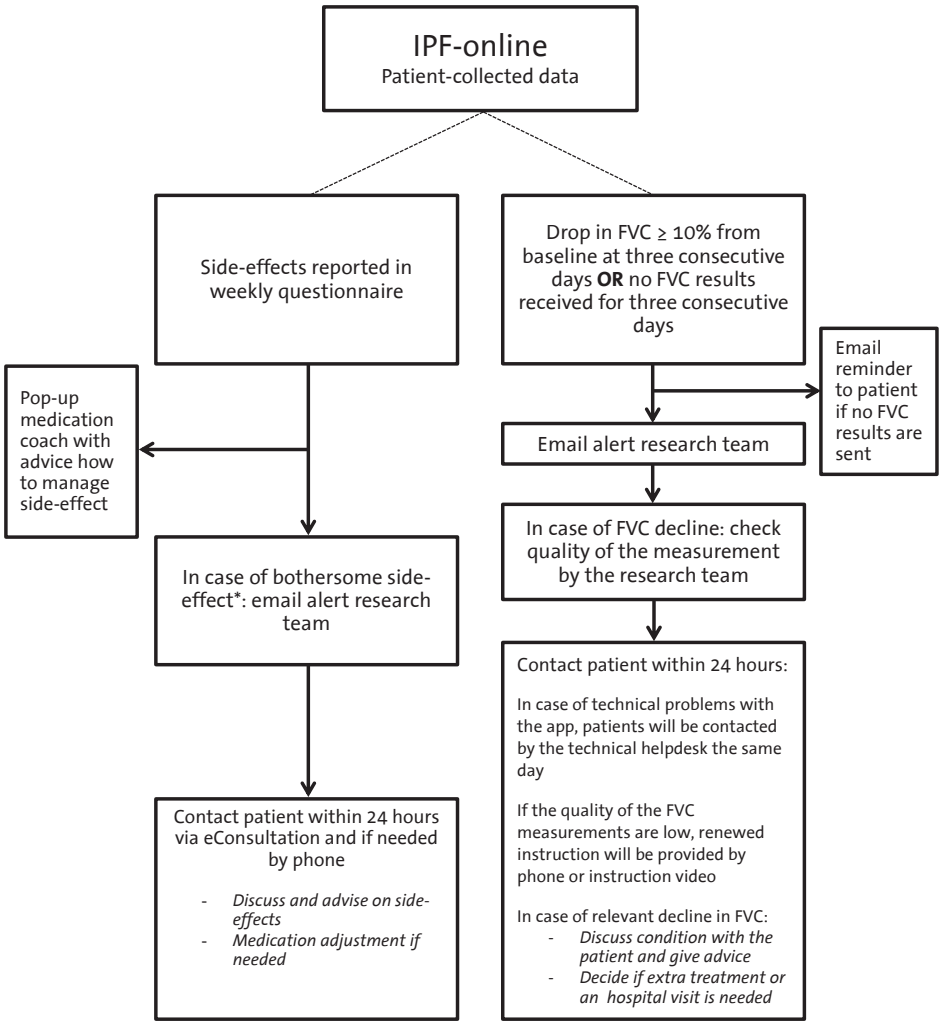
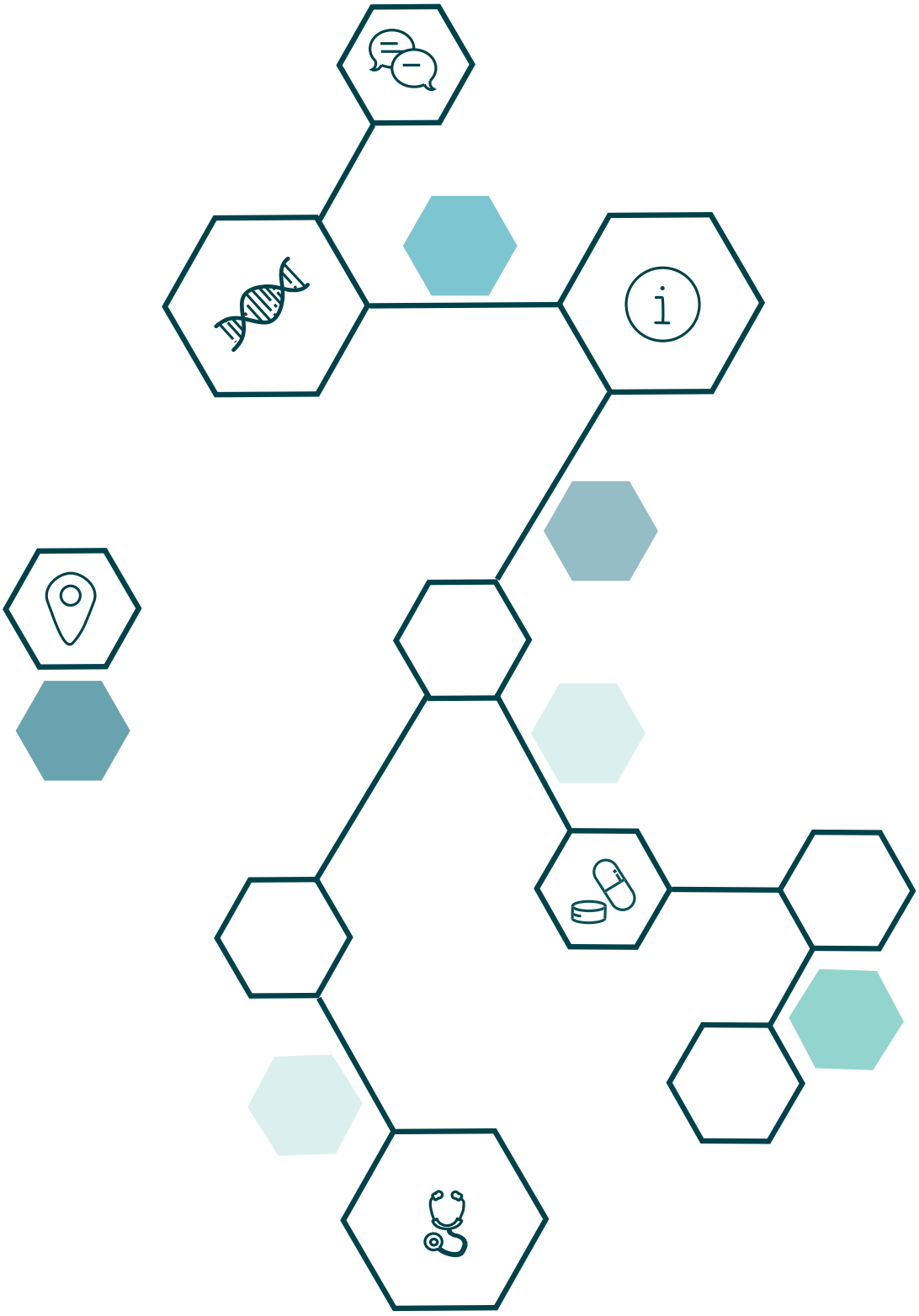


Figure S5: Flowchart alert system and medication coach
*Only in case of bothersome side-effects an email alert is sent to the research team. Side-effects are considered bothersome if patients report a score of 4 or 5 on a 5-point Likert scale from 1 (not bothersome at all) to 5 (very bothersome).



Chapter 13

Exhaled breath analysis by use of eNose technology: a novel diagnostic tool for interstitial lung disease

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ABSTRACT

Background

Early and accurate diagnosis of interstitial lung diseases (ILDs) remains a major challenge. Better non-invasive diagnostic tools are highly needed. We aimed to assess the accuracy of exhaled breath analysis using eNose technology to discriminate between ILD patients and healthy controls, and to distinguish ILD subgroups.

Methods

In this cross-sectional study, exhaled breath of consecutive ILD patients and healthy controls (HC) was analyzed using eNose technology (SpiroNose). Statistical analyses were done using Partial Least Square Discriminant Analysis (PLS-DA) and Receiver Operating Characteristic (ROC) analysis. An independent training and validation set (2:1) was used in larger subgroups.

Results

A total of 322 ILD patients and 48 HCs were included; sarcoidosis (n=141), idiopathic pulmonary fibrosis (n=85), ILD associated with connective tissue disease (n=33), chronic hypersensitivity pneumonitis (n=25), idiopathic NSIP (n=10) and interstitial pneumonia with autoimmune features (n=11), and other ILDs (n=11). eNose sensors fully accurately discriminated between ILD and HCs, with an AUC of 1.0 in the training and validation set. Comparison of patients with IPF and patients with other ILDs yielded an AUC of 0.91 (95% CI 0.85-0.96) in the training set, and an AUC of 0.87 (95% CI 0.77-0.96) in the validation set. The eNose reliably distinguished between individual diseases, with AUCs ranging from 0.85 to 0.99.

Conclusion

eNose technology can completely distinguish ILD patients from healthy controls, and can accurately discriminate between different ILD subgroups. Hence, exhaled breath analysis using eNose technology could be a novel new biomarker in ILD, enabling timely diagnosis in the future.

BACKGROUND

Interstitial lung diseases (ILDs) encompass a diverse group of more than 200 different disorders, which are associated with substantial morbidity and mortality (1, 2). Idiopathic pulmonary fibrosis (IPF) is the most common ILD and has the worst prognosis (3). The disease course of ILDs is very heterogeneous; some ILDs are reversible and may be self-limiting, others remain stable, and a subgroup of patients has a progressive phenotype (1). Moreover, a substantial minority of patients (around 10%) have unclassifiable ILD (4, 5). Establishing an accurate diagnosis can be challenging, because symptoms as cough and dyspnea are non-specific (6). Many patients receive one or more misdiagnoses, and often undergo invasive diagnostic procedures, before the diagnosis of ILD is confirmed (7). A study in IPF showed that 55% of patients consulted three or more physicians before receiving a final diagnosis. Furthermore, the majority of patients reported a treatment delay of more than one year between initial presentation and confirmed diagnosis (8). Currently, a multidisciplinary team (MDT) discussion is considered as the "gold standard" for diagnosis of ILD (9).

With the availability of different treatment options, it has become increasingly important to achieve an early diagnosis (10, 11). For IPF, two antifibrotic drugs (nintedanib and pirfenidone) are available that slow down disease progression. More recently, antifibrotic drugs have also shown efficacy in other progressive fibrotic ILDs, which will change the treatment landscape for these patients (12). Patients with fibrotic ILDs other than IPF can have a predominantly inflammatory phenotype, a more fibrotic phenotype, or a combination of both (3). This emphasizes the importance of accurate phenotyping of patients, to decide which treatment should be given (i.e. immunosuppressive medication, antifibrotic medication, or a combination). Currently, no biomarkers are available to reliably make this distinction. Thus, there is a major need for non-invasive, widely available, inexpensive tools for diagnosis and monitoring of disease course, especially in the current era with advancing treatment options.

An emerging non-invasive diagnostic technique is the analysis of volatile organic compounds (VOCs) in exhaled breath. The body creates volatile organic compounds (VOCs) during metabolic and pathological processes; thousands of these VOCs can be found in exhaled breath (13). The composition of VOCs in exhaled breath could serve as biomarker in a wide range of diseases (14, 15). One method to analyze VOCs is by using electronic nose (eNose) technology. ENoses have several cross-reactive gas sensors, which react to multiple compounds in the VOC mixture. This results in a unique pattern of sensor responses: the breathprint. Individual cases can be classified in disease groups by use of pattern recognition algorithms. The field of breathomics is rapidly evolving,

and relatively high diagnostic accuracies have been published in other (lung) diseases (16-19). Hence, eNose technology has been proposed as a diagnostic tool, for clinical and inflammatory phenotyping, and to predict response to therapy (16, 17). In ILD, studies on breathomics are scarce. One study in sarcoidosis showed that the breathprint of patients with untreated pulmonary sarcoidosis could be distinguished from healthy controls. Treated sarcoidosis patients could not be discriminated from healthy controls (20). Another recently published study evaluated the ability of eNose technology to identify different ILD subgroups, and to compare ILD with healthy controls and COPD patients (21). This study also showed adequate distinction between patients with ILD from healthy controls and COPD patients. However, different ILD subgroups could not be accurately separated from each other.

In this study, we aimed to investigate the reliability of exhaled breath analysis using eNose technology to discriminate between ILD patients and healthy controls, and to distinguish ILD subgroups.

METHODS

Study design and population

This was a single-center, cross-sectional study in the Erasmus Medical Center, Rotterdam, the Netherlands. This study was approved by the medical ethics committee (MEC-2019-0230). Between July 2019 and February 2020, consecutive outpatients with a diagnosis of ILD, according to the ATS/ERS criteria (1, 9), or a diagnosis of sarcoidosis, according to the WASOG criteria (22) were eligible to participate. We also included patients with interstitial pneumonia with autoimmune features (IPAF), for which we used the proposed classification criteria by Fischer et al (23). All patients signed written informed consent before inclusion in the study. The healthy controls (HCs) were hospital staff without a history of lung diseases, who gave informed consent.

Measurements

Measurements were performed using a cloud-connected eNose; SpiroNose (Breathomix, Leiden, the Netherlands). The SpiroNose is an integration between eNose technology and routine spirometry, and has been technically and clinically validated (24, 25). The SpiroNose has seven different types of cross-reactive metal-oxide semiconductor sensors. These sensors are present in duplicate in sensor arrays on both the inside (to measure VOCs in exhaled breath) and on the outside of the SpiroNose (to measure VOCs in ambient air). A SpiroNose measurement consists of five tidal breaths, followed by an inspiratory capacity maneuver to total lung capacity, a five second breath hold, and sub-

sequently a slow expiration (flow <0.4L/s) to residual volume. All eNose measurements were performed in duplicate. The sensor readings were sent in real time via a gateway to the online analysis platform, BreathBase, which includes the secured online database of Breathomix (ISO27001 and NEN7510 certified). A more detailed description of the methods and set up can be found in a previous publication by de Vries et al. (25).

Data collection

Participants completed a short survey about factors relevant for the measurement, such as smoking history and food intake in the last two hours. Data about medication use, lung function tests, pathology results, radiology, and recent laboratory parameters were collected from the medical records. Patients were labeled as having pulmonary fibrosis in case of reticulations with traction bronchiectasis, and/or honeycombing on the most recent CT scan. Data about forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide were collected if available.

Data analysis

The eNose sensor signals were processed, and corrected for ambient VOCs as previously published (24, 26). The peak value of each sensor for exhaled breath was determined, and normalized to the most stable sensor (sensor 2). Sensor-to-sensor ratios were used to reduce inter-array differences. Lastly, the ratio between peak sensor values and sensor values during breath hold were calculated. Both the normalized sensor peaks and the ratio between peak sensor values and breath hold values were used in data analysis. Statistical analysis was done using Partial Least Square Discriminant Analysis (PLS-DA) and receiver operating characteristic (ROC) analysis. In the ROC analysis, the areas under the curve (AUCs) and corresponding 95% confidence intervals (CIs) were determined. Sensitivity, specificity and accuracy were calculated. For larger subgroups (ILD vs HC, IPF vs non-IPF ILD, pulmonary fibrosis vs no pulmonary fibrosis), a training and validation set by split analysis (2:1) were used, as recommended for metabolomics experiments (27). During the validation step, the PLS-DA model derived from the training set was tested on the validation set (Figure S1). We compared the training and validation set based on the AUC of the ROC curves of PLS-DA components 1 and 2. For comparisons between individual diagnoses we did not use a training and validation set, because of the small sample sizes. For these groups only PLS-DA component 1 was used for ROC analysis. We focused on comparing diagnoses that often cause diagnostic dilemmas in clinical practice because of their similarities in clinical presentation and imaging. Descriptive statistics were used to analyze baseline data. Between-group comparisons were done using independent sample t-tests, ANOVA, chi square tests, Kruskal-Wallis tests, and Fisher's exact tests. Analyses were done using R version 3.6.2 (using the mixOmics package, Version 6.1.1) and SPSS (IBM SPSS statistics for Windows, Version 25).

RESULTS

In total, 322 consecutive patients with ILD and 48 healthy controls were included in this study. The overall mean age for ILD patients was 61.6 years (SD 13.3), 59.9% of patients were male and 5.3% of patients were current smokers. Mean FVC (n=316) was 3.23L (SD 1.1), or 82.4% of predicted (SD 19.1), and mean DLCO (n=305) was 60.6% of predicted (SD 21.9). Mean age and percentage of males were significantly higher in the ILD group, compared with healthy controls (**Table 1**). Furthermore, ILD patients had significantly more pack years than healthy controls, but there was no difference in the percentage of current smokers.

ILD patients were categorized in seven groups: idiopathic pulmonary fibrosis (IPF), sarcoidosis, connective tissue disease-associated interstitial lung diseases (CTD-ILD), chronic hypersensitivity pneumonitis (CHP), interstitial pneumonia with autoimmune features (IPAF), idiopathic non-specific interstitial pneumonia (iNSIP) and other ILDs. Diagnoses with less than ten included patients (cryptogenic organizing pneumonia, respiratory bronchiolitis-interstitial lung disease, asbestosis, drug-induced ILD, granulomatosis with polyangiitis and unclassifiable ILD) were classified as 'other ILDs'. Baseline characteristics of these individual groups can be found in supplementary table 1. There were significant differences in age, gender, pack years, FVC and DLCO between ILD subgroups, but no difference in the percentage of current smokers.

ILD versus healthy controls

The breathprint of 322 ILD patients and 48 healthy controls were compared; groups were divided in a training and a validation set. The training set consisted of 215 ILD patients and 32 healthy controls, the validation set of 107 ILD patients and 15 healthy controls. The results of PLS-DA for the training set, accompanied by the corresponding ROC curve are shown in **figure 1**. The eNose perfectly discriminated between ILD patients and healthy controls with an AUC of 1.00, for both the training and the validation set. Accordingly, the sensitivity, specificity and accuracy of the model were 100% (**Table 2**).

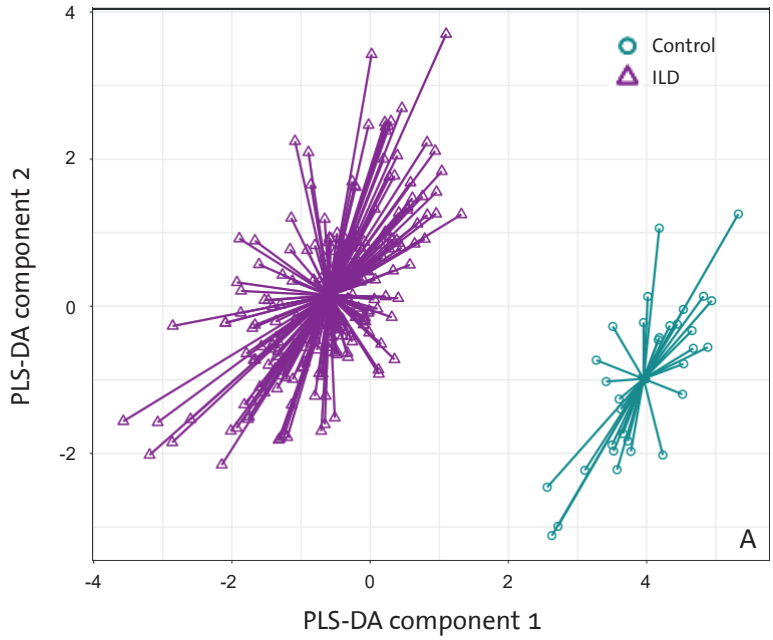
ILD subgroups

Patients with ILD were divided in IPF (n=85) and non-IPF ILDs (n=237), and separated in a training and validation set. The training set consisted of 57 IPF patients and 158 patients with non-IPF ILDs, the validation set consisted of 28 IPF patients and 79 patients with non-IPF ILDs. The results of PLS-DA for the training set are shown in **figure 2**, together with the corresponding ROC curve. In the training set, the AUC was 0.91 (95% CI 0.85-0.96), in the validation set the AUC reached 0.87 (95% CI 0.77-0.96). In the validation set the sensitivity was 95%, the specificity was 79% and the accuracy of the model was 91%. Results of the training set are shown in table 2.

Table 1. Baseline characteristics of ILD patients and healthy controls

	Sarcoidosis	IPF	CTD-ILD	CHP	IPAF	iNSIP	Other ILDs	Healthy controls
	n = 141	n = 85	n = 33	n =25	n = 11	n = 10	n = 17	n = 48
Mean age	53 ± 11	74 ± 7	57 ± 13	67 ± 8	61 ± 13	68 ± 9	66 ± 16	37 ± 12
Males (%)	72 (51.1)	77 (90.6)	11 (33.3)	13 (52.0)	0 (0.0)	6 (60.0)	14 (82.4)	15 (31.3)
Smoking history								
never	82 (58.2%)	10 (11.8%)	15 (45.5%)	12 (48.0%)	5 (45.5%)	3 (30.0%)	3 (17.6%)	37 (77.1%)
stopped	47 (33.3%)	73 (85.9%)	17 (51.5%)	13 (52.0%)	6 (54.5%)	7 (70.0%)	12 (70.6%)	7 (14.6%)
current	12 (8.5%)	2 (2.4%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	4 (8.3%)
Median pack years (IQR)	0.0 (0.0-3.9)	20.0 (6.8-37.9)	0.5 (0.0-20.0)	0.0 (0.0-15.0)	0.0 (0.0-16.9)	8.8 (0.0-33.0)	9.5 (2.3-27.3)	0.0 (0.0-0.0)
Mean FVC (L)	3.56 ± 1.06	3.17 ± 0.94	2.68 ± 0.76	3.03 ± 1.02	1.97 ± 0.86	2.54 ± 0.98	3.41 ± 1.11	NA
Mean FVC (% predicted)	87 ± 16	81 ± 20	73 ± 19	83 ± 19	65 ± 23	67 ± 11	85 ± 20	NA
Mean DLCO (% predicted)	76 ± 18	43 ± 13	54 ± 15	53 ± 14	46 ± 20	51 ± 15	57 ± 23	NA

± standard deviation, ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, CTD-ILD: connective tissue disease-associated interstitial lung disease, CHP: chronic hypersensitivity pneumonitis, IPAF: interstitial pneumonia with autoimmune features, iNSIP: idiopathic non-specific interstitial pneumonia, other ILDs: other interstitial lung diseases, IQR: interquartile range, FVC: forced vital capacity, DLCO: diffusing capacity of the lungs for carbon monoxide



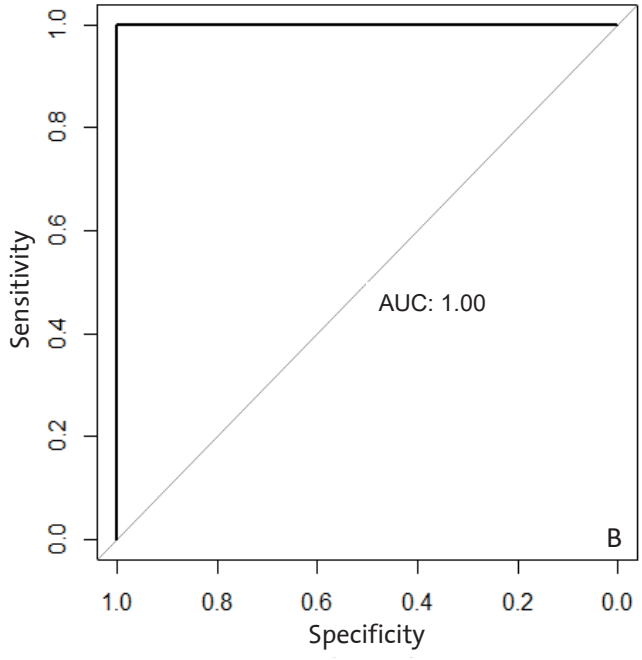


Figure 1A: Training set of breathprints from patients with interstitial lung disease (n=215) compared to breathprints from healthy controls (n=32)
Figure 1B: ROC curve of PLS-DA components 1&2 for training set

Table 2. Diagnostic performance of training and validation sets

Groups	AUC	95% CI	Sensitivity (%)	Specificity (%)	Accuracy (%)
ILD vs HC - training	1	-	100	100	100
ILD vs HC - validation	1	-	100	100	100
IPF vs non-IPF ILD - training	0.91	0.85-0.96	92	88	91
IPF vs non-IPF ILD - validation	0.87	0.77-0.96	95	79	91
Fibrosis vs no fibrosis - training	0.83	0.77-0.89	84	77	80
Fibrosis vs no fibrosis - validation	0.78	0.69-0.87	74	81	78

AUC = area under the curve, CI = confidence interval, ILD = interstitial lung disease, HC = healthy controls, IPF = idiopathic pulmonary fibrosis

The breathprints of ILD patients with pulmonary fibrosis (n=194) were compared to patients without pulmonary fibrosis (n=128). This group was split in a training set of 130 patients with fibrosis and 86 patients without fibrosis, and a validation set of 64 patients with fibrosis and 42 patients without fibrosis. The ROC curve reached an AUC of 0.83 (0.77-0.89) in the training set (**Figure 3**) and 0.78 (0.69-0.87) in the validation set. In the validation set the sensitivity of the model was 74%, the specificity 81% and the accuracy 78% (for training set see table 2).

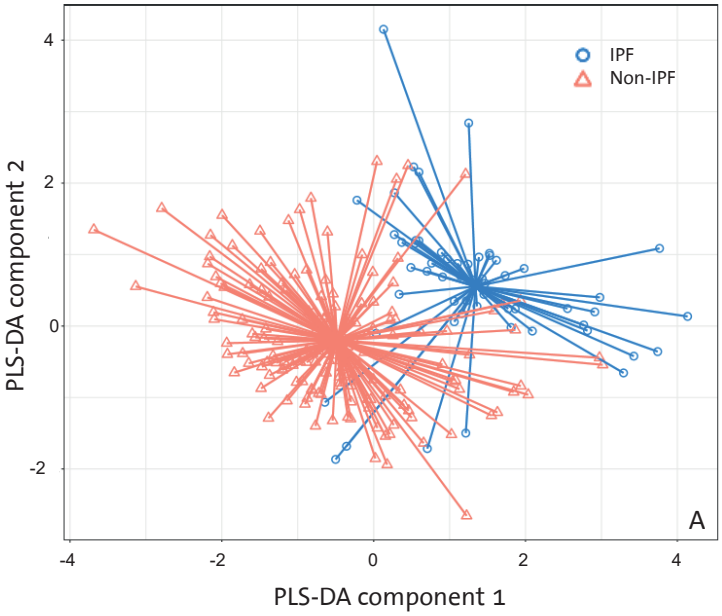
Individual ILDs

Subsequently, breathprints of individual diagnoses were compared with each other. The diagnostic performances of the models for comparison between different ILDs are presented in **table 3**, all figures can be found in the supplementary material (Figure S2). As we included a group of patients that did not have a classifying ILD diagnosis but fulfilled the criteria of IPAF, we did an exploratory analysis comparing these patient with both IPF and CTD-ILD, as these are the most common clinical differential diagnoses in IPAF (**Figure 4**).

Table 3 . Models for direct comparison between individual diagnoses

Groups	AUC	95% CI	Sensitivity (%)	Specificity (%)	Accuracy (%)
IPF vs CHP	0.85	0.76-0.94	75	84	77
IPF vs CTD-ILD	0.96	0.93-1.00	98	85	94
IPF vs iNSIP	0.94	0.86-1.00	92	90	92
IPF vs IPAF	0.94	0.90-0.99	87	100	89
CTD-ILD vs IPAF	0.99	0.80-1.00	100	67	75
CTD-ILD vs iNSIP	0.93	0.79-1.00	90	100	98
CHP vs sarcoidosis	0.89	0.80-0.98	94	72	90

AUC = area under the curve, CI = confidence interval, IPF = idiopathic pulmonary fibrosis, CHP = chronic hypersensitivity pneumonitis, CTD-ILD = connective tissue disease – interstitial lung disease, iNSIP = idiopathic non-specific interstitial pneumonia, IPAF = interstitial pneumonia with autoimmune features



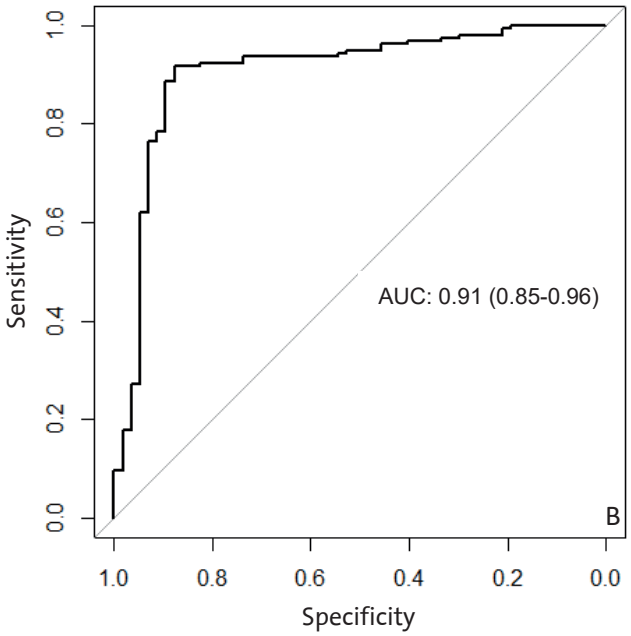
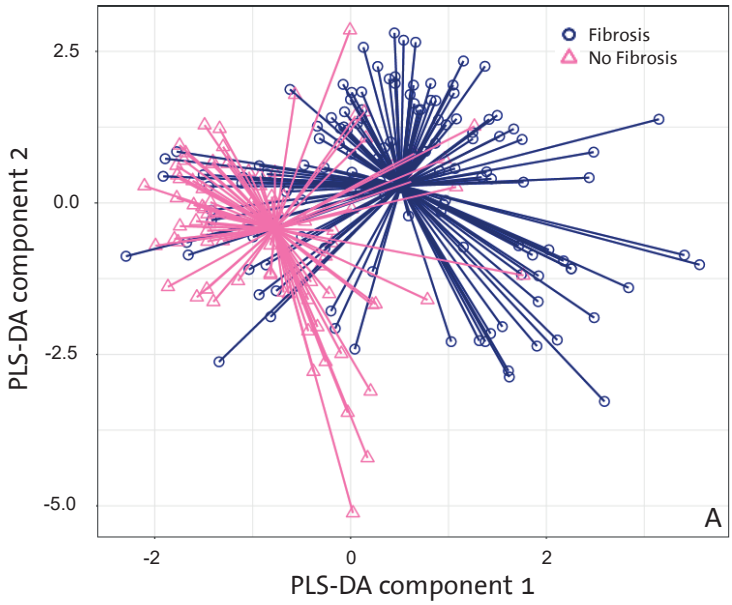


Figure 2A: Training set of breathprints from IPF patients (n=57) compared to breathprints from patients with non-IPF ILDs (n=158)
Figure 2B: ROC curve of PLS-DA components 1&2 for training set



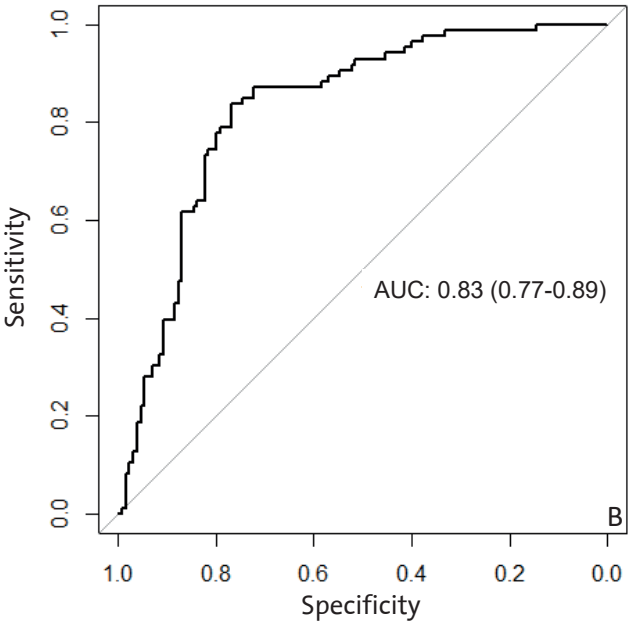


Figure 3A: Training set of breathprints from patients with fibrosis (n=130) compared to breathprints of patients without fibrosis (n=86)

Figure 3B: ROC curve of PLS-DA components 1&2 for training set

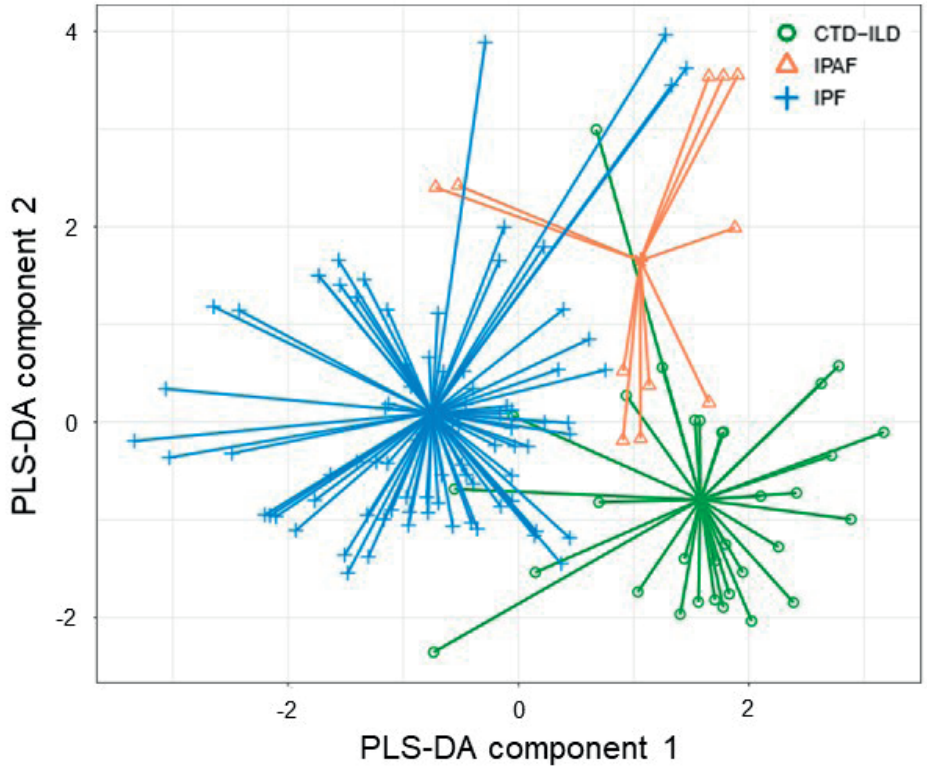


Figure 4: PLS-DA results of IPF, CTD-ILD and IPAF. IPF = idiopathic pulmonary fibrosis, CTD-ILD = connective tissue disease-ILD, IPAF = interstitial pneumonia with autoimmune features.

DISCUSSION

In this study, we aimed to evaluate the reliability of exhaled breath analysis using eNose technology to discriminate between ILD patients and healthy controls, and to distinguish ILD subgroups. The eNose fully accurately discriminated between ILD patients and healthy controls, both in the training and validation set. Moreover, the eNose adequately discriminated between individual ILDs, IPF and non-IPF ILDs, and patients with pulmonary fibrosis versus patients without pulmonary fibrosis.

Until now, one other pilot study in ILD investigated the ability of eNose technology to recognize ILDs (21). In line with our results, healthy controls could be distinguished from ILDs (IPF, CTD-ILD and cryptogenic organizing pneumonia). In the present study, we have confirmed and extended this finding in an independent training and validation cohort. The eNose in the current study could discriminate between individual diagnoses with a high sensitivity, specificity, and accuracy. This was not shown by Krauss et al. pre-

sumably due to a smaller number of ILD patients in their study (n=174) compared with the current study (n=322), which could have led to insufficient training of the device (21). The encouraging results in our study warrant further confirmation and external validation in larger (multi-center) cohorts. A larger cohort for the individual ILDs coming from different MDTs, will further increase the accuracy of eNose technology to detect ILD and distinguish between different diagnoses, making this a potentially new tool for rapid, non-invasive diagnosis of ILD.

The comparison of patients with and without pulmonary fibrosis yielded an acceptable accuracy, but the area under the curve was slightly lower than in other subgroups. Data of HRCT scans were collected from medical records, and most scans were not made at the same outpatient clinic visit as the eNose measurements. We only determined presence of pulmonary fibrosis and did not look at signs of inflammation, as this may have changed over time. Inflammatory processes change the VOC mixture in exhaled breath (16). Inflammation may have been present both in patients with pulmonary fibrosis, as well as patients without pulmonary fibrosis. Hence, it could be speculated that inflammation dominates the breathprint, leading to an overlap in breathprints of patients who have an inflammatory phenotype, irrespective of the presence of fibrosis. Future studies should further elucidate whether inflammatory and fibrotic phenotypes can be reliably distinguished, and whether specific HRCT patterns could be discriminated by exhaled breath analysis.

Surprisingly, patients with IPF, IPAF and CTD-ILD had a distinctive breathprint, and could be discriminated with a high accuracy. This raises the question whether IPAF could be a separate disease entity. Until now, the term IPAF is primarily used as a research concept, but not as a clinical diagnosis. IPAF is thought to have a significant overlap with IPF and CTD-ILD, and is often considered as undifferentiated CTD-ILD (23, 28). Moreover, IPAF is a very heterogeneous concept, as the classification criteria are based on a combination of features from three different domains (a clinical, serological, and morphological domain). This makes the clear discrimination between IPAF, CTD-ILD and IPF in the current study even more interesting. eNose technology could potentially be used to determine whether distinct phenotypic clusters can be identified within the patient group currently classified as IPAF. Obviously, these results need to be confirmed in larger studies. Nevertheless, our results highlight the importance of refining the classification criteria for IPAF in the coming years. (23, 28).

A potential limitation in this study is the fact that the group of healthy controls was younger, had less pack years, and consisted of a significantly lower percentage of males. A previously published study showed that age and gender do not affect the breathprint

(29). Hence, we believe that these differences in demographics have not impacted our results. A possible obstacle for the further development of eNose technology towards a point-of-care tool in ILD, is the lack of gold standard for the diagnosis of ILD. Diagnoses are based on multidisciplinary team meetings, and a substantial part of ILD remains unclassifiable (1, 4, 5, 9). Because there is no real gold standard, it is highly likely that a minority of patients has been incorrectly diagnosed. This means that the pattern recognition algorithms receive wrong so-called 'gold-standard' information, and the algorithm is trained based on partly incorrect information. This same limitation has been mentioned by Walsh et al., in a recent study where a deep learning algorithm learned to classify fibrotic lung disease on HRCT (30). A larger training dataset would result in a better performing algorithm, as the percentage of incorrectly labelled patients will be relatively smaller. This further emphasizes the need of future research on eNose technology in ILD, preferably as a multicenter effort, to increase the size of the available datasets and account for difference in diagnoses between MDTs (31).

Based on our data, we believe that exhaled breath analysis has the potential to enable early and accurate diagnosis of ILD in the future. Results of eNose measurements could give guidance during multidisciplinary team meetings and enhance diagnostic certainty in clinical practice. Furthermore, unsupervised cluster analysis can be performed to cluster patients based on their breathprint, irrespective of the underlying diagnosis, similar to a recent study among patients with asthma or COPD (26). This data-driven approach could potentially distinguish different disease phenotypes which have not yet been clinically identified. Further studies should reveal whether patients with distinct eNose-based phenotypes have a different disease behavior and/or response to therapy. If so, this may be a novel technology to predict disease progression and prognosis in ILD.

In conclusion, eNose technology has the potential to become a novel diagnostic tool for ILDs. ENose measurements can hopefully be used in the future to increase diagnostic confidence, and allow for point-of-care diagnostics in the doctor's office, thereby reducing diagnostic delays and improving care and treatment for patients with ILD.

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Supplementary table 1. Baseline characteristics of individual groups classified as 'other ILDs'

	Asbestosis	RB-ILD	(C)OP	Drug-induced ILD	Unclassifiable ILD	GPA
	n = 1	n =1	n = 6	n = 2	n = 4	n = 3
Mean age	81	54	68 ± 9	67 ± 12	75 ± 2	46 ± 26
Males (%)	1 (100)	1 (100)	4 (66.7)	2 (100)	3 (75)	3 (100)
Smoking history						
never	1 (100)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (25.0%)	0 (0.0%)
stopped	0 (0.0%)	0 (0.0%)	5 (83.3%)	2 (100%)	3 (75.0%)	2 (66.7%)
current	0 (0.0%)	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Median pack years (IQR)	0.0	25.0	6.3 (2.3-17.2)	41.7	10.0 (1.0-20.5)	NA
Mean FVC (L)	3.16	4.80	3.67 ± 0.97	3.45 ± 1.01	2.21 ± 0.51	4.56 ± 1.20
Mean FVC (% predicted)	92	103	93 ± 25	71 ± 25	71 ± 11	87 ± 6
Mean DLCO (% predicted)	30	41	75 ± 19	46 ± 21	43 ± 19	76 ± 4

± standard deviation, RB-ILD: respiratory bronchiolitis-interstitial lung disease, (C)OP: (cryptogenic) organizing pneumonia, drug-induced ILD: drug-induced interstitial lung disease, unclassifiable ILD: unclassifiable interstitial lung disease, GPA: granulomatosis with polyangiits, IQR: interquartile range, FVC: forced vital capacity, DLCO: diffusing capacity of the lungs for carbon monoxide

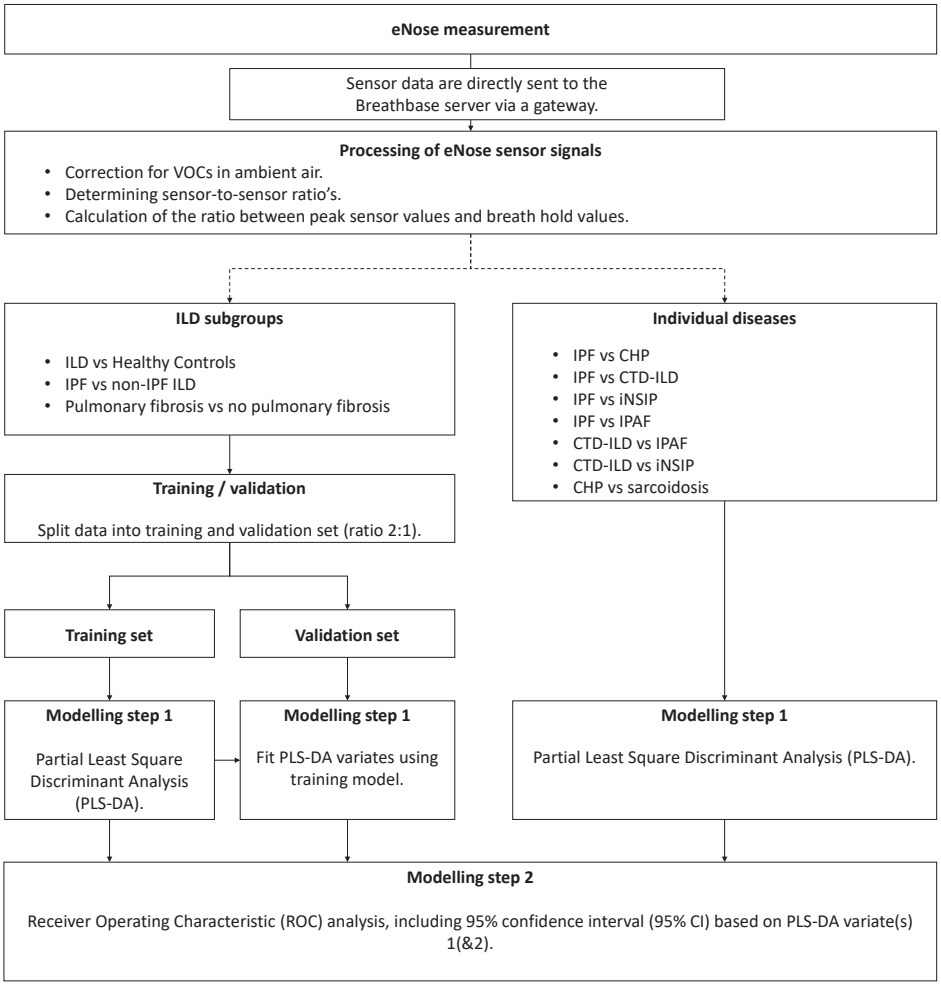


Figure S1: Data analysis flow chart

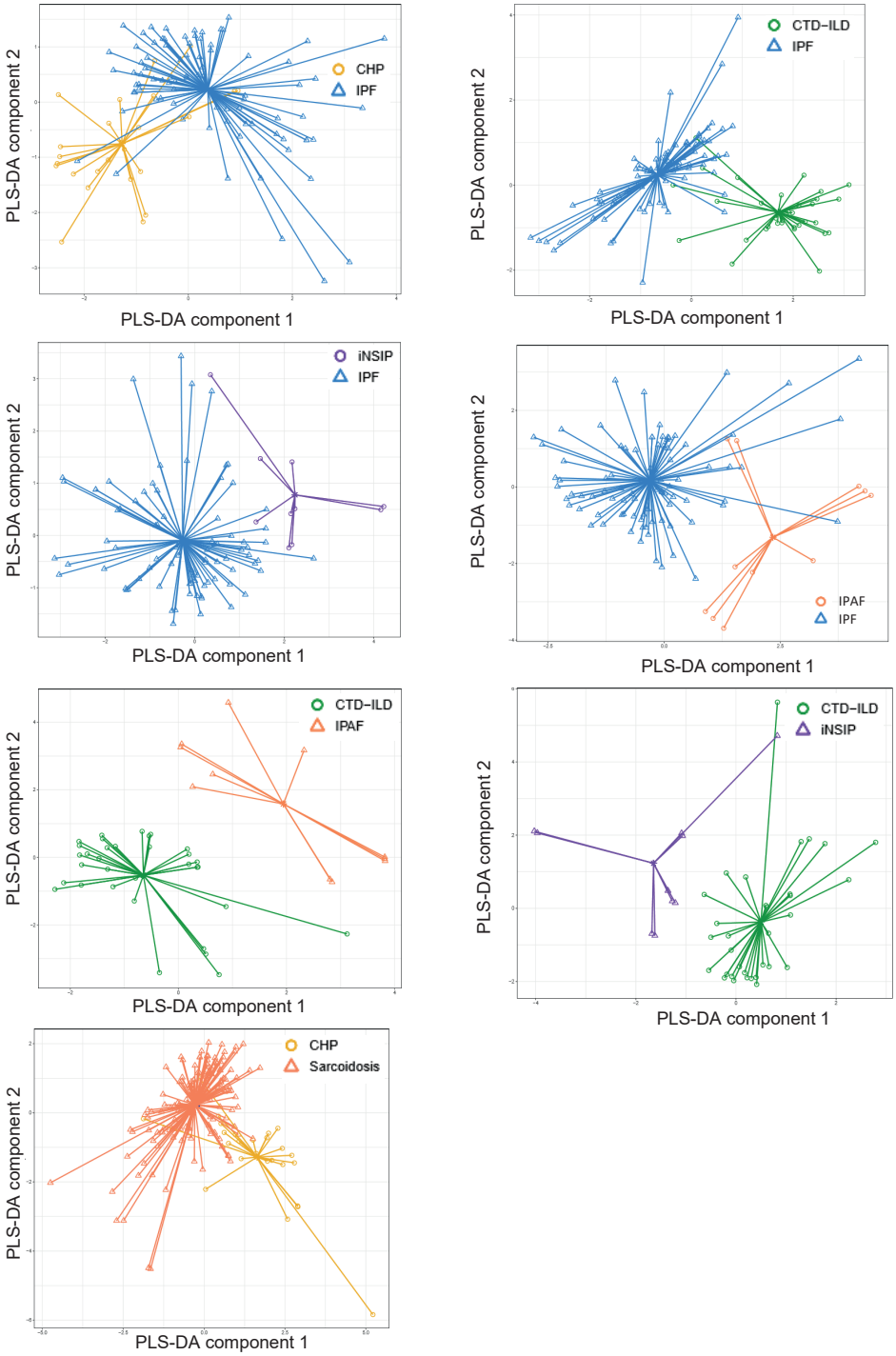
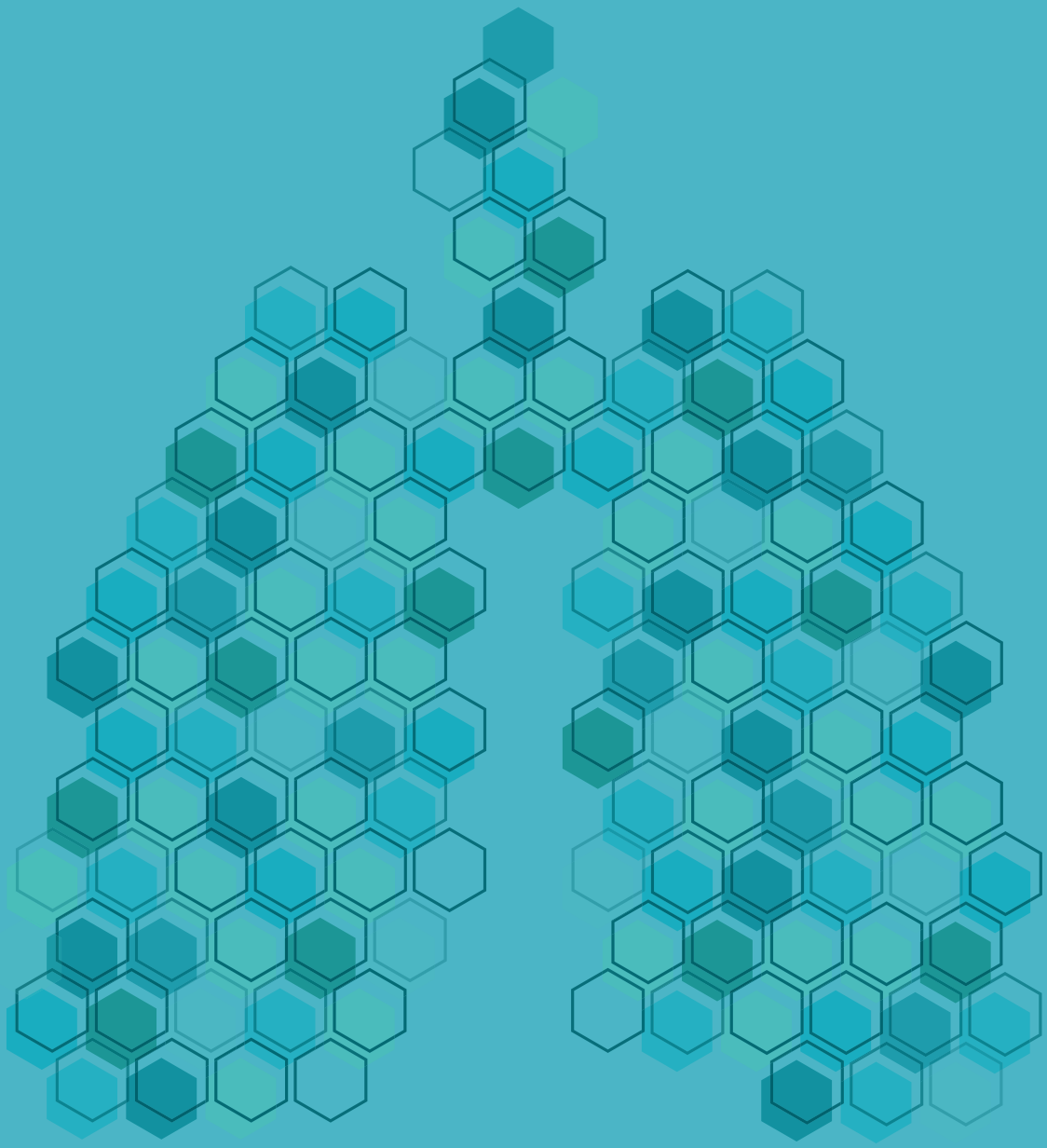


Figure S2: Results of the PLS-DA analysis for comparison of individual diseases



PART 4

Discussion

Chapter 14

General discussion

The first aim of this thesis was to gain novel insights in patient experiences, perspectives, unmet needs, and gaps in care, as we can only improve health outcomes for patients with ILD if these aspects are considered. For this purpose, we performed surveys among patients, partners, and healthcare providers, and structurally evaluated patient experiences and satisfaction with antifibrotic medication (chapter 3, chapter 5, chapter 6). In order to improve quality of care, we have proposed a model to enhance personalized medicine in IPF, and suggested a comprehensive approach to optimize treatment of fatigue in ILD (chapter 4, chapter 7). Below, I will discuss recent advances in treatment, current gaps in care, and elaborate on ongoing initiatives to close these gaps in care.

GAPS IN CARE

Unmet needs in pulmonary fibrosis

Much efforts have been made in recent years to raise more awareness for pulmonary fibrosis and to improve care for patients; however, despite these efforts, we found that current needs of patients and healthcare providers still largely overlap with reported unmet needs during the past decade (chapter 3). Important gaps identified by patients and healthcare providers in chapter 3, were access to pharmacological treatment, access to ILD specialists, lack of disease-specific information and education, and a lack of awareness for symptom-centered, supportive interventions. Nevertheless, it should be noted that advances have been made in the last years, for instance regarding symptom relief, organization of care, and palliative care. During the last years, a number of studies have shown promising results regarding symptom relief and optimizing quality of life in pulmonary fibrosis (chapter 1). For instance, the ambOx trial investigated the effect of ambulatory oxygen on quality of life in ILD patients with exercise-induced hypoxemia. Ambulatory oxygen reduced dyspnea and improved HRQOL, measured with the K-BILD questionnaire. Further studies are needed to assess long-term effects, as this study only evaluated HRQOL after two weeks (1). A pilot study recently revealed that a triple-blinded randomized trial, using portable oxygen concentrators for a longer period of time, seems feasible in this patient group (2). A randomized trial (PFOX) is currently being conducted by this research group to evaluate whether ambulatory oxygen will increase physical activity, HRQOL, and symptoms in patients with pulmonary fibrosis after six months (3).

A recent single-center RCT analyzed the safety and efficacy of low-dose morphine on dyspnea and cough in 36 patients with pulmonary fibrosis. The first results of this study showed that one week of low-dose morphine improved cough scores and tended to improve the 6-minute walking distance, but had no effects on dyspnea (4). A prospec-

tive study on the safety of benzodiazepines and morphine in pulmonary fibrosis yielded similar findings; low-dose benzodiazepines and morphine seem to be a safe option in symptomatic patients with pulmonary fibrosis (5). These studies paved the way for larger studies evaluating the efficacy of these medications on relief of dyspnea and cough. Inhaled sodium cromoglicate (PA101) has emerged as another promising pharmacological treatment option for chronic cough in IPF; a phase II trial showed that PA101 reduced cough frequency with 31% after 2 weeks (6). The phase 2B SCENIC trial us with a slightly adjusted formulation (RVT-1601) is ongoing (7). Besides pharmacological treatment options, a number of studies are currently evaluating the efficacy of non-pharmacological treatment options, such as psychosocial and symptom management interventions, activity programs, and pulmonary rehabilitation, to improve symptoms and HRQOL in patients with pulmonary fibrosis. Outcomes of these studies will hopefully lead to novel, evidence-based treatment options, and optimize comprehensive care for patients with ILD (8). Comprehensive, personalized care models, as proposed in chapters 1 and 4, should prompt physicians to focus on more supportive and holistic approaches to care, taking into consideration recent advances made in trials of symptom relief and supportive measures.

Although evidence-based guidelines for palliative care in ILD are still lacking, an international expert working group recently generated a consensus statement, which answers important questions and provides considerations for future research on palliative care in ILD (9). The unpredictable nature and heterogeneous disease course of ILDs hamper early palliative care interventions, specifically end-of-life care (9-12). Hence, one of the proposed topics for future research is to identify markers to predict disease progression and mortality, which will allow for timely focus on end-of-life care. In other patient populations the 'surprise question' has shown to be a reliable tool to predict mortality and refer patients to palliative care services (13). This tool consists of only one question: "Would you be surprised if this patient died in the next year?". Advance care planning could be initiated if the answer on this question is 'no', obviously not without taking into account patients' needs and wishes. Preliminary data from our own cohort indicate that the surprise question predicts 1-year mortality in IPF, and could be a simple tool to improve end-of-life care for patients with IPF. Future studies should reveal whether this holds true for other ILDs.

Lack of evidence-based treatment options for sarcoidosis

In sarcoidosis, many gaps in care exist (chapter 2, chapter 6, chapter 7). We have proposed the comprehensive ABCDE model for sarcoidosis to facilitate a systematic approach to comprehensive care in sarcoidosis, and enhance individually-tailored treatment by structural (re)assessment of patients' needs and perspectives (chapter 2). Whether the

use of this model in clinical practice will improve outcomes for patients remains to be elucidated. At the moment, one of the most important gaps in care for sarcoidosis is the limited availability of evidence-based treatment options (chapter 2, chapter 7) (14). As described in chapter 2, the only available guideline for sarcoidosis is the ATS/ERS/WASOG consensus statement published in 1999 (15). Although this guideline gives certain recommendations for the use of corticosteroids and cytotoxic agents, dosing schedules and optimal duration of treatment are not well defined. Moreover, this statement does not include any recommendations about symptom relief and non-pharmacological management.

Due to the heterogeneity of sarcoidosis, trial design is complicated. Most evidence for treatment of sarcoidosis stems from retrospective studies, case series, or small randomized trials (15). Many published studies evaluated efficacy of new agents on top of treatment with immunosuppressive medication, or in patients with treatment-resistant sarcoidosis. Furthermore, it proved to be difficult to choose appropriate outcome measures, especially for extrapulmonary sarcoidosis (16). These are potential reasons for the relatively high number of sarcoidosis trials which did not meet the primary endpoint (16, 17). Nevertheless, promising new compounds are being investigated at the moment (8). For instance, the JAK-STAT signaling pathway is thought to be involved in the pathogenesis of sarcoidosis; consequently, inhibition of this pathway could be a novel treatment target. The first case reports with JAK-inhibitors described positive results, and prospective phase I studies are ongoing (18, 19). Next to anti-inflammatory therapy, antifibrotic medication is also being investigated in sarcoidosis. The INBUILD study demonstrated the efficacy of nintedanib on reducing FVC decline in patients with non-IPF ILDs, including patients with sarcoidosis. Nonetheless, the results especially in sarcoidosis should be regarded with caution as the subgroup of patients with sarcoidosis was very small. (20). A study with pirfenidone for fibrotic sarcoidosis is currently recruiting patients (21).

It should however be noted that evidence-based treatment options are not only scarce for chronic progressive sarcoidosis, but also for first- and second-line treatment. Prednisolone and methotrexate are the most commonly used therapies for sarcoidosis in clinical practice, but data supporting their effectiveness are limited (14, 15, 22). Moreover, the efficacy and side-effects of prednisolone and methotrexate have never been compared head-to-head.

Because of this major unmet need, we have designed and initiated a multicenter randomized controlled trial to compare the efficacy of prednisolone and methotrexate in newly treated patients with pulmonary sarcoidosis (PREDMETH study). We hypothesize that first-line treatment with methotrexate is as effective as prednisolone, with fewer

side-effects and a better (health-related) quality of life for sarcoidosis patients. As previously mentioned, sarcoidosis is a very heterogeneous disease, with a variable response to treatment (23, 24). At the moment, we are not able to predict disease behavior and treatment response in individual patients. Hence, under- and overtreatment is common, and patients and their partners have to deal with uncertain prospects (23). In the PREDMETH study, clinical research will be combined with translational research, with the aim to discover novel biomarkers, and to evaluate the prognostic value of recently identified biomarkers (25, 26). Results of this study will hopefully lead to increasing insights in the pathophysiological mechanisms of sarcoidosis, and identification of new therapeutic targets. If our hypothesis will be confirmed, this has important implications for future clinical practice and existing treatment guidelines.

Chapter 6 in this thesis revealed that many sarcoidosis patients and their partners experienced stress and anxiety, and would appreciate more psychological support. The majority of patients considered fatigue as their most burdensome symptom. The high prevalence and burden of fatigue has also been highlighted in other recent studies (27, 28). Nevertheless, pharmacological and non-pharmacological therapies for sarcoidosis-associated fatigue are scarce (chapter 7). In two small randomized studies, the neurostimulants armodafinil and methylphenidate had positive effects on sarcoidosis-associated fatigue (29, 30). At present, an ongoing study is assessing the feasibility and optimal design of a larger scale RCT with methylphenidate (31). A study published in 2018 demonstrated that a single mindfulness training (45 min) improved fatigue and other symptoms in patients with sarcoidosis (32). This prompted us to develop a study with a supportive intervention, aimed at improving fatigue, stress, and quality of life for patients with sarcoidosis. The Dutch Helen Dowling Institute developed a 12-week online mindfulness-based cognitive therapy for treatment of fatigue in patients with chronic diseases; in patients with cancer this has proven to be effective (33). We hypothesize that this online psychologist-guided intervention will also be an effective treatment for sarcoidosis-associated fatigue. Our randomized controlled trial (TIRED trial) will investigate the effectiveness of the online intervention on fatigue, stress levels, anxiety, depression, and quality of life in sarcoidosis patients with chronic fatigue. The effects will be assessed with subjective (patient-reported outcomes) and objective outcomes (blood biomarkers and hair cortisol levels) (34). We expect that the outcomes of this study will yield new insights into the pathobiology of sarcoidosis-associated fatigue, and the relation between fatigue and the immune system in sarcoidosis. If this study turns out positive, online mindfulness-based cognitive therapy could be offered to all patients with sarcoidosis-associated fatigue in the Netherlands, as this therapy is already reimbursed by insurance companies and geographical distances are bridged online.

Improving collaboration

Chapter 3 described a collaborative effort of the European patient association for pulmonary fibrosis and the European reference network for rare lung diseases. Especially in rare diseases such as ILD, (international) collaboration between healthcare providers, researchers, patients and other stakeholders is crucial to close gaps in care. Only in this way can we move forward to improve outcomes for patients with these debilitating disorders. Moreover, active patient participation in the design and conduct of clinical trials will likely increase the number of patient-relevant outcomes, and can enhance patient inclusion, dissemination, and implementation of study outcomes (35). Importantly, an earlier study in pulmonary fibrosis revealed that the majority of patients would like to be involved in the development of clinical trials (36). In this thesis, we have put this into practice by involving patients in the design and evaluation of our home monitoring program (chapter 8-10); this will hopefully also facilitate broader scale implementation in clinical practice.

Advances in pharmacological treatment for pulmonary fibrosis

Major steps forward have been made in the pharmacological treatment for patients with pulmonary fibrosis. Until now, immunosuppressive medication is the mainstay of treatment in most non-IPF ILDs, often based on limited evidence from retrospective studies, case series, or extrapolation from other diseases (37-39). Since the approval of antifibrotic medication for IPF, a number of studies have evaluated the efficacy of nintedanib and pirfenidone in a range of other progressive fibrotic ILDs (40, 41). First, the SENSCIS trial demonstrated the efficacy of nintedanib in patients with ILD associated with systemic sclerosis (SSc-ILD), both as monotherapy as well as add-on to immunosuppressive therapy (42). More recently, the INBUILD trial showed that nintedanib also slowed down lung function decline in patients with progressive fibrotic ILD, comparable to its effect in IPF (20). A phase II trial with pirfenidone in progressive unclassifiable fibrotic ILD described a similar effect on FVC, though the primary endpoint could not reliably be analyzed due to technical issues (43). The phase II RELIEF trial of pirfenidone in progressive fibrotic ILDs also suggested a reduction in FVC decline over time compared to placebo, but was stopped early due to the slow recruitment rate (44). Several other phase II and III trials with pirfenidone are ongoing (37). Recently, nintedanib has been approved by the FDA for patients with progressive fibrotic ILDs. The availability of antifibrotic medication for non-IPF ILDs will significantly change treatment for patients with these diseases. However, it also raises important questions which should be addressed in the upcoming years. Can we predict which patients will progress? In which patients should antifibrotic medication be initiated and in which patients immunosuppressive medication? Can antifibrotic medication be safely combined with immunosuppressive medication? If so, does this combination improve outcomes? What is the best method

to assess response to therapy and disease progression? How about the experiences with side-effects in different fibrotic ILDs? These questions highlight the importance of future trials, and real-world data collection in large registries (45).

In this thesis, we have used the PESaM questionnaire to assess patient experiences and satisfaction with medication in IPF (chapter 5, chapter 12). Most patients had positive experiences, and were relatively satisfied with their antifibrotic medication. Use of the PESaM questionnaire may aid patient education and shared-decision making in clinical practice. Long-term experiences and influence of patient satisfaction on adherence and treatment outcomes still need to be elucidated. If we validate this questionnaire in other fibrotic ILDs, patient satisfaction with antifibrotic medication and experiences with side-effects can be compared across different subgroups of patients. For instance, it could be speculated that experiences are different in patients who use a combination of antifibrotic and immunosuppressive medication. I believe that novel technological solutions, such as online home monitoring and eNose technology (chapter 8-13), will further help to answer these essential questions.

DEVELOPMENT AND EVALUATION OF EHEALTH SOLUTIONS IN ILD

The second aim of this thesis was to develop and evaluate novel eHealth solutions in ILD. We hypothesized that a comprehensive eHealth intervention could address some of the earlier identified gaps in care (chapter 3), such as the need for better information and education, improved access to care, and a greater focus on symptom-centered management. Moreover, eHealth interventions can potentially be used to gain more insights in disease course in individual patients, and thereby enable personalized treatment. Hereafter, I will give an overview of the scientific advances of the last years regarding home spirometry, eHealth, outcome measures, and artificial intelligence in ILD. Moreover, identified challenges, proposed solutions, and future perspectives on these topics will be discussed.

Home spirometry in ILD

In the field of ILD, home spirometry has gained increasing attention in the last few years. The first study of home spirometry in IPF, published in 2016, showed that home spirometry was feasible, reliable and allowed for better prediction of mortality compared with hospital-based spirometry (46). This study has led to worldwide enthusiasm regarding home spirometry in IPF, and inspired us to develop our home monitoring program IPF-online (chapter 8, chapter 9, chapter 12). A second study in IPF revealed that the use of home spirometry as endpoint for clinical trials could decrease sample size and

shorten the duration of clinical trials (47). A feasibility study suggested that patient characteristics, such as age or education were not associated with the ability to perform home monitoring of lung function and activity (48). Altogether, these studies showed an acceptable variability of home-based FVC. Adherence was relatively good, although it declined over time. This may be due to the fact that in two of these studies patients were blinded for their own results. Patients may be less motivated to adhere to daily or weekly measurements if they are unable to see how they performed (48).

Promising results from these studies led to the design of a multinational, randomized trial with pirfenidone in unclassifiable ILD; change in home-based FVC was the primary outcome measure in this study (43). Unfortunately, the primary outcome could not be analyzed according to the prespecified statistical plan, due to the high variability of the FVC measurements. For instance, some patients provided implausibly high FVC values, such as a 33L predicted change in FVC from baseline to week 24. The high variability was caused by a number of different factors: a lack of good instruction regarding home spirometry, adherence problems, and technical problems with the algorithms and quality assessment of the devices (43). In 2019, a few other home monitoring studies were presented at the congress of the European Respiratory Society (ERS). The multinational INMARK study evaluated the effects of nintedanib on biomarkers associated with extracellular matrix turnover (49). Patients who participated in this study, were asked to perform home spirometry at least once a week for 52 weeks. Results of this study showed that there was a strong correlation between home and hospital spirometry at different time points, but changes in lung function over time were only weakly correlated, possibly due to a higher variability in home-based FVC compared with hospital-based FVC (50). This is in contrast with the findings in chapter 12 of this thesis, showing similar slopes of home-based FVC and hospital-based FVC over time. In the INMARK study, adherence rate of patients remained high over time. Patients were asked to perform home spirometry at approximately the same time every day; however, more than 60% of patients alternated between morning and afternoon measurements (51). Chapter 11 in this thesis demonstrated that a diurnal variation in FVC exists in patients with fibrotic ILD. Patients provided higher and less variable FVC measurements in the morning compared with the afternoon. Accordingly, diurnal variation may have played a role in the relatively high variability observed in home spirometry measurements in the INMARK study (6, 50, 51). Two studies presented at the ERS congress in 2019 used eHealth systems for home-based collection of lung function, activity and patient-reported outcomes. Although use of novel eHealth technologies seemed promising, a number of challenges have been identified during the conduct of these studies. The multinational STARLINER study was designed to assess disease behavior of patients with suspected ILD in the peri-diagnostic period (52). Home-based measurements were used

for assessment of disease behavior. Patients collected data with a home spirometer and wrist-worn activity tracker connected to an online platform on a tablet. Interim results revealed that in patients with IPF, FVC declined during the diagnostic trajectory; in the same period, FVC seemed relatively stable in patients with non-IPF ILD (53). More than half of patients provided technically good FVC measurements, but compliance with home spirometry varied, mainly because of technical problems with the online platform. Apart from these technical problems, home spirometry has the potential to be used as a tool for early detection of FVC decline in ILD, and thereby enable timely and accurate diagnosis (53). The STARMAP study was an observational study, which assessed the feasibility of measuring disease outcomes with online home monitoring devices in a multicenter study among patients with IPF (54). Due to technical challenges and the lack of an alert system when no FVC measurements were performed, missing data were common. Moreover, home spirometry data were variable and often poorly correlated with hospital-based spirometry measurements. The authors suggested that this may be due to lack of patient training and monitoring during the study.

In our home monitoring program, the number of technical issues and missing data was lower than in most of the studies mentioned above. The most likely reason for this is the integration of an automated feedback and alert system (chapter 9, chapter 12). Additionally, patients had access to their own collected data, and a technical helpdesk in local language was available during weekdays. Patients were thoroughly instructed before start of the study, and in case of technically unacceptable measurements, patients received a follow-up training. These efforts have led to more reliable home spirometry data in our studies compared to some of the other studies mentioned here (chapter 9-12). A few prospective observational studies with novel eHealth systems in ILD are currently ongoing, and will hopefully yield new insights, for instance regarding the detection of acute exacerbations using home spirometry (55, 56).

eHealth

Novel eHealth solutions have increasingly been investigated in the past years, in a wide range of diseases. Reported benefits of eHealth in other lung diseases are improved quality of care and quality of life for patients, enhanced self-management, more cost-effective care delivery, reduction in hospitalizations and exacerbations, symptom reduction, improved medication adherence, and prolonged survival (57-63). Nevertheless, a substantial number of studies yielded mixed or negative results regarding health outcomes and quality of life (64-66).

Because eHealth is such a broad umbrella term, interventions are very diverse and study outcomes can be difficult to compare. Needs and opinions regarding eHealth vary

between patients with different diseases (67). This implies that eHealth solutions should be tailored to a specific disease, and preferably even to individual patients' needs (68). Furthermore, it is important to notice that the opinions and expectations of patients and healthcare providers regarding the preferred content of eHealth interventions can be largely different (69). Hence, a user-centered design of eHealth tools is essential for a successful intervention. According to a recently proposed model, the development of an eHealth intervention has six distinct phases (70) (**Figure 1**). The eHealth intervention in this thesis has been developed with this 'framework' in mind. In the *design phase* researchers conceptualize an idea based on an existing clinical problem, end users and stakeholders are identified, and estimated costs and technological requirements are evaluated (69, 71) (chapter 8 in this thesis). In the *pretesting and pilot study phase* short-term studies should be performed to evaluate practical, ethical and legal issues, and feasibility and reliability of the eHealth technology in a small group of participants (chapter 8-10). The *pragmatic trial phase* comprises a (randomized) trial in a larger group of participants to evaluate efficacy of the eHealth intervention in different domains (chapter 12). The *evaluation phase* can be considered as on ongoing process which al-

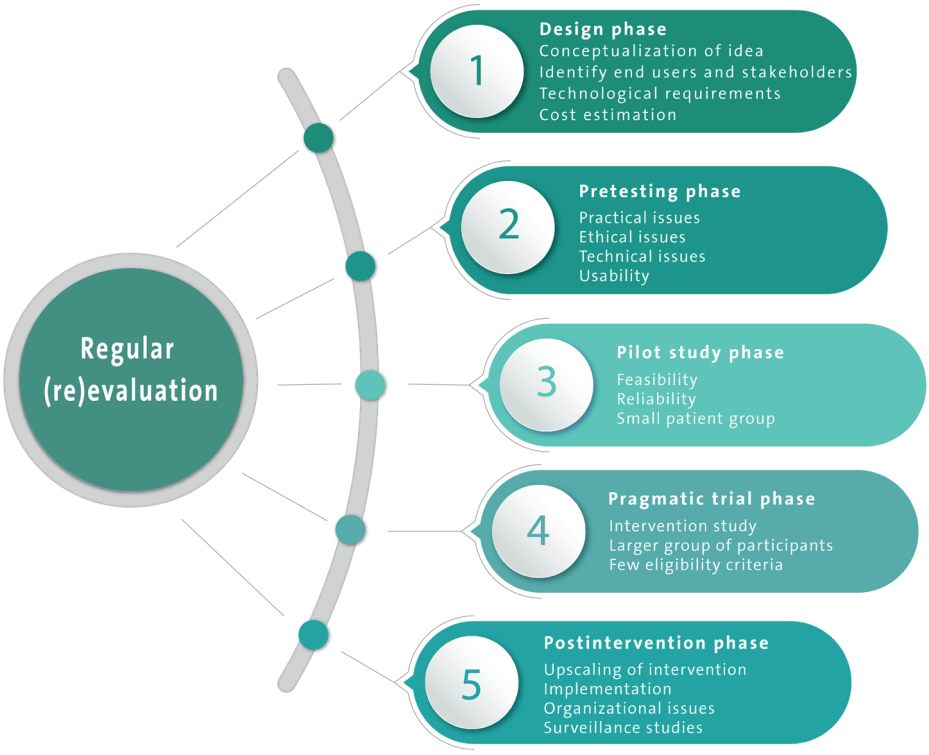


Figure 1. Framework of a user-centered development of eHealth interventions. Regular (re)evaluation plays a central role in this model. Adapted from (70).

ready starts after the conceptualization of an idea. Qualitative research, including focus groups, online surveys, and semi-structured interviews during different phases can be used for further improvement of the eHealth intervention (chapter 8-10 and 12) (72). In the *postintervention phase*, the eHealth intervention is scaled up and implemented in daily care. To evaluate the use in clinical practice, surveillance studies could be performed, for example using surveys, face-to-face or phone interviews (70).

This model for the development and evaluation of eHealth interventions could enhance wide-scale implementation in daily care. eHealth interventions will likely be better tailored to the actual end users, when a patient-centered approach with regular (re)evaluation is followed, as we did in the studies presented in this thesis (chapter 8-12). Moreover, the conduction and evaluation of eHealth studies in a more structured way may enable comparison and interchangeability of results between different diseases and patient groups in the future (70). Our eHealth intervention is currently in the *postintervention* phase; we are exploring possibilities for upscaling, implementation in daily practice, and integration into current healthcare systems, together with different stakeholders.

The coronavirus disease (Covid-19) pandemic in 2020 has accelerated this process. eHealth solutions could not only be used for screening and remote monitoring of patients with Covid-19, but also enable follow-up of patients in high-risk groups without Covid-19 (73). At the moment, we replace the regular outpatient clinic visits of patients with pulmonary fibrosis by videoconsultations, using our online home monitoring program. Patients measure their lung function at home and record symptoms and side-effects. Thus, this eHealth solution allows for frequent monitoring and follow-up at a distance, and seems to be a safe option, especially from a Covid-19 perspective. Nevertheless, the long-term effects and impact on quality of care need further study after this crisis. Home monitoring can potentially lead to more efficient healthcare delivery, as patients collect and record their own data at home. Hopefully, eHealth solutions will assure the continuity of care for patients who need frequent follow-up, and at the same time lower the burden on our healthcare system in these times of Covid-19.

Although our randomized controlled trial in patients with IPF showed that a comprehensive home monitoring program did not improve health-related quality of life measured with the K-BILD questionnaire total score (primary endpoint), many positive aspects were revealed (chapter 12). This trial provided important messages for clinicians and researchers in this field. First of all, eHealth solutions are feasible in an elderly population, such as patients with IPF. According to Eurostat, 98% of the households in the Netherlands had access to internet in 2018 (74). The proportion of people who never use internet has rapidly decreased over the past years; in 2018, only 11% of people in

the European Union had never used internet. Access to internet remains the lowest in Eastern and Southern European Countries (74). The studies in this thesis showed that only a small minority of patients with ILD in the Netherlands had no access to internet. Secondly, the vast majority of patients highly appreciated the use of an online home monitoring program, not only in IPF, but also in other fibrotic ILDs and sarcoidosis. Psychological wellbeing tended to improve, and home monitoring did not increase anxiety and depression levels. Adherence to daily spirometry and completion rate of online questionnaires remained very high over time. Feedback from patients included that the use of the home monitoring program gave them better insights in their disease course and made them feel more in control. Most patients wished to continue after the study and would recommend home monitoring to others. Thirdly, this home monitoring program allowed for individually-tailored treatment adjustments in patients who experienced bothersome side-effects. Finally, home-based FVC measurements were reliable, within-patient variability was low, and slopes of home and hospital-based FVC were comparable over time.

Taking all these findings together, I believe that (i) home monitoring has the potential to enable personalized treatment for patients with ILD in the future, and that (ii) home spirometry can be a reliable tool for frequent monitoring of lung function at home, at a low burden for patients. Nevertheless, as other home spirometry studies indicated, a number of issues have to be taken into account before eHealth interventions and home spirometry can be used on a broader scale (**Figure 2**) (43, 46-48, 50, 51, 53, 54). As described in the paragraph on home spirometry in ILD, we have already addressed many of these issues in our home monitoring program by increasing patient participation, use of alert systems, and thorough instruction of patients. For research purposes, legal, ethical and privacy issues of eHealth interventions are well covered. However, when eHealth interventions are implemented in daily care, new dilemmas may emerge. For daily care purposes, we need to take several factors into consideration, such as data ownership, data storage, legislation issues, and equal access to care for patients who choose not to use new eHealth technologies (57, 68, 75). Most importantly, the personal relationship between patients and healthcare providers should be preserved, without losing the human touch of face-to-face contacts (76).

Some important questions about the use and efficacy of home monitoring in ILD need to be addressed in future studies (**Figure 2**).

Future perspectives on home monitoring and eHealth in ILD

The home monitoring program in this thesis was used as add-on to standard care: home monitoring did not replace any outpatient clinic visits. Recently, the option for video

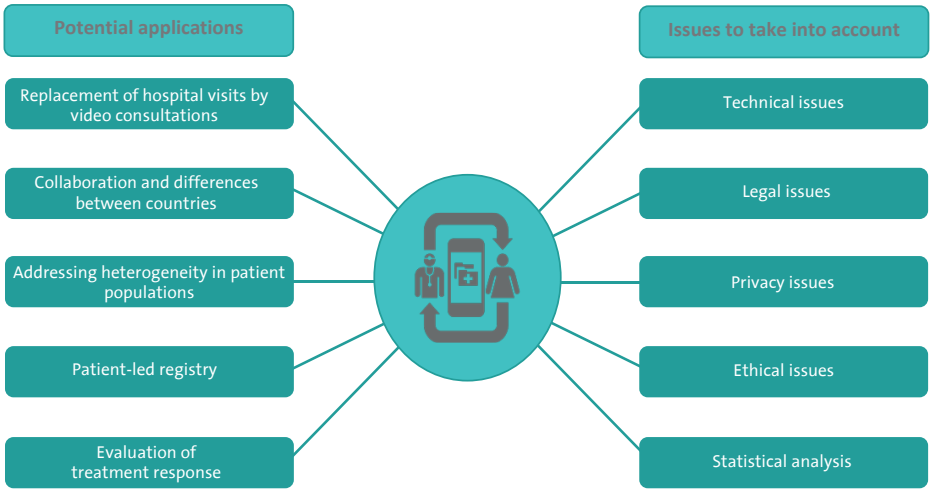


Figure 2. Potential future applications of home monitoring (left panel) and issues which should be taken into account in future studies and daily practice (right panel).

consultations has been integrated in the home monitoring program. This allows for replacement of hospital visits by remote consultations, as we currently do during the Covid-19 outbreak. A systematic review of videoconferencing in other chronic conditions concluded that patient satisfaction was generally good, and that follow-up with video consultations yielded similar health outcomes as face-to-face consultations (77). So far, evaluation of healthcare provider experiences with videoconferencing is scarce (77). The studies in this thesis showed that physiological parameters, such as lung function, and information about symptoms and side-effects could reliably be measured by ILD patients at home (chapter 8-12). The finding that these important parameters do not necessarily have to be measured in the hospital, enables the use of video consultations in clinical practice. Remote follow-up using video consultations lowers the burden of frequent hospital visits on patients and caregivers, and has the potential to improve healthcare efficiency and reduce costs. In current practice, patients with pulmonary fibrosis visit the hospital every three to four months, although strict guidelines are not available (78). I hypothesize that replacing half of the outpatient clinic visits by video consultations would be non-inferior to standard care, with regard to health outcomes and quality of life. Remote follow-up could potentially even be superior in terms of patient experiences and satisfaction with care.

Obviously, not all face-to-face visits can be substituted by video consultations, as some investigations can only take place in the hospital. Furthermore, the impact of video consultations on the quality of the relationship between patients and healthcare providers has not been fully elucidated (79). Video consultations may especially be

beneficial for patients in rural and remote areas. Although care for ILD is centralized in the Netherlands, it is a relative small country, and patients in larger countries often have to travel considerably longer to visit the hospital (80, 81). Policymakers increasingly encourage the use of web-based consultations in standard care, which leads to a better technological infrastructure, and adequate financial reimbursement, but policy makers should also be encouraged to provide adequate funding for research into safety and impact of these changes in medical practice (77, 82). Hopefully, this will facilitate future studies, which are definitely needed to gain more insights into the (long-term) efficacy of remote follow-up in patients with ILD. Clearly, the use of video consultations for patients with ILD during the Covid-19 pandemic will also provide valuable information about the feasibility, experiences, and satisfaction of patients and healthcare providers in daily practice.

The eHealth studies in this thesis have all been conducted in the Netherlands. However, the organization of care for patients with ILD differs throughout Europe (chapter 3), and internet access also varies (74). So far, only one eHealth study in ILD included patients in different European countries and in Canada, but final results of this study have not yet been published (52). Hence, it would be desirable to evaluate whether online home monitoring, including spirometry, is feasible and yields similar results across subregions in Europe. Because home monitoring programs enable frequent collection of relevant outcomes outside of the hospital, a real-world patient-led registry could be established with these data. In recent years, many national IPF registries and a number of ILD registries have been initiated, but trans-border collaboration and pooling of data have encountered multiple hurdles and have had limited success so far (45, 83-87).

In a multinational patient-led registry, patients will be able to give informed consent for the use of their data for different projects on an ongoing basis; in this way, many hurdles of current collaborative efforts can be overcome. This will open the door to meaningful collaboration between patients, doctors, researchers, and other stakeholders to improve insights in disease behavior and response to therapy across diseases and borders. Taking this in consideration, we have set up the multinational I-FILE study, in which 500 newly diagnosed patients with fibrotic ILD will be included and monitored during two years. Patients will perform frequent home spirometry and complete (health-related) quality of life questionnaires every six months. Moreover, clinical characteristics, radiology features, and pathology data will be collected. The main aims of this study will be to assess long-term FVC change in patients with fibrotic ILD measured with home spirometry, to evaluate the feasibility of a multinational patient-led registry in fibrotic ILD, and to better validate patient-reported outcome measures in different ILD subgroups. Home spirometry will hopefully enable earlier detection of disease progression compared to

less frequent hospital-based measurements. This online patient-led registry will provide much needed insights in disease behavior, progression, and response to (new) treatments in a large and diverse group of fibrotic ILDs.

Home monitoring can also allow for timely detection of treatment response in diseases where we expect an improvement in lung function, such as sarcoidosis (88). In the earlier mentioned PREDMETH study, online home spirometry will be used to assess time to pulmonary improvement for prednisolone and methotrexate. For prednisolone, the time to maximum improvement in lung function is approximately 2-3 weeks (88). Although methotrexate is thought to work much slower, with a maximal effect after 4-6 months, this has never been properly investigated before (89). Weekly home spirometry after initiation of sarcoidosis treatment will provide us with increasing insights in these drugs. Subsequently, a follow-up study could look at home monitoring as a way to better titrate and taper medication in patients with sarcoidosis and possibly also other lung diseases, thereby enhancing individually-tailored treatment.

Endpoint for clinical trials

Physiological outcome measures

In almost all medication trials in ILD so far, FVC has been used as primary endpoint (20, 40-42, 90). FVC is widely accepted as the best assessment of progression of fibrosis, and is considered as a surrogate endpoint for mortality (91-93). A difference in FVC of 2-6% has been reported as clinically meaningful (91). FVC measurements have an inherent variability and fibrotic ILDs have an unpredictable disease course (94). Hence, the standard daily care practice of FVC measurement once per three to six months might be not enough to reliably assess changes in disease course in the individual patient, guide treatment decisions, and timely detect acute exacerbations. Furthermore, from a clinical trial perspective, more refined techniques are needed to measure FVC. In IPF, new drugs will be investigated on top of background antifibrotic therapy in most patients. This will complicate the design of future studies, and likely result in even smaller margins of change in FVC, lengthy trials, and larger sample sizes (94, 95).

Previous phase III trials in IPF showed around 100 ml annual FVC decline in patients receiving nintedanib or pirfenidone. If, for instance, addition of a new anti-fibrotic drug also leads to 50% reduction in annual FVC decline, the estimated difference in annual decline between intervention and placebo would only be around 50 mL. Hence, evaluating treatment response will probably become even more challenging in the future (95). Home spirometry has been suggested as a tool to improve endpoint efficiency, as smaller sample sizes would be needed due to the high frequency of FVC measurements (47). In chapter 11, we demonstrated that there is a diurnal variation in FVC in fibrotic

ILD, which should be taken into account in future trials using home spirometry as primary or secondary endpoint. Patients had a higher FVC in the morning compared to the afternoon. The difference of 36 mL may seem rather small; however, differences of 30-40 mL are definitely relevant for future research purposes. For instance, in a phase III trial with nintedanib in SSc-ILD, the difference in FVC between nintedanib and placebo after 52 weeks was 41 mL (42). Further suggestions to improve the reliability of home spirometry as endpoint for clinical trials have been described earlier in this general discussion.

Physical activity has recently also been proposed as surrogate endpoint for mortality in IPF, though evidence for this is very limited. One study showed that steps per day, measured with an activity tracker, predicted mortality in IPF (96), but this has not been validated yet in other cohorts and definitely needs further study. Decline in physical activity might be a sensitive measure to capture disease deterioration, as it seems to reflect the overall health status of a patient (96). In this study patients wore the activity tracker for two periods of a week, with three years in between (96). In chapter 11, we described that patients with fibrotic ILD were able to wear bluetooth-connected activity trackers for a prolonged period of time (three months) and directly send their results to the research team. Patients included in this study will be followed over time to assess whether we can confirm the previous findings that physical activity predicts disease mortality in IPF. In this thesis, we have shown that sarcoidosis patients highly appreciated the use of an activity tracker with inbuilt behavioral change techniques (chapter 10). eHealth interventions with incorporated activity trackers could facilitate telerehabilitation programs in ILD. At the moment, pulmonary fibrosis patients across Europe do not have equal access to pulmonary rehabilitation (chapter 3), mainly because of reimbursement issues and long travel distances (97). Telerehabilitation has the potential to overcome geographical barriers, as distances are bridged online (98). In COPD studies, telerehabilitation has been proposed as safe and feasible alternative of institution-based pulmonary rehabilitation. Moreover, pilot studies have indicated that telerehabiliation has similar outcomes with regard to exercise capacity and health-related quality of life (98-100). Whether telerehabilitation also improves health outcomes and quality of life for patients with ILD, should be investigated in future studies. Two telerehabilitation studies are currently ongoing, one in patients with pulmonary sarcoidois, and one in a diverse group of ILDs (101, 102).

Patient-reported outcome measures

Next to physiological outcomes, patient-reported outcome measures (PROMs) have increasingly been used as endpoint in clinical trials. In 2018, the first medication trial in IPF using HRQOL as primary endpoint was published (103). This trial investigated the effect of sildenafil added to nintedanib on HRQOL, measured with the Saint George

Respiratory Questionnaire (SGRQ), in IPF patients with a severely decreased DLCO. A combination of sildenafil and nintedanib did not improve HRQOL, even though patients who used both medications had a lower risk of FVC decline (>5%) or death. The SGRQ has been originally developed for COPD. It could be questioned whether this questionnaire is sensitive enough to capture subtle changes in HRQOL in this patient group, as some of the questions might be less applicable in IPF than in COPD.

In the last years, more disease-specific PROMs have become available in ILD, although some of these PROMs have not been properly validated yet, or only in a subgroup of ILDs (chapter 4). The ambOx trial was the first randomized study in ILD showing an effect on HRQOL with a non-pharmacological intervention (1). Ambulatory oxygen improved HRQOL measured with the K-BILD questionnaire, in patients with pulmonary fibrosis who had exertional hypoxemia. For our comprehensive eHealth intervention, which targets multiple domains of a patients' life, it proved to be more difficult to select an appropriate endpoint (chapter 12). Results of this RCT suggest that it might be a better option to choose psychological wellbeing as primary endpoint for this type of eHealth interventions. Besides quality of life, it would also be interesting to study the effects of eHealth interventions on patient activation and self-management. For this purpose, validated PROMs exist, although these have never been used in ILD so far (chapter 12) (104, 105). Surprisingly, valid PROMs to assess patient satisfaction with eHealth are currently lacking. Consequently, efforts should be made to develop this type of PROM, especially since patient satisfaction is an important secondary outcome in many eHealth studies.

Next to PROMs, patient-reported experiences measures (PREMs) can be used to evaluate patient experiences with healthcare processes (chapter 4). Research into PREMs has expanded during the last years, both in ILD as well as in other fields (106). In ILD, one generic PREM concerning patient experiences with care during the disease trajectory, is currently under development (IPF-PREM) (107). Furthermore, the PESaM questionnaire, which assesses patient experiences and satisfaction with medication, has recently been validated in IPF (108, 109). In this thesis, we showed that the PESaM questionnaire enabled structured evaluation of patient experiences and satisfaction with antifibrotic medication (chapter 5). Hence, PREMs may be of added value for future research purposes, but also to enhance shared-decision making and facilitate treatment choices in clinical practice. PREMs could probably also be used to evaluate 'best practices' in care among different centers and healthcare systems, and to compare patient experiences with eHealth interventions to standard care.

In the upcoming years, we need to better validate existing outcome measures in ILD subgroups, and define the most appropriate PROMs for future studies. Although the

growing number of available PROMS in ILD can be seen as an important step forward, we also have to be aware of an overkill of newly developed questionnaires. Having too many available PROMs will make it even more difficult to choose the most appropriate endpoints, and will hamper the interpretation and interchangeability of study results. Nevertheless, I believe that PROMs and PREMs have the potential to be used in daily practice to improve quality of care and health outcomes for patients with ILD. In this thesis, we have shown that the online administration of PROMs (ePROMs) is feasible and reliable in elderly patients with ILD (chapter 8, 9, 11 and 12); this will facilitate implementation in daily care, as results of ePROMs are directly available for patients and healthcare providers.

Artifical intelligence

eNose technology

Exhaled breath analysis using eNose technology has shown to be a promising new tool in the diagnosis of ILD (chapter 13). The eNose used in this thesis (SpiroNose) reliably discriminated ILDs from healthy controls, patients with IPF from patients with non-IPF ILD, and fibrotic from non-fibrotic ILD. Moreover, the eNose could distinguish between individual diseases. Even though this was only a first pilot study, the number of included patients was relatively high, and we have confirmed most results in an external validation cohort. In other chronic lung diseases, eNose technology yielded reliable, repeatable, and interchangeable results (110). In asthma and COPD, eNose technology has been used to cluster patients based on their phenotype (e.g. exacerbation rate, atopy, eosinophilia), and to predict eosinophilic and neutrophilic blood count (111). In non-small cell lung cancer, response to immunotherapy could be reliably predicted with exhaled breath analysis (112). These promising findings indicate that eNose technology can be used for both diagnosing as well as monitoring of chronic lung diseases.

In ILD, new technologies with the potential to predict response to therapy, disease progression, and mortality are urgently needed. Currently, we are investigating the potential of eNose analysis of exhaled breath as a biomarker for disease progression and response to treatment in a diverse group of fibrotic ILDs. It would especially be of added value if the eNose could differentiate between a more inflammatory and a fibrotic phenotype, and thereby guide often difficult treatment choices in fibrotic ILDs (i.e. start antifibrotic medication, immunosuppressive medication, or a combination of both). Many other important topics could potentially be addressed using eNose technology in the next years. For instance, one of our questions is whether different clusters of patients can be identified based on exhaled breath analysis in sarcoidosis. Sarcoidosis is as a very heterogeneous disease; being able to better phenotype patients could help to increase our knowledge about sarcoidosis, and facilitate future research. Further studies should

also reveal whether eNose technology could function as biomarker for disease activity in sarcoidosis and be used to monitor disease course.

The SpiroNose is integrated with an online artificial intelligence based platform (Breathbase®). Sensor data are directly transferred to the extensive online cloud, which classifies patients through pattern recognition. Because of the self-learning algorithms, the classification of patients is becoming increasingly more accurate when more patient data are added in the cloud (so-called machine learning). As data can be analyzed real-time, this solution could potentially be used for point-of-care diagnosis in the doctors' office. Hopefully, this will enable earlier diagnosis of ILD in the future, and enhance individually-tailored management. So far, this is one of the few examples of technology based on artificial intelligence in ILD.

What is artifical intelligence?

Before contemplating about potential appliations of artificial intelligence in ILD, the concept of artificial intelligence and related terms, such as big data, should be further clarified. *Artifical Intelligence* (AI) is a broad concept, which can be defined as the ability of computer systems to simulate human intelligent behavior. Numerous AI applications have been integrated in healthcare since 1956, when the term AI was introduced for the first time (113). A few examples of existing AI applications in healthcare are the automated interpretation of electrocardiography, automated detection of lung nodules with CT scans, and AI-assisted robotic surgery (113-115). Particularly in the field of radiology AI applications have been emerging in the past decades (114).

Machine learning is a subset of AI and entails the ability of computers to learn from data; it applies statistical models to (large) data sets without explicit programming (115). Machine learning algorithms can be used to find patterns in data and predict outcomes. Importantly, machine learning algorithms are self-learning: input of new data will be automatically used to optimize the accuracy of predictive models (115). Machine learning consists of supervised and unsupervised learning. In supervised learning models, data are labelled (i.e. specific diagnoses), and the algorithm is trained to recognize these different outcomes (chapter 13) (116). If adequately trained, the algorithm will be able to predict the outcome of unlabelled data (115). Conversely, unsupervised learning utilizes unlabelled data; the algorithm determines whether distinct clusters can be detected in the based on communalities in the presented data. Unsupervised learning could be used to phenotype patients, and identify subgroups of patients that may clinically not have been identified yet, thereby enhancing personalized medicine (117).

Deep learning, a subset of machine learning, goes one step further. Deep learning models consist of a network of algorithms mimicking the neural networks in the brain. A wide variety of datatypes can be used simultaneously in deep learning algorithms

(118). Hence, deep learning will particularly have added value for large datasets with heterogeneous data (119). Datasets with a large volume, a wide variety of structured and unstructured data, and continuous update of data can be classified as *big data* (120). Accordingly, big data is characterized by three 'V's: volume, variety and velocity. Especially in the current era of 'omics', internet and mobile devices, massive amounts of data are generated, which cannot always be analyzed with 'classic' statistical methods (120).

The future of artificial intelligence in lung diseases

Current AI applications in lung diseases include automated recognition of pulmonary function tests, detection and interpretation of CT patterns, eNose technology, and eHealth interventions (116). In COPD and asthma, machine learning algorithms have been incorporated in a few eHealth systems to predict exacerbations (121). To realize this, a combination of physiological and patient-reported outcomes have been combined in a predictive model. Although some of these studies yielded promising results, further validation in larger cohorts is needed (121). Within ILD, one study used deep learning algorithms to detect distinct CT patterns in patients with pulmonary fibrosis. The deep learning model classified CT patterns with the same accuracy as a group of 91 thoracic radiologists, and outperformed around two thirds of individual radiologists (122).

Currently, an important limitation for use of AI in ILD is the relatively small amount of available data, due to the low prevalence of ILD (122). However, with expanding multinational collaborations, real-world registries and online home monitoring systems, we will move further towards more data-driven medicine and big data. For instance, our current home monitoring program already collects data about lung function, clinical, radiological and pathological features, symptoms, side-effects, quality of life, physical activity and geographical location of patients. These data can be combined with data from electronic health records, biomarkers, and 'omics' data. Integrating all these data into AI-based algorithms will hopefully allow us to improve diagnostics, and to predict disease course and response to treatment for individual patients in the future.

CONCLUSION

Altogether, the innovative approaches to patient-centered care and research presented in this thesis could be used to address identified needs and gaps in care, and thereby optimize the care pathway for patients with ILD. By using novel eHealth solutions and eNose technology we will gain increasing insights in disease behavior in individual patients in the future, facilitating personalized treatment.

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Summary

Interstitial lung diseases (ILDs) encompass a diverse group of more than 200 different disorders, which diffusely affect the lungs. ILDs can be characterized by inflammation, fibrosis, or a combination of both. The disease course of different ILDs widely varies. A subgroup of patients with fibrotic ILDs has a progressive disease course, with a poor prognosis. IPF is the most common ILD, and has a mean survival of approximately 3-5 years after diagnosis. For IPF, two antifibrotic drugs are available that slow down disease progression. Up to now, immunosuppressive medication is the mainstay of treatment in other ILDs. Recently, antifibrotic drugs have also shown to reduce lung function decline in patients with progressive, fibrotic ILDs other than IPF. Thus, the treatment landscape for patients with these diseases will importantly change in the upcoming years. Next to IPF and other fibrotic ILDs, this thesis also focused on patients with sarcoidosis. Sarcoidosis is a chronic, heterogeneous disease, which can affect almost every organ. The lungs are involved in around 90% of patients. Sarcoidosis may resolve spontaneously or after treatment, but becomes chronic and progressive in a substantial minority of patients.

ILDs often have a major impact on (health-related) quality of life (HR(QOL)) of patients and their families, due to symptoms as dyspnea, cough, and fatigue. Besides disease-modifying treatment, non-pharmacological treatment options, such as ambulatory oxygen, psychological support, and pulmonary rehabilitation, are important components of comprehensive care for patients with ILD. Despite evolving treatment options, many (unmet) needs of patients and healthcare providers have been identified in the past decade. In part 2 of this thesis, we aimed to assess current gaps in care, patients' needs and experiences with the care pathway. These novel insights are highly needed to facilitate a patient-centered approach to care and research in ILD. In part 3 of this thesis, we developed and evaluated innovative eHealth solutions for patients with ILD. We hypothesized that a comprehensive eHealth intervention could improve health outcomes for patients with ILD, and enable personalized treatment.

PART 2: GAPS IN CARE IN ILD

Chapter 3 describes the results of a Europe-wide survey among patients with different forms of pulmonary fibrosis, and healthcare providers with ILD expertise. The aim of this survey was to identify current gaps and unmet needs in care for patients with pulmonary fibrosis. Furthermore, a literature search was performed to compare previously reported unmet needs with the results of the current study. Patients and healthcare providers from 14 different countries completed the survey. Timely and equal access to ILD specialists, pharmacological, and non-pharmacological treatment were reported as important gaps in care. Moreover, patients mentioned the need for accurate informa-

tion, more awareness for pulmonary fibrosis, symptom-centered management, and support throughout the disease course. Unmet needs reported in this study were in line with previously identified needs of patients. Based on the results of the survey, a panel of patients and ILD experts proposed recommendations to improve the care pathway for patients with pulmonary fibrosis, which could be taken into consideration for future healthcare decisions.

In **chapter 4** we discussed a new concept for personalized medicine in IPF. Until now, the field of personalized medicine has mainly focused on biology (i.e. genetics, molecular biomarkers). However, patients have different personal circumstances, beliefs, experiences, needs, personalities, and lifestyles, often summarized as "personomics". Personomics can influence response to treatment and disease behavior. In order to enhance individually-tailored treatment in IPF, these patient factors should also be taken into account. Patient-collected outcomes, such as patient-reported outcome measures (PROMs), can be used for systematic evaluation of patient perspectives. PROMs are increasingly used in research and daily care to assess (health-related) quality of life, experiences with care, symptoms, and side-effects. Other patient-collected outcomes, such as home-based monitoring of lung function, can facilitate monitoring of disease progression and response to treatment. Only by integrating biological information with patient-collected information, will we be able to optimize personalized treatment for patients with IPF.

In **chapter 5,** patient expectations, experiences, and satisfaction with antifibrotic medication were systematically evaluated using the PESaM questionnaire. Patients completed the PESaM questionnaire before start of antifibrotic medication, after three months, and after six months of treatment, as part of a randomized controlled home monitoring trial (chapter 12). Patient expectations before start of treatment were high. Experiences and satisfaction with effectiveness, side-effects, and ease of use of antifibrotic drugs were relatively positive, and similar for nintedanib and pirfenidone. Nevertheless, patients rated effectiveness of antifibrotic medication after six months lower than expectations at baseline, which emphasizes the importance of realistic expectation management. Patients considered the perceived effectiveness of medication significantly more important than side-effects and ease of use. In line with this, experience with effectiveness was the main factor associated with overall medication satisfaction after six months of antifibrotic treatment. We believe that systematic evaluation of patient experiences using the PESaM questionnaire can facilitate shared-decision making in clinical practice.

In **chapter 6**, we assessed (unmet) needs and perceptions of patients with sarcoidosis. Although the high burden of sarcoidosis is well known, needs of patients with sarcoidosis

and their partners had never been investigated before. During two sarcoidosis information meetings, attendees were interviewed with interactive voting boxes. Fatigue was reported as most burdensome symptom by almost half of patients. This study revealed that sarcoidosis not only has a major impact on patients, but also on their partners. Many patients and partners experienced anxiety; more attention for psychological support was warranted by the majority of patients. Moreover, participants reported the need for better information about sarcoidosis, access to a center of expertise, practical support, contact with peers, and more supportive care for partners. The vast majority of patients appreciated the interactive interviewing and considered it a good method to receive education.

Fatigue is not only one of the most common and burdensome symptoms in sarcoidosis (chapter 6), but also in other ILDs. **Chapter 7** describes the most recent insights into the prevalence, etiology, impact, and treatment of fatigue in ILD. Even though the high burden of fatigue in ILD is increasingly recognized, studies focusing on pharmacological and non-pharmacological treatment options are scarce. The current knowledge about fatigue is largely extrapolated from areas outside ILD; many factors causing fatigue in other chronic diseases also play a role in ILD. Fatigue is often a complex, multifactorial problem, which is caused and aggravated by a combination of predisposing, precipitating, and perpetuating factors, such as deterioration of the underlying disease, comorbidities, side-effects of medication, physical and psychological symptoms, and behavioral factors. A comprehensive, structured evaluation of all these different factors is essential to determine the best treatment strategy in individual patients. If all treatable causes are excluded, or fatigue persists despite optimal treatment of possible underlying causes, general treatment options, such as pulmonary rehabilitation or psychological interventions can be considered. Hopefully, the results of ongoing and future studies will eventually lead to better evidence-based treatment options for fatigue in ILD.

PART 3: DEVELOPMENT AND EVALUATION OF EHEALTH SOLUTIONS IN ILD

During two pulmonary fibrosis information meetings in 2014 and 2015, we have asked patients whether they would like to keep track of their own health data online. Because the vast majority of our IPF patients responded positively, we have developed the eHealth tool IPF-online. **Chapter 8** reports on the multi-step co-development of this eHealth tool in IPF, together with patients. As this was the first eHealth initiative in IPF worldwide, the content of IPF-online was based on literature from other fields, suggestions from patients and healthcare providers. The first version of IPF-online consisted of an information library, an eConsultation option, online PROMs, and an overview of

medication. Two groups of patients with IPF participated; the first group of used IPF-online for 14 days, and completed PROMs at baseline and at the end of the pilot study. Suggestions of the first group were incorporated to improve the eHealth tool. Another group of patients tested and evaluated the adjusted version of IPF-online. Overall, the use of IPF-online was highly appreciated by patients. In the second group, all patients continued the use of IPF-online after the end of the pilot. Moreover, all patients in this elderly patient group managed to complete online PROMs; these are encouraging results for future research, as this will probably minimize missing data.

Based on the suggestions of patients from the first pilot study in chapter 8, IPF-online has been expanded with home-based measurements of FVC. In **chapter 9**, we performed a second pilot study with this home monitoring program. Ten patients performed once daily home spirometry for four consecutive weeks. In addition, patients completed a weekly questionnaire about symptoms and side-effects, and completed validated PROMs at baseline and after four weeks. The system generated automated email alerts if FVC data were missing for three consecutive days, if FVC significantly declined (≥10% from baseline) on three consecutive days, or if patients reported bothersome side-effects. Home-based FVC was highly correlated with hospital-based FVC, and variability of home-based FVC was low. Adherence to daily home spirometry was high, and all patient considered home spirometry useful and not burdensome. No major barriers for online home spirometry were identified in this study. For all potential issues, relatively easy solutions were proposed by patients and the research team.

In **chapter 10**, we have adapted our home monitoring program for sarcoidosis, and evaluated feasibility and patient satisfaction in a pilot study. Ten patients with sarcoidosis used the home monitoring program for a month. After one month experiences were evaluated during a phone interview. The home monitoring program for sarcoidosis included daily home spirometry, activity tracking with a wrist-worn activity tracker, and patient-reported outcome measures at baseline and after one month. Compliance with daily home spirometry and activity tracking was high, and within-patient variability of FVC measurements was acceptable. Overall, patient experiences were positive, and most patients mentioned that it was useful to keep track of their disease at home. Moreover, some patients answered that the use of an activity tracker motivated them to become more active. This study showed that home monitoring is feasible in sarcoidosis and could be used for research purposes, and possibly also in daily practice.

In **chapter 11**, we evaluated whether there is diurnal variation in FVC in patients with fibrotic ILD, using our previously developed home monitoring program (chapter 8-10). Furthermore, we investigated the relation between FVC and activity just before the

FVC measurement. FVC was measured with twice daily home spirometry, once in the morning and once in the afternoon. Steps were continuously counted with a wrist-worn activity tracker. Results of this study revealed that patients had a significantly higher FVC in the morning than in the afternoon, although the difference was numerically small. FVC variability was lower in the morning than in the afternoon. Step count was lower before the FVC measurement in the morning than in the afternoon; however, in general, patients were relatively inactive before both measurements. Thus, the mechanism behind the observed diurnal variation in FVC could not be fully explained and needs to be explored further. As the margins in FVC change in medication trials in fibrotic ILD can be very small, we believe that timing of home spirometry should be standardized in future studies.

Chapter 12 presents the results of the first-ever multi-center randomized controlled trial with an eHealth intervention in IPF. In total, 90 patients were included and randomly assigned to either standard care or the use of the home monitoring program IPF-online on top of standard care for 24 weeks. The primary outcome was the between-group difference in change in the total score of the King's Brief Interstitial Lung Disease Questionnaire (K-BILD). All patients completed patient-reported outcomes on (health-related) quality of life, anxiety and depression, medication, symptoms and side-effects at baseline, 12 weeks and 24 weeks. Patients in the home monitoring group performed daily home spirometry and completed weekly questionnaires about symptoms and side-effects. The research team received email alerts in case of missing FVC values, significant decline in FVC, and bothersome side-effects (see chapter 9). We found that the use of this home monitoring program did not significantly improve health-related quality of life, measured with K-BILD. Nevertheless, psychological wellbeing tended to improve in the home monitoring group, medication was more often adjusted, and patients highly appreciated the use of the home monitoring program. Adherence was high and most patients wished to continue home monitoring after they had completed the study. Importantly, daily home monitoring did not lead to higher anxiety and depression scores. Furthermore, this study showed that daily home spirometry was feasible and reliable in a multicenter trial. Slopes of home and hospital spirometry over time were comparable, and variability of home-based FVC was low. Altogether, these findings suggest that eHealth solutions can potentially enhance personalized treatment and improve health outcomes for patients with IPF in the future.

Chapter 13 describes the potential of exhaled breath analysis using eNose technology as non-invasive diagnostic tool for ILD. The many different volatile organic compounds in exhaled breath form a unique breathprint, which can be detected with an eNose. In this cross-sectional study we analyzed exhaled breath of ILD patients and healthy controls.

We included ILD patients with sarcoidosis, IPF, ILD associated with connective tissue disease, chronic hypersensitivity pneumonitis, idiopathic NSIP, interstitial pneumonia with autoimmune features, and other ILDs. eNose technology perfectly distinguished ILD patients from healthy controls in a training and validation set. Subsequently, we compared breathprints of ILD subgroups. The eNose adequately discriminated between individual ILDs, IPF and other ILDs, and patients with pulmonary fibrosis versus patients without pulmonary fibrosis. Hence, we believe that eNose technology may be a promising novel biomarker in ILD, enabling timely and accurate diagnosis.

Chapter 14 is a general discussion of the findings described in this thesis and future perspectives.

Samenvatting

Interstitiële longziekten (ILD) is een verzamelnaam voor een groep van meer dan 200 verschillende longziekten die over het algemeen beide longen diffuus aantast. ILDs kunnen worden gekenmerkt door inflammatie, fibrose (littekenvorming), of een combinatie van beide. Het ziektebeloop kan erg variëren. Een subgroep van patiënten met longfibrose heeft een progressief ziektebeloop met een slechte prognose. Idiopathische longfibrose (IPF) is de meest voorkomende ILD en heeft een gemiddelde overleving van 3-5 jaar na diagnose. Voor de behandeling van IPF zijn twee fibroseremmers beschikbaar (nintedanib en pirfenidon), die de achteruitgang van de longfunctie remmen. Tot nu toe worden andere ILDs voornamelijk behandeld met middelen die de werking van het afweersysteem onderdrukken (immuunsuppressiva). Recent zijn echter studies gepubliceerd waaruit blijkt dat fibroseremmers ook de achteruitgang van de longfunctie remmen in andere vormen van longfibrose. Hierdoor zal de behandeling voor deze patiëntengroep de komende jaren substantieel gaan veranderen. Een andere veel voorkomende interstitiële longziekte is sarcoïdose. Sarcoïdose is een chronische, heterogene ziekte, die in bijna ieder orgaan kan voorkomen. De longen zijn in ongeveer 90% van de patiënten aangedaan. Soms verbetert sarcoïdose spontaan of na behandeling, maar in een deel van de patiënten wordt de ziekte chronisch en progressief.

Het hebben van een interstitiële longziekte heeft een grote impact op de (gezondheidsgerelateerde) kwaliteit van leven van patiënten en hun familie, met name door symptomen als benauwdheid, hoesten en vermoeidheid. Naast medicamenteuze behandeling, zijn niet-medicamenteuze behandelopties zoals zuurstoftherapie, psychologische ondersteuning en longrevalidatie, belangrijke componenten van holistische zorg voor patiënten met ILD. Ondanks alle nieuwe behandelmogelijkheden van de laatste jaren, zijn er veel verschillende zorgbehoeften geïdentificeerd door patiënten en zorgverleners. In deel 2 van dit proefschrift hebben we de huidige zorgbehoeften, hiaten in de zorg en ervaringen van patiënten met het zorgproces in kaart gebracht. Deze nieuwe inzichten zijn hard nodig om de zorg verder te optimaliseren en onderzoeken te kunnen initiëren die erop gericht zijn om relevante uitkomsten voor patiënten te verbeteren. In deel 3 van dit proefschrift hebben we een innovatieve eHealth interventie ontwikkeld en geëvalueerd voor patiënten met ILD. De hypothese was dat een uitgebreide eHealth interventie gezondheidsuitkomsten voor patiënten zou kunnen verbeteren en gepersonaliseerde behandeling mogelijk kan maken.

DEEL 2: HIATEN IN DE ZORG VOOR PATIËNTEN MET ILD

Hoofdstuk 3 beschrijft de resultaten van een Europese enquête onder patiënten met verschillende vormen van longfibrose en zorgverleners gespecialiseerd in ILD. Het doel

van de enquête was om de huidige hiaten in de zorg en zorgbehoeften te identificeren. Patiënten en zorgverleners uit 14 verschillende landen hebben de enquête ingevuld. Tijdige toegang tot ILD specialisten, medicamenteuze en niet-medicamenteuze behandeling en gelijke zorg voor patiënten in verschillende landen werden gerapporteerd als belangrijke hiaten in de zorg. Verder noemden patiënten de behoefte om betere informatie te krijgen, meer aandacht voor longfibrose, symptoomgerichte behandeling en betere ondersteuning gedurende het ziekteproces. De gerapporteerde zorgbehoeften in deze studie waren grotendeels hetzelfde als in eerdere studies. Naar aanleiding van de studieresultaten, hebben een panel van patiënten en ILD experts aanbevelingen opgesteld om de zorg voor patiënten met longfibrose te verbeteren.

In **hoofdstuk 4** hebben we een nieuw concept voorgesteld voor gepersonaliseerde behandeling in IPF; tot nu werd er vooral gefocust op genetica, biomarkers en andere biologische processen. Echter hebben alle patiënten een verschillende persoonlijkheid, omstandigheden, ervaringen, behoeften en leefstijl. Dit wordt soms samengevat met de term 'personomics'. Niet alleen biologische processen, maar ook personomics kunnen de reactie op behandeling en het verloop van de ziekte beïnvloeden. Om werkelijk 'op maat gemaakte' behandeling mogelijk te maken voor patiënten, moet ook met deze persoonlijke factoren rekening gehouden worden. Door de patiënt verzamelde uitkomstmaten, zoals patiënt-gerapporteerde uitkomstmaten (PROMs), kunnen gebruikt worden voor systematische beoordeling van patiënt perspectieven. PROMs worden steeds meer gebruikt in onderzoek, maar ook in de dagelijkse zorg, om kwaliteit van leven, ervaringen met zorg, symptomen en bijwerkingen te kunnen evalueren. Andere uitkomsten die verzameld worden door patiënten, zoals thuismeting van de longfunctie met een draagbare spirometer, maken het mogelijk om het ziekteverloop en de reactie op medicamenteuze behandeling nauwkeurig op afstand te monitoren. Alleen door het integreren van 'biologische informatie' met door de patiënt verzamelde informatie, kunnen we persoonlijke behandeling voor patiënten met IPF optimaliseren.

In **hoofdstuk 5** werden de verwachtingen, ervaringen en tevredenheid van patiënten met fibroseremmers systematisch geëvalueerd met de PESaM vragenlijst. Patiënten vulden deze vragenlijst in vóór start van fibroseremmers, na drie maanden en na zes maanden in het kader van een gerandomiseerde studie (hoofdstuk 12). Verwachtingen van patiënten voor start van de behandeling waren hoog. Ervaringen en tevredenheid met de effectiviteit, bijwerkingen en gebruiksgemak van fibroseremmers waren vrij positief, en waren vergelijkbaar voor nintedanib en pirfenidon. De ervaringen van patienten na zes maanden waren iets lager dan de verwachtingen, wat het belang van realistisch verwachtingsmanagement benadrukt. Patiënten vonden de ervaren effectiviteit belangrijker dan bijwerkingen en gebruiksgemak; de ervaren effectiviteit was dan ook

de enige factor die geassocieerd was met tevredenheid over de medicatie. We geloven dat systematische evaluatie van verwachtingen en ervaringen met de PESaM vragenlijst kan bijdragen aan 'shared-decision making' in de dagelijkse praktijk.

In **hoofdstuk 6** evalueerden we de zorgbehoeften en ervaringen van patiënten met sarcoïdose en hun partners. Alhoewel de hoge ziektelast van sarcoïdose bekend is, zijn de zorgbehoeften van patiënten en hun partners nog nooit onderzocht. Tijdens twee sarcoïdose informatie bijeenkomsten werden aanwezigen geïnterviewd door middel van interactieve stemkastjes. Bijna de helft van de patiënten gaf aan dat vermoeidheid hun meest belastende symptoom was. Een belangrijke bevinding uit dit onderzoek was dat sarcoïdose niet alleen veel impact heeft op de patiënten, maar ook op hun partners. Veel patiënten en partners hadden angstklachten; de meerderheid van de patiënten wenste daarom meer aandacht voor psychologische ondersteuning. Verder rapporteerden deelnemers de behoefte aan betere informatie, toegang tot een expertisecentrum, praktische ondersteuning, contact met andere patiënten, en meer ondersteuning voor partners. Een grote meerderheid van de deelnemers waardeerden het interactieve interviewen en vond dit een goede methode om informatie en uitleg te krijgen.

Vermoeidheid is niet alleen één van de meest voorkomende en belastende symptomen in sarcoïdose (hoofdstuk 6), maar ook in andere ILDs. **Hoofdstuk 7** beschrijft de meest recente inzichten in het voorkomen, de oorzaken, impact en behandeling van vermoeidheid in ILD. Alhoewel bekend is dat vermoeidheid een groot probleem is voor veel ILD patiënten, zijn er slechts enkele studies gedaan die gericht zijn op medicamenteuze of niet-medicamenteuze behandeling van vermoeidheid. De huidige kennis over vermoeidheid in ILD komt voornamelijk vanuit andere ziekten; veel factoren die vermoeidheid veroorzaken spelen zowel een rol in ILD als in andere chronische ziekten. Vermoeidheid is een complex, multifactorieel probleem wat veroorzaakt en verergerd wordt door een combinatie van factoren, zoals verslechtering van de onderliggende ziekte, comorbiditeiten, bijwerkingen van medicatie, fysieke en psychologische symptomen, en gedragsfactoren. Een uitgebreide, gestructureerde evaluatie van al deze verschillende factoren is essentieel om de beste behandelstrategie te bepalen in individuele patiënten. Als alle behandelbare oorzaken zijn uitgesloten, of vermoeidheid blijft bestaan ondanks optimale behandeling van mogelijke oorzaken, kunnen ook algemene behandelopties, zoals longrevalidatie of psychologische interventies worden overwogen. Hopelijk zullen de resultaten van nieuwe studies leiden tot betere behandelopties voor vermoeidheid in ILD.

DEEL 3: ONTWIKKELING EN EVALUATIE VAN EHEALTH TOEPASSINGEN IN ILD

Tijdens twee informatiebijeenkomsten voor patiënten met longfibrose in 2014 en 2015, vroegen we patiënten of ze thuis hun gezondheidsgegevens zouden willen bijhouden. Omdat de overgrote meerderheid van de patiënten hier positief op antwoordde, hebben we de eHealth tool IPF-online ontwikkeld. **Hoofdstuk 8** beschrijft de stapsgewijze ontwikkeling van deze eHealth tool voor IPF, samen met patiënten. Omdat dit wereldwijd het eerste eHealth initiatief was in IPF, is de inhoud van IPF-online gebaseerd op literatuur uit andere ziekten, en suggesties van patiënten en zorgverleners. De eerste versie van IPF-online bestond uit een infotheek, een optie voor eConsulten, online PROMs, en een medicatie overzicht. Twee groepen patiënten met IPF hebben deelgenomen; de eerste groep gebruikte IPF-online twee weken en vulde PROMs in op baseline en aan het einde van de pilot studie. Suggesties van de eerste groep werden gebruikt om het systeem te verbeteren. Een andere groep patiënten testte en evalueerde de aangepaste versie van IPF-online. In het algemeen werd het gebruik van IPF-online zeer gewaardeerd door patiënten. In de tweede groep wilde iedereen zelfs doorgaan met IPF-online nadat de studie afgelopen was. Verder lukte het alle patiënten in deze oudere patiëntengroep om online PROMs in te vullen; deze resultaten zijn hoopgevend voor toekomstig onderzoek, omdat dit waarschijnlijk zal leiden tot minder missende data.

Mede op basis van de suggesties van patiënten uit de eerste pilot studie in hoofdstuk 8, is IPF-online uitgebreid met thuismetingen van de longfunctie met een draagbare spirometer. In **hoofdstuk 9** hebben we een tweede pilot studie gedaan met dit thuismonitoring programma. Tien patiënten hebben dagelijks thuis de longfunctie gemeten gedurende vier weken. Verder vulden patiënten wekelijks een korte vragenlijst in over hun symptomen en klachten, en uitgebreidere PROMs op baseline en na vier weken. Het systeem genereerde automatische email alerts als er geen longfunctie resultaten werden doorgestuurd gedurende drie dagen, als de longfunctie (geforceerde vitale capaciteit, FVC) meer dan 10% daalde ten opzichte van baseline gedurende drie dagen, of als patiënten hinderlijke bijwerkingen rapporteerden. De FVC thuis correleerde goed met de FVC in het ziekenhuis en de variabiliteit van de thuismetingen was laag. Alle patiënten vonden thuismeting van de longfunctie nuttig en niet belastend. In deze studie werden geen grote barrières gevonden voor online thuis spirometrie. Voor alle mogelijke problemen werden relatieve eenvoudige oplossingen voorgesteld door patiënten en het onderzoeksteam.

Vervolgens hebben we het thuismonitoring programma aangepast voor sarcoïdose. In **hoofdstuk 10** onderzochten we de haalbaarheid en de tevredenheid van patiënten in een pilot studie. Tien patiënten met sarcoïdose gebruikten het thuismonitoring

programma gedurende een maand. Na een maand werden ervaringen van patiënten geëvalueerd tijdens een telefonisch interview. Het thuismonitoring programma voor sarcoïdose bestond uit dagelijks thuis spirometrie, het meten van de activiteit met een stappenteller, en PROMs op baseline en na een maand. Bijna alle patiënten deden dagelijks trouw hun metingen, en variabiliteit van de longfunctiemetingen thuis was acceptabel. In het algemeen waren ervaringen van patiënten positief, en de meeste patiënten vonden het nuttig om hun ziekte thuis te kunnen monitoren. Verder antwoorden sommige patiënten dat het gebruik van de stappenteller hen motiveerde om meer actief te worden. Deze studie liet zien dat thuismonitoring haalbaar is in sarcoïdose en gebruikt kan worden voor vervolgonderzoek en mogelijk ook in de dagelijkse praktijk.

In **hoofdstuk 11** evalueerden we of de FVC over de dag varieert in patiënten met longfibrose. Hiervoor maakten we gebruik van ons eerder ontwikkelde thuismonitoring programma (hoofdstuk 8-10). Verder onderzochten we de relatie tussen FVC en activiteit net voor de FVC meting. De FVC werd twee keer per dag gemeten, één keer in de ochtend en één keer in de avond. Stappen werden continu geteld met een stappenteller. De resultaten van deze studie lieten zien dat patiënten een significant hogere FVC hadden in de ochtend in vergelijking met de avond, alhoewel het verschil relatief klein was. De longfunctie varieerde in de ochtend minder sterk dan in de middag. Het gemiddeld aantal stappen per patiënt was lager voor de FVC meting in de ochtend dan voor de meting in de middag. Echter waren patiënten over het algemeen relatief inactief voor beide metingen. Hiermee kunnen we het mechanisme achter de dagelijkse variatie in FVC dus niet volledig verklaren. Omdat de veranderingen in FVC in medicatie studies in longfibrose meestal ook vrij klein zijn, denken we dat thuis spirometrie in vervolgstudies op een vast tijdstip plaats moet vinden voor het meest betrouwbare resultaat.

Hoofdstuk 12 beschrijft de resultaten van het allereerste multicenter gerandomiseerde onderzoek met een eHealth interventie in IPF. In totaal werden 90 patiënten geïncludeerd. Vervolgens werd geloot voor standaardzorg of het gebruik van een thuismonitoring programma in combinatie met standaardzorg voor 24 weken. De primaire uitkomst was het verschil in beide groepen in de totaalscore van de K-BILD vragenlijst. Alle patiënten vulden PROMs in over (gezondheidsgerelateerde) kwaliteit van leven, angst, depressie, medicatie, symptomen en bijwerkingen op baseline, 12 weken en 24 weken. Patiënten in de thuismonitoring groep bliezen dagelijks thuis hun longfunctie en vulden wekelijks een korte vragenlijst in over symptomen en bijwerkingen. Het onderzoeksteam kreeg email alerts bij missende waarden, achteruitgang in longfunctie en hinderlijke bijwerkingen. We vonden dat het gebruik van het thuismonitoring programma niet leidde tot een betere kwaliteit van leven gemeten met de K-BILD vragenlijst. Niettemin leek het psychologische welzijn in de thuismonitoring groep te verbeteren, werd de medicatie

vaker aangepast en waardeerden patiënten het gebruik van het thuismonitoring programma. De meeste patiënten wilden na afloop van de studie doorgaan met thuismonitoren. Dagelijkse thuismetingen leidden niet tot verhoogde angst of depressie scores. Verder liet deze studie zien dat dagelijkse thuismeting van de longfunctie haalbaar en betrouwbaar was in een multicenter studie. Het beloop van de longfunctie thuis en in het ziekenhuis was vergelijkbaar over de tijd en de variabiliteit van de thuismetingen was laag. Alles bij elkaar genomen denken we dat eHealth toepassingen gepersonaliseerde behandeling mogelijk kunnen maken in de toekomst en gezondheidsuitkomsten voor patiënten kunnen verbeteren.

In **hoofdstuk 13** onderzochten we de mogelijkheden en betrouwbaarheid van het gebruik van een elektronische neus (eNose) als diagnostische tool voor ILD. De vele 'vluchtige organische stoffen' in uitgeademde lucht vormen een uniek ademhalingspatroon, wat gedetecteerd kan worden met een eNose. In deze cross-sectionele studie analyseerden we uitgeademde lucht van patiënten met ILD en gezonde controles. We includeerden patiënten met verschillende interstitiële longziekten (o.a. sarcoïdose, IPF, en ILD geassocieerd met auto-immuunziekten). De eNose kon perfect onderscheid maken tussen patiënten met ILD en gezonde controles in een training en validatie set. Vervolgens vergeleken we het ademhalingsprofiel van verschillende ILD subgroepen. De eNose kon adequaat onderscheid maken tussen individuele ILDs, tussen IPF en andere ILDs, en tussen ILD patiënten mét longfibrose versus ILD patiënten zonder longfibrose. eNose technologie lijkt dus een veelbelovende biomarker in ILD en zou in de toekomst kunnen helpen bij het stellen van een vroege en accurate diagnose.

Hoofdstuk 14 is een algemene discussie van de bevindingen in dit proefschrift en toekomstperspectieven.

PhD portfolio

PhD portfolio Summary of PhD training and teaching	
Name PhD student: C.C. Moor **Erasmus MC Department**: Respiratory Medicine **Research School**: Molecular Medicine	**PhD period**: February 2017 – April 2020 **Promotor**: Prof. dr. J.G.J.V. Aerts **Supervisor**: Dr. M.S. Wijsenbeek

1. PHD TRAINING

Courses, seminars and workshops	Year	Workload (ECTS)
Systematic Literature Search and Endnote courses	2017	1.0
BROK course	2017	1.5
Biostatistical methods I: Basic principles (CC02A)	2017	2.0
Interstitial Lung Disease course – Davos	2017	1.0
National Course on lung diseases and lung research	2017	3.0
Workshop on Photoshop and Illustrator CS6	2017	0.3
Workshop on InDesign CS6	2017	0.15
Medical Business Masterclass	2018	0.5
Masterclass H2020	2018	0.3
Good clinical practice	2018	0.1
Course on R	2018	1.8
Biomedical English Writing and Communication	2019	1.5
Young Investigator Symposium NRS	2019	0.3
Networked Science Symposium – Thema Thorax, Erasmus MC	2019	0.2
Mobile healthcare congress	2018-2019	0.6
Presentations and (inter)national conferences		
Lung days – Ermelo, the Netherlands (*oral presentation)*	2017	1.0
ERS conference – Milan, Italy *(1 poster discussion)*	2017	1.0
WASOG conference – Bejing, China *(1 poster discussion)*	2017	1.0
AIR meeting – Barcelona, Spain	2017	1.0
Lung days – Ermelo, the Netherlands *(1 poster, 1 oral presentation)*	2018	1.0
ATS conference – San Diego, U.S.A. *(1 poster discussion)*	2018	1.0
ERS conference – Paris, France. *(1 poster discussion)*	2018	1.0
ICLAF conference – Monterey, U.S.A. *(1 poster presentation)*	2018	1.0
National Lung Fibrosis Patient Association day – Nijkerk, the Netherlands *(presentation)*	2018	0.3
National Sarcoidosis Patient Association day – Amersfoort, the Netherlands *(presentation)*	2018	0.3
Lung days – Ermelo, the Netherlands *(1 poster presentation)*	2019	1.0

Regional Sarcoidosis Patient Meeting – Goes, the Netherlands	2019	0.3
ERS conference – Madrid, Spain *(1 poster discussion)*	2019	1.0
WASOG conference – Yokohama, Japan *(1 oral presentation)*	2019	1.0
Lung fibrosis patient information meeting – Rotterdam, the Netherlands *(presentation)*	2019	0.1
Scientific Advisory Board meeting – Boehringer Ingelheim *(presentation)*	2019	0.3

Teaching

Supervising internship bachelor student healthcare management	2017	3
International Pulmonary Fibrosis Academy for nurses	2018	1
Workshops blood gas analysis (1st year bachelor students)	2018-2020	1
Supervising Italian PhD student	2018	0.8
Coach bachelor students	2019-2020	1
Supervising bachelor student medicine – DIVA study and eNose	2019	0.5
Supervising master student medicine – eNose project, master thesis	2019-2020	3
Supervising bachelor students technical medicine, TU Delft	2019	0.4

Other

Movie Lung Days Public Award – IPF online	2018	0.3
Interview lung fibrosis patient association – home monitoring IPF	2018	0.1
Article ILD care – Sterk Patient Participation Award	2018	0.1
Movie Sterk Patient Participation Award	2018	0.2
Chair Poster Presentation Session - ERS conference, Paris, France	2018	0.3
Movie home monitoring IPF	2019	0.2
Article Research Outreach – home monitoring	2019	0.3
Interview article Lucht & Longen – home monitoring	2019	0.1
Interview article NRC – home monitoring	2019	0.1
Article Open Access Government - eHealth	2019	0.3
Reviewer abstracts ERS conference	2019-2020	0.7
Chair Poster Presentation Session – ERS conference, Madrid, Spain	2019	0.3
Organization Networked Science Symposium	2019	0.5
EU-IPFF scientific advisory board meeting – Amsterdam, the Netherlands	2019	0.3
Peer-review of 25 articles in international journals	2018-2020	3.0

Awards and Grants

Certificate of Excellent Poster – WASOG conference	2017
Trust fonds scholarschip – WASOG conference	2017
Co-applicant Netherlands Organisation for Health Research and Development (ZonMw) Grant IPF online	2017
Nomination Lung Foundation Public Award 2018 for 'IPF online'	2018

Sterk Patient Participation Award – Lung foundation	2018	
Sarcoidose.nl PhD award	2018	
Co-applicant Grant Sarcoidose.nl – TIRED trial	2018	
NRS young investigator travel grant – ICLAF conference	2018	
Co-applicant Lung Foundation Consortium Grant – PREDMETH study sarcoidosis	2019	
Abstract Scholarship, ATS assembly of Clinical Problems	2020	
Total ECTS		**43.75**

List of publications

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- Wijsenbeek M, Bendstrup E, Valenzuela C, Henry MT, **Moor CC**, Bengus M, Perjesi A, Gilberg F, Kirchgaessler KU, Vancheri C. Design of a Study Assessing Disease Behaviour During the Peri-Diagnostic Period in Patients with Interstitial Lung Disease: The STARLINER Study. Adv Ther. 2019 Jan;36(1):232-243.

- Heukels P, **Moor CC**, von der Thüsen JH, Wijsenbeek MS, Kool M. Inflammation and immunity in IPF pathogenesis and treatment. Respir Med. 2019 Feb;147:79-91.

- Alfaro TM, **Moor CC**, Alfieri V, Jeny F, Kreuter M, Wijsenbeek MS, Renzoni EA, Bargagli E, Nunes H, Spagnolo P, Bonella F, Molina-Molina M, Antoniou K, Poletti V. Research highlights from the 2018 ERS International Congress: interstitial lung diseases. ERJ Open Res. 2019 Feb 18;5(1).

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- Santermans E, Ford P, Kreuter M, Verbruggen N, Meyvisch P, Wuyts WA, Brown KK, Lederer DJ, Byrne AJ, Molyneaux PL, Sivananthan A, **Moor CC**, Maher TM, Wijsenbeek M. Modelling Forced Vital Capacity in Idiopathic Pulmonary Fibrosis: Optimising Trial Design. Adv Ther. 2019 Nov;36(11):3059-3070.

- **Moor CC,** Kahlmann V, Culver D, Wijsenbeek M, Comprehensive Care for Patients with Sarcoidosis. J. Clin. Med. 2020, 9(2), 390.

- **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 Jan; 6(1): 00054-2020.

- Kreuter M*, Polke M*, Walsh SLF, Krisam J, Collard HR, Chaudhuri N, Avdeev S, Behr J, Calligero G, Corte T, Flaherty K, Funke-Chambour M, Kolb M, Kondoh Y, Maher TM, Molina Molina M, Morais A, **Moor CC**, Morisset J, Pereira C, Quadrelli S, Selman M, Tzouvelekis A, Valenzuela C, Vancheri C, Vicens-Zygmunt V, Wälscher J, Wuyts W, Wijsenbeek M##, Cottin V##, Bendstrup E##. Acute exacerbation of idiopathic pulmonary fibrosis: International survey and call for harmonization. Eur Respir J. 2020 Apr 3;55(4):1901760.

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- **Moor CC**, Mostard RLM, Grutters JC, Bresser P, Aerts JGJV, Chavannes NH, Wijsenbeek MS. Home monitoring in patients with idiopathic pulmonary fibrosis: a randomized controlled trial. Am J Respir Crit Care Med. 2020 Apr 23.

- Hellemons M*, **Moor CC*,** von der Thusen J, Rossius M, Odink A, Thorgersen L.H, Verschakelen J, Wuyts W, Wijsenbeek MS, Bendstrup E. Desquamative Interstitial Pneumonia - a Systematic Review of its Features and Outcomes, European Respiratory Review, in press. *These authors share first authorship

- **Moor CC**, Kreuter M, Luppi F, Wuyts WA. The world is not enough – the value of increasing registry data in idiopathic pulmonary fibrosis. Respir Res. 2020 May 6;21(1):105.

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Book chapter

- Wijsenbeek MS, **Moor CC**. Comprehensive Care of Interstitial Lung Disease. Encyclopedia of Respiratory Medicine. https://doi.org/10.1016/B978-0-12-801238-3.11301-7

About the author

Catharina Christina (Karen) Moor was born on January 10th 1992 in 's-Gravenhage, the Netherlands, and was raised in Monster. She attended secondary education at the ISW (Gymnasium) in 's-Gravenzande, from which she graduated cum laude in 2008. At the age of 16, she started medical school at the Erasmus University Rotterdam. During her study, she was involved in several committees from the medical and rowing student associations, and gained her first medical experience abroad (Kathmandu, Nepal).

After obtaining her M.Sc. degrees in Medicine in 2015, she started working as a resident-not-in-training at the department of Internal Medicine at the Maasstad Hospital in Rotterdam. During this period, she developed a growing interest in Respiratory Medicine and clinical research. In February 2017, Karen started her PhD project at the department of Respiratory Medicine of the Erasmus Medical Center under the supervision of Dr. M.S. Wijsenbeek and Prof. Dr. H.C. Hoogsteden (from 2018 Prof. Dr. J.G.J.V. Aerts). Since then, many national and international collaborations have been established, resulting in the present thesis.

In October 2020, Karen will start her residency in Respiratory Medicine at the Erasmus MC. Besides, she will continue her current research projects as a postdoctoral researcher.

Interstitial lung diseases (ILDs) are a large, heterogeneous group of more than 200 diseases, that diffusely affect the lungs. This thesis primarily focuses on (idiopathic) pulmonary fibrosis and sarcoidosis. ILDs often have a major impact on quality of life, due to symptoms as dyspnea, cough, and fatigue.

The first aim of this thesis was to evaluate gaps in care, unmet needs, patient perspectives, and patient experiences with the care pathway. These insights are highly needed to facilitate a patient-centered approach to care and research in ILD.

The second part of this thesis describes the development and evaluation of eHealth solutions, aimed at improving health outcomes, optimizing quality of life, and enabling personalized treatment for patients with ILD.