An Official American Thoracic Society/European Respiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation

Executive Summary

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***Background*: Pulmonary rehabilitation is recognized as a core component of the management of individuals with chronic respiratory disease. Since the 2006 American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement on Pulmonary Rehabilitation, there has been considerable growth in our knowledge of its efficacy and scope.**
***Purpose*: The purpose of this Statement is to update the 2006 document, including a new definition of pulmonary rehabilitation and highlighting key concepts and major advances in the field.**
***Methods*: A multidisciplinary committee of experts representing the ATS Pulmonary Rehabilitation Assembly and the ERS Scientific Group 01.02, "Rehabilitation and Chronic Care," determined the overall scope of this update through group consensus. Focused literature reviews in key topic areas were conducted by committee members with relevant clinical and scientific expertise. The final content of this Statement was agreed on by all members.**
***Results*: An updated definition of pulmonary rehabilitation is proposed. New data are presented on the science and application of pulmonary rehabilitation, including its effectiveness in acutely ill individuals with chronic obstructive pulmonary disease, and in individuals with other chronic respiratory diseases. The important role of pulmonary rehabilitation in chronic disease management is highlighted. In addition, the role of health behavior change in optimizing and maintaining benefits is discussed.**
***Conclusions*: The considerable growth in the science and application of pulmonary rehabilitation since 2006 adds further support for its efficacy in a wide range of individuals with chronic respiratory disease.**

Keywords: COPD; pulmonary rehabilitation; exacerbation; behavior; outcomes

OVERVIEW

Pulmonary rehabilitation has been clearly demonstrated to reduce dyspnea, increase exercise capacity, and improve quality of life in individuals with chronic obstructive pulmonary disease (COPD) (1). The Official ATS/ERS Statement, *Key Concepts and Advances in Pulmonary Rehabilitation*, available online at www.atsjournals.org, provides a detailed review of progress in the science and evolution in the concept of pulmonary rehabilitation

This Executive Summary is part of the full official ATS/ERS pulmonary rehabilitation statement, which readers may access online at http://www.atsjournals.org/doi/abs/10.1164/rccm.201309-1634ST. Only the Executive Summary is appearing in the print edition of the Journal. The article of record, and the one that should be cited, is: An Official American Thoracic Society/European Respiratory Society Statement: Key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188:e11–e40. Available at http://www.atsjournals.org/doi/abs/10.1164/rccm.201309-1634ST

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since the 2006 Statement. It represents the consensus of 46 international experts in the field of pulmonary rehabilitation. This printed Executive Summary, by necessity, must focus on only those key concepts and advances that have emerged over the past 6 years.

On the basis of current insights, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have adopted the following new definition of pulmonary rehabilitation: "*Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.*"

Since the previous Statement, we now more fully understand the complex nature of COPD, its multisystem manifestations, and frequent comorbidities. Therefore, integrated care principles are being adopted to optimize the management of these complex patients (2). Pulmonary rehabilitation is now recognized as a core component of this process (Figure 1) (3). Health behavior change is vital to optimization and maintenance of benefits from any intervention in chronic care, and pulmonary rehabilitation has taken a lead in implementing strategies to achieve this goal.

Noteworthy advances in pulmonary rehabilitation that are discussed in the online Statement and briefly outlined in this document include the following:

- There is increased evidence for use and efficacy of a variety of forms of exercise training as part of pulmonary rehabilitation; these include interval training, strength training, upper limb training, and transcutaneous neuromuscular electrical stimulation.
- Pulmonary rehabilitation provided to individuals with chronic respiratory diseases other than COPD (i.e., interstitial lung disease, bronchiectasis, cystic fibrosis, asthma, pulmonary hypertension, lung cancer, lung volume reduction surgery, and lung transplantation) has demonstrated improvements in symptoms, exercise tolerance, and quality of life.
- Symptomatic individuals with COPD who have lesser degrees of airflow limitation and who participate in pulmonary rehabilitation derive similar improvements in symptoms, exercise tolerance, and quality of life as do those with more severe disease.
- Pulmonary rehabilitation initiated shortly after a hospitalization for a COPD exacerbation is clinically effective, safe, and associated with a reduction in subsequent hospital admissions.
- Exercise rehabilitation commenced during acute or critical illness reduces the extent of functional decline and hastens recovery.
- Appropriately resourced home-based exercise training has proven effective in reducing dyspnea and increasing exercise performance in individuals with COPD.
- Technologies are currently being adapted and tested to support exercise training, education, exacerbation management, and physical activity in the context of pulmonary rehabilitation.
- The scope of outcomes assessment has broadened, allowing for the evaluation of COPD-related knowledge and self-efficacy, lower and upper limb muscle function, balance, and physical activity.
- Symptoms of anxiety and depression are prevalent in individuals referred to pulmonary rehabilitation, may affect outcomes, and can be ameliorated by this intervention.

In the future, we see the need to increase the applicability and accessibility of pulmonary rehabilitation; to effect behavior

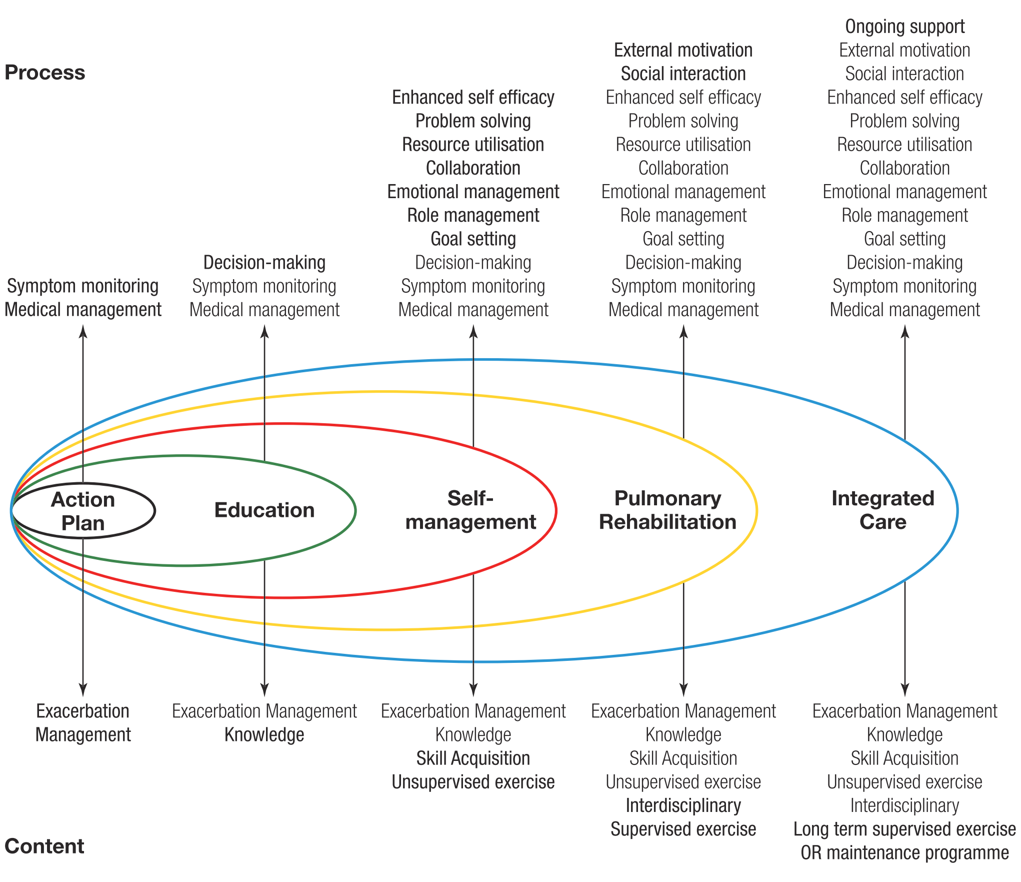

Figure 1. A spectrum of support for chronic obstructive pulmonary disease. Reprinted by permission from Reference 3.

change to optimize and maintain outcomes; and to refine this intervention so that it targets the unique needs of the complex patient.

INTRODUCTION

The Official ATS/ERS Statement, *Key Concepts and Advances in Pulmonary Rehabilitation*, available online at www.atsjournals.org, provides a detailed review of progress in the science and evolution in the concept of pulmonary rehabilitation since the 2006 Statement. This printed Executive Summary, by necessity, must focus on only those key concepts and advances that have emerged over the past 6 years.

METHODS

A multinational, multidisciplinary group of 46 clinical and research experts participated in an American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force with the charge to update the previous Statement (1). Task Force members were identified by the leadership of the ATS Pulmonary Rehabilitation Assembly and the ERS Scientific Group 01.02, "Rehabilitation and Chronic Care." Members were vetted for potential conflicts of interest according to the policies and procedures of the ATS and ERS. This document represents the consensus of these Task Force members. Table 1 provides a summary of the methods used to accumulate the evidence.

DEFINITION AND CONCEPT

On the basis of our current insights, the ATS and ERS have adopted the following new definition of pulmonary rehabilitation: "*Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.*"

Pulmonary rehabilitation is implemented by a dedicated, interdisciplinary team, including physicians and other health care professionals; the latter may include physiotherapists, respiratory therapists, nurses, psychologists, behavioral specialists, exercise physiologists, nutritionists, occupational therapists, and social workers. The intervention should be individualized to the unique needs of the patient, based on initial and ongoing assessments, including disease severity, complexity, and comorbidities. Although pulmonary rehabilitation is a defined intervention, its components should be integrated throughout the clinical course of a patient's disease. Pulmonary rehabilitation may be initiated at any stage of the disease, during periods of clinical stability or during or directly after an exacerbation. The goals of pulmonary rehabilitation include minimizing symptom burden, maximizing exercise performance, promoting autonomy, increasing participation in everyday activities, enhancing (health-related) quality of life, and effecting long-term health-enhancing behavior change.

This document places pulmonary rehabilitation within the concept of integrated care. The World Health Organization defines integrated care as "a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion" (4). Integration of services improves access, quality, user satisfaction, and efficiency of medical care. As such, pulmonary rehabilitation provides an opportunity to coordinate care throughout the clinical course of an individual's disease.

TABLE 1. METHODS CHECKLIST

	Yes	No
Panel assembly		
• Included experts from relevant clinical and nonclinical disciplines	X	
• Included individual who represents views of patients in society at large		X
• Included methodologist with documented expertise	X	
Literature review		
• Performed in collaboration with librarian		X
• Searched multiple electronic databases	X	
• Reviewed reference lists of retrieved articles	X	
Evidence synthesis		
• Applied prespecified inclusion and exclusion criteria		X
• Evaluated included studies for sources of bias	X	
• Explicitly summarized benefits and harms		X
• Used PRISMA to report systematic review		X
• Used GRADE to describe quality evidence		X
Generation of recommendations		
• Used GRADE to rate the strength of recommendations		X

Definition of abbreviations: GRADE = Grading of Recommendations Assessment, Development and Evaluation; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

EXERCISE TRAINING

Endurance Training

Endurance exercise training is typically prescribed three to five times per week. A high level of intensity of continuous exercise (>60% maximal work rate) for 20 to 60 minutes per session maximizes physiologic benefits (i.e., exercise tolerance, muscle function, and bioenergetics) (5). Before starting an exercise training program, an exercise assessment is needed to individualize the exercise prescription, evaluate the potential need for supplemental oxygen, help rule out some cardiovascular comorbidities, and help ensure the safety of the intervention (6–11).

There has been increased awareness of the efficacy of leisure walking as a mode of exercise training in chronic obstructive pulmonary disease (COPD). For example, indoor ground walk training increased endurance walking capacity more than cycle training and was similar to stationary cycle training in improving peak walking capacity, peak and endurance cycle capacity and quality of life (12). Moreover, a randomized, controlled trial of a 3-month outdoor Nordic walking exercise program (vs. control) in 60 patients with COPD resulted in significant improvements in exercise capacity and physical activity. These gains were sustained at 6 and 9 months after the initial intervention (13).

Interval Training

Interval training is a modification of endurance training where high-intensity exercise is interspersed regularly with periods of rest or lower intensity exercise. It results in lower symptom scores and fewer unintended breaks (14, 15) despite high absolute training loads, while reproducing the effects of endurance continuous training (14–16), even in cachectic individuals with severe COPD (17). Interval and continuous training modes generally have comparable improvements in exercise capacity, health-related quality of life, and skeletal muscle adaptations immediately after training (16, 18–25).

Resistance/Strength Training

Resistance/strength training, in which local muscle groups are trained by repetitive lifting of relatively heavy loads (26–28), is frequently provided to individuals who have reduced skeletal muscle mass and/or strength (29–31). Resistance training provides greater increases in muscle mass and strength (27, 31–33), and induces less dyspnea (34) than endurance training, thereby making it attractive for individuals with severe dyspnea (35) and/or with a COPD exacerbation (36). The combination of endurance and strength training provides complementary benefits when treating peripheral muscle dysfunction in patients with chronic respiratory disease (33, 37).

Upper Limb Training

A systematic review demonstrated that upper limb resistance and endurance training improves upper limb function in COPD (38). Moreover, upper limb training improved functional task completion and fatigue scores (39), but did not show benefits in dyspnea during activities in daily life or in quality of life (40).

Neuromuscular Electrical Stimulation

Transcutaneous neuromuscular electrical stimulation (NMES) of leg muscles is a technique in which involuntary muscle contraction is elicited, and selected muscles can thereby be trained (41, 42). Muscle contraction induced by electrical stimulation does not lead to dyspnea; poses minimal cardiocirculatory demand (43, 44); and bypasses the cognitive, motivational, and psychological aspects involved in conventional exercise that may hinder or prevent effective exercise training.

NMES is safe, generally well tolerated, improves leg muscle strength and exercise capacity, and reduces dyspnea in stable outpatients with severe COPD and poor baseline exercise tolerance (41). NMES can be continued during COPD exacerbations (45–47). The duration of these benefits has not been studied.

Inspiratory Muscle Training

Systematic reviews have concluded that inspiratory muscle training (IMT), given as an adjunct to whole-body exercise training in individuals with COPD, leads to benefits in inspiratory muscle strength and endurance, but not on dyspnea or maximal exercise capacity (48, 49).

Maximizing the Effects of Exercise Training

Optimizing the use of maintenance bronchodilator therapy within the context of a pulmonary rehabilitation program for individuals with COPD augments the benefits of exercise training (50, 51), potentially allowing individuals to exercise at higher intensities. Anabolic drug supplementation to enhance the effects of exercise training has not received sufficient study for its routine use in pulmonary rehabilitation (52).

The evidence to date is equivocal on the widespread use of oxygen supplementation during exercise training for all individuals with COPD (53) apart from those already receiving long-term oxygen therapy. Individualized oxygen titration trials may identify individuals with COPD who respond to oxygen supplementation during exercise testing (54).

Studies testing the potential benefits of helium–oxygen mixtures as adjuncts to exercise training in COPD have had varied results, and its application as an adjunct to pulmonary rehabilitation remains to be established (55–57).

A systematic review evaluating the effects of noninvasive positive-pressure ventilation (NPPV) as an adjunct to pulmonary rehabilitation in individuals with COPD concluded that NPPV (either given nocturnally or during exercise) augments the benefits of an exercise program (58). The presumed mechanism is through allowing increased work rate to be performed via unloading the respiratory muscles. The benefit appears to be most marked in individuals with severe COPD, and higher positive pressures may lead to greater improvements.

PULMONARY REHABILITATION IN CONDITIONS OTHER THAN COPD

Individuals with chronic respiratory diseases other than COPD also experience exercise and activity limitation, dyspnea and fatigue, and impaired quality of life (59–92). Although the evidence-base supporting pulmonary rehabilitation in non-COPD disorders remains smaller than for COPD, randomized controlled trials and uncontrolled trials have shown its benefits in chronic respiratory diseases, such as interstitial lung disease, bronchiectasis, cystic fibrosis, asthma, pulmonary hypertension, lung cancer, lung volume reduction surgery, and lung transplantation (Table 2).

BEHAVIOR CHANGE AND COLLABORATIVE SELF-MANAGEMENT

The educational component of pulmonary rehabilitation that promotes adaptive behaviors such as self-efficacy (i.e., the confidence in successfully managing one's health) stands next to exercise training as an essential component of this comprehensive intervention. A traditional didactic approach alone is likely to be insufficient to achieve optimal benefits (93).

Collaborative self-management strategies promote self-efficacy through increasing the patients' knowledge and skills required to participate with health care professionals in optimally managing their illness and comorbidities (94). This multifaceted approach can be implemented through pulmonary rehabilitation (95, 96).

Self-management includes core generic strategies, such as goal setting, problem solving, decision-making, and taking action on the basis of a predefined action plan. These strategies should apply to any individual with any chronic respiratory disease. Action plans for the early recognition and treatment of COPD exacerbations have been shown to reduce health care use, improve time to recovery, and reduce costs (97–101). Action plans are integral to pulmonary rehabilitation, but can also be used independently, using a case manager.

Advance care planning is the process of communication among individuals and their caregivers that includes, but is not limited to, options for end-of-life care and the completion of advance directives (81, 102–105). Advance care planning can be effective in changing outcomes for individuals and their loved ones and can provide support for the implementation of advance directives (106–109). Pulmonary rehabilitation can provide the forum to discuss these issues.

BODY COMPOSITION ABNORMALITIES

Since the previous Statement, some data have indicated that a program of exercise and standardized nutritional supplements in individuals with mild to moderate COPD and low fat-free mass index (FFMI) may have clinical and health service use benefits compared with usual care (110). At the other end of the disease severity spectrum, a randomized controlled trial of 3 months of home rehabilitation (including health education, oral nutritional supplements, exercise, and oral testosterone) evaluated exercise performance, body composition, and survival in 122 underweight individuals with chronic respiratory failure (111). Improvements were seen in body mass index, FFMI, peak cycling work rate, and quadriceps muscle function. However, no significant improvement in the primary outcome, 6-minute walk distance (6MWD), was noted and there was no overall survival benefit up to 15 months (111). Creatine supplementation has not been found to enhance outcomes in patients with COPD participating in pulmonary rehabilitation (112, 113).

TABLE 2. EXERCISE-BASED REHABILITATION IN PATIENTS WITH CHRONIC RESPIRATORY DISEASE OTHER THAN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Population	Evidence for PR	Outcomes of PR	Special Considerations	Specific Assessment Tools
Interstitial lung disease	Two RCTs of exercise training (272, 273); one observational pulmonary rehabilitation study (274); one systematic review (275)	Improved 6-min walk distance, dyspnea, and quality of life. Magnitude of benefits smaller than that seen in COPD (275, 276). Benefits not maintained at 6 mo (275, 276).	Exercise-induced desaturation and pulmonary hypertension are common. Supplemental oxygen should be available and appropriate monitoring of oxyhemoglobin saturation during exercise is indicated.	An IPF-specific version of the St. George's Respiratory Questionnaire is available, with fewer items than the standard version (277)
Bronchiectasis	One RCT of exercise ± inspiratory muscle training (278); one large retrospective study of standard PR (279)	Improvement in incremental shuttle walk test distance and endurance exercise time. Benefits maintained after 3 mo only in group that did inspiratory muscle training in addition to whole body exercise training (278). Benefits of equivalent magnitude to those seen in COPD (279).	Role of airway clearance techniques not yet established. Importance of inspiratory muscle training muscle training unclear—associated with better maintenance of benefit in RCT (278)	Consider measuring impact of cough, e.g., Leicester Cough Questionnaire (280)
Cystic fibrosis	Six RCTs of aerobic training (281–283), anaerobic training (283, 284), combined training (285), or partially supervised sports (286); one systematic review (287)	Improvements in exercise capacity, strength, and quality of life; slower rate of decline in lung function; effects not consistent across trials	Walking exercise decreases sputum mechanical impedance (288), indicating a potential role for exercise in maintaining bronchial hygiene. No specific recommendations regarding pulmonary rehabilitation are included in CF infection control guidelines (289); however, it is noted that people with CF should maintain a distance of at least 3 ft from all others with CF when in the outpatient clinic setting. Local infection control policies may preclude participation in group exercise programs.	CF-specific quality of life questionnaires are available—Cystic Fibrosis Quality of Life Questionnaire (290) and Cystic Fibrosis Questionnaire (291)
Asthma	One systematic review (292); two RCTs of exercise training (293, 294)	Improved physical fitness asthma symptoms, anxiety, depression, and quality of life (292–294)	Preexercise use of bronchodilators and gradual warm-up are indicated to minimize exercise-induced bronchospasm. Cardiopulmonary exercise testing may be used to evaluate for exercise-induced bronchospasm (295).	Consider measures of asthma symptoms and asthma-specific quality of life measures, e.g., Asthma Quality of Life Questionnaire (296)
Pulmonary hypertension	One RCT (297); two prospective case series (87, 298)	Improved exercise endurance, WHO functional class, quality of life, peak $\dot{V}O_2$ (87, 297, 298), increased peak workload (298), and increased peripheral muscle function (87)	Care must be taken to maintain $Sa_{O_2} > 88\%$ during exercise and supplemental O_2 should be available. BP and pulse should be monitored closely. Telemetry may be needed for patients with known arrhythmias. Avoid falls for patients receiving anticoagulant medication. Light or moderate aerobic, and light resistive, training are recommended forms of exercise (299). High-intensity exercise, activities that involve Valsalva-like maneuvers or concurrent arm/leg exercises are generally not recommended. Close collaboration between PR providers and pulmonary hypertension specialists is needed to ensure safe exercise training. Exercise should be discontinued if the patient develops lightheadedness, chest pain, palpitations, or syncope.	Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) (300) WHO Functional Class (301) SF-36 (302) Assessment of Quality of Life instrument (AQoL) (303)

(Continued)

TABLE 2. (CONTINUED)

Population	Evidence for PR	Outcomes of PR	Special Considerations	Specific Assessment Tools
Lung cancer	Preoperative PR: Small, uncontrolled observational studies (304, 305)	Improved exercise tolerance (304, 305), possible change in status from noncandidate for surgical resection to operative candidate	Short duration (e.g., 2–4 wk), up to 5 times per week, needed to avoid delay in potential curative surgery	Functional Assessment of Cancer Therapy-Lung Cancer (FACT-L) (313, 314)
	Postoperative PR: Small uncontrolled trials (306–308); two RCTs comparing aerobic training, resistive training, or both in postsurgical lung cancer patients are ongoing (309, 310); one systematic review (311)	Increased walking endurance, increased peak exercise capacity, reduced dyspnea and fatigue (306–308). Variable impact on quality of life (311)		Trial Outcome Index (314, 315) Functional Assessment of Cancer Therapy Fatigue Scale (316, 317)
	Medical treatment: Case series of patients with nonresectable stage III or IV cancer (312)	Improved symptoms and maintenance of muscle strength (312)		
Lung volume reduction surgery	Prospective observational study (318): Analysis of data from the National Emphysema Treatment Trial; a small case series (efficacy of home-based PR before LVRS) (319)	Pre-LVRS PR and exercise training: Improved exercise capacity (peak workload, peak $\dot{V}O_2$, walking endurance), muscle strength, dyspnea, and quality of life (318, 319)	Oxygen saturation should be monitored. Explanations of the surgical procedure, postoperative care including chest tubes, lung expansion, secretion clearance techniques, and importance of early postoperative mobilization should be included in the educational component of PR	Quality of Well-Being Score (320, 321) Usual outcome assessments for COPD, such as CRQ (322) and SGRQ (323), are appropriate. Consider generic tools such as SF-36 (302) to allow comparison with population normative values postoperatively
Lung transplantation	Pretransplant PR: One RCT comparing interval versus continuous training (324); small uncontrolled trials evaluating benefits of pretransplant PR, including Nordic walking (325–328) Post-transplant PR: Two RCTs; a few cohort studies; one systematic review assessing PR after lung transplantation (83, 329–331)	Pretransplant PR: Improved exercise tolerance and well-being (325–327) Post-transplant PR: Increased muscle strength, walking endurance, maximal exercise capacity, and quality of life (83, 329–331)	Exercise prescription must be tailored to patients with severe end-stage lung disease and to specific considerations pertaining to the disease for which the transplant is being considered. Patients may require lower intensity or interval training. Hemodynamic parameters and oxygenation should be monitored closely; O_2 should be available. Educational component should cover surgical techniques, risks, benefits of the surgery, postoperative care (controlled cough, incentive spirometry, chest tubes, wound care, secretion clearance techniques, importance of early mobilization, risk and benefits of immunosuppressive agents)	SF-36 and other assessment tools appropriate for the individual disease state

Definition of abbreviations: BP = blood pressure; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; CRQ = Chronic Respiratory Questionnaire; IPF = interstitial pulmonary fibrosis; LVRS = lung volume reduction surgery; PR = pulmonary rehabilitation; RCT = randomized controlled trial; Sa_{O_2} = oxygen saturation; SF-36 = Short Form-36; SGRQ = St. George's Respiratory Questionnaire; $\dot{V}O_2$ = aerobic capacity; WHO = World Health Organization.

An increasing number of individuals with obesity-related dyspnea and respiratory disturbances as well as those with chronic respiratory diseases and coexisting obesity are being referred for pulmonary rehabilitation (114). Despite less severe airflow obstruction and comparable constant work rate cycling endurance time, obese individuals with COPD have lower 6MWD compared with overweight and normal weight individuals (115). Although obesity may have a negative impact on exercise tolerance in individuals with COPD (115), it does not diminish the magnitude of gains made in pulmonary rehabilitation (115–118).

PHYSICAL ACTIVITY

Individuals with chronic respiratory disease are physically inactive (119–123). This inactivity is associated with poor outcomes, including higher mortality risk (124–127) and increased risk of readmission after a hospitalization for a COPD exacerbation (124, 127–130).

Pulmonary rehabilitation, with its goals of increasing exercise tolerance and improving self-efficacy, has the potential to promote increased levels of physical activity. However, studies evaluating the effectiveness of pulmonary rehabilitation on physical activity have had inconsistent results, with some showing benefit and others showing no effect (131–143). No study characteristics seem to consistently explain these differences. This disparity highlights the fact that there is, to date, little knowledge on how to transfer the gains in exercise capacity into increased physical activity in daily life. This is compounded by the fact that the optimal method for measuring physical activity is not known (144, 145).

TIMING OF PULMONARY REHABILITATION

Earlier in the Course of the Disease

Most randomized trials of pulmonary rehabilitation have involved individuals with COPD with a mean FEV_1 less than

50% of the predicted value (95, 146). Because physical inactivity and the systemic effects of COPD often occur earlier in the disease process (29, 35, 147–151), pulmonary rehabilitation for individuals with less severe disease may be beneficial and may impact long-term disease outcomes. In support of this, a community-based pulmonary rehabilitation program in individuals with mild to moderate COPD who had baseline exercise impairment was effective in improving exercise performance and in maintaining this benefit for 24 months (152). A 10-week pulmonary rehabilitation program in individuals with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II to IV led to improvements in functional capacity and beneficial morphologic adaptations in leg muscle fibers (23). These improvements were similar across GOLD stages.

During the Periexacerbation Period

Since the previous Statement, considerable evidence has been published supporting exercise-based pulmonary rehabilitation during and immediately after hospitalization for COPD exacerbations. Although ventilatory limitation may preclude endurance training in this setting, resistance training of the leg muscles during exacerbations is well tolerated and safe, can lead to improvements in muscle strength, and may confer gains in exercise tolerance (36). NMES is an alternative training method that can prevent muscle function decline and hasten recovery of mobility for hospitalized individuals, including those in critical care settings (41, 153–155).

Pulmonary rehabilitation initiated early (e.g., within 3 wk) after hospital discharge for a COPD exacerbation is feasible, safe, and effective, and leads to gains in exercise tolerance, symptoms, and quality of life (156–165), and reductions in subsequent health care use (160, 163–165). A 2011 Cochrane review of randomized controlled trials comparing outcomes of pulmonary rehabilitation versus usual care after a hospitalization for a COPD exacerbation showed at least a 42% reduction in readmissions over 25 weeks (163). However, a trial involving 60 patients with COPD did not show a reduction in health care use at 1 year (166), although patients were probably not medically optimized. Pulmonary rehabilitation started during or shortly after a hospitalization for COPD may also favorably influence survival (163). More data would be needed before a firm conclusion can be made.

The provision of exercise rehabilitation during periods of critical illness prevents functional decline and hastens recovery (153, 154, 167–169). This is feasible even for individuals receiving mechanical ventilation.

MAINTENANCE OF BENEFITS FROM PULMONARY REHABILITATION

The benefits of pulmonary rehabilitation tend to diminish over 6–12 months, with quality of life being better maintained than exercise capacity (143, 170–172). Developing methods to extend the benefits of pulmonary rehabilitation is an important goal, although maintenance strategies thus far have been largely disappointing.

A small, controlled trial suggested that training effects obtained from an outpatient rehabilitation program can be maintained by home-based exercise training (accompanied by monthly phone calls) in patients with moderate COPD (173). However, periodic phone calls alone to individuals after a pulmonary rehabilitation program have had inconsistent results (138, 171).

Several randomized controlled trials have examined the effects of maintenance strategies (138, 171, 174). The evidence for supervised maintenance exercise remains equivocal, with one study finding no additional benefits of weekly sessions over routine follow-up (171) and another reporting that weekly sessions resulted in improved exercise capacity but not in health-related quality of life (175). Reducing the frequency of supervised sessions to every 2–4 weeks demonstrated no significant benefits for either outcome measure (175, 176). Repeating pulmonary rehabilitation appears to have comparable results to those of the initial program (177, 178). The precise format and timing of maintenance strategies have yet to be established (157).

PATIENT-CENTERED OUTCOMES

Since the previous Statement, studies have shown that pulmonary rehabilitation reduces symptoms of depression and anxiety (179), especially in individuals with high symptom scores at baseline (180).

In the area of new outcome tools, a new quality of life instrument, the COPD Assessment Test (181), has been shown to be responsive to pulmonary rehabilitation (182–184). Newer questionnaires to assess the information needs of individuals include the Lung Information Needs Questionnaire and the Bristol COPD Knowledge Questionnaire (185, 186). Both have been shown to demonstrate knowledge gains after pulmonary rehabilitation (93, 186, 187). The COPD Self-Efficacy Scale and the Pulmonary Rehabilitation Adapted Index of Self-Efficacy (PRAISE) tool have been shown to be responsive measures of self-efficacy in individuals attending pulmonary rehabilitation (188–190). The usefulness and applicability of these newer measures in pulmonary rehabilitation assessment remain to be determined. Importantly, in participants with chronic respiratory disorders other than COPD, alternative outcome assessments may be needed to understand the impact of the disease and document the benefits of pulmonary rehabilitation (Table 2).

Resistance training of lower and upper limbs is now a routine component of pulmonary rehabilitation that includes the assessment of skeletal muscle function before and after pulmonary rehabilitation (191).

Balance is generally impaired in individuals with COPD (192, 193), resulting in frequent falls (194). Pulmonary rehabilitation resulted in minor improvements in balance and had no effect on balance confidence in people with COPD (195), whereas a 12-week supervised Sun-style tai chi training program did improve balance compared with a usual care control group (196).

Elevated arterial stiffness and cardiac autonomic dysfunction occur in individuals with COPD and are related to quality of life, exercise performance, and physical inactivity (197–200). First studies show small but significant decreases in aortic and brachial pulse-wave velocity in individuals with COPD after pulmonary rehabilitation (200, 201). Effects of pulmonary rehabilitation on heart rate variability are equivocal (202–204).

The term “minimal important difference” (MID) has been defined as the smallest difference in a measurable clinical parameter that indicates a meaningful change in the condition, for better or for worse, as perceived by the patient, clinician, or investigator (205). MIDs for the shuttle field tests of exercise performance have been identified. After pulmonary rehabilitation, the MID has been determined to be 47.5 m for the incremental shuttle walk test and approximately 186 seconds for the endurance shuttle walk test (206, 207). The MID for 6MWD for COPD interventions was previously considered to be 54 m (208), although more recent studies support lower values in the range of 25 to 35 m (209–211). Comparable values were derived for individuals with pulmonary arterial hypertension or idiopathic pulmonary fibrosis (212, 213).

PROGRAM ORGANIZATION

Although all pulmonary rehabilitation programs share essential features, the available resources, program setting, structure, personnel, and duration vary considerably among different health care systems (214, 215).

Patient Selection

Pulmonary rehabilitation can be beneficial for any individual with chronic respiratory disease with persistent symptoms and/or functional status limitation despite otherwise optimal therapy (216). There is evidence that this intervention is effective irrespective of age, disease severity, or disease stability (23, 163, 217–221). Contraindications to pulmonary rehabilitation are few, but include any condition that precludes safe exercise training or would substantially interfere with the pulmonary rehabilitative process.

Comorbidities

COPD is commonly associated with comorbidities (222–235), which often have significant impact on symptoms, functional status, and outcomes (236–238). The presence of comorbidities needs to be considered in the context of enrolling individuals for and monitoring individuals within pulmonary rehabilitation programs, to ensure safety and enhance outcomes. The impact of comorbidities on attendance, completion, and outcomes of pulmonary rehabilitation is as yet unknown (117, 118, 239, 240).

Rehabilitation Setting

Pulmonary rehabilitation can be provided in inpatient and outpatient settings, and exercise training can also be provided in the individual's home. Since the previous Statement, one large randomized trial compared appropriately resourced home-based with hospital-based exercise training in COPD (241). There were comparable improvements in the primary outcome, dyspnea, as measured by the Chronic Respiratory Questionnaire. Smaller randomized controlled trials have demonstrated similar improvements in home- and center-based exercise training (242, 243). Home exercise training (vs. usual care) in 50 oxygen-dependent individuals showed increased exercise performance and decreased dyspnea (244). Albores and colleagues tested the effectiveness of a 12-week home exercise program based on a user-friendly, computer system (five or more days per week) in 25 clinically stable patients with COPD (245). Significant improvements in exercise performance, arm-lift and sit-to-stand repetitions, and health status scores were noted.

Technology-assisted Pulmonary Rehabilitation

Telehealth is a promising way of delivering health services to individuals, particularly for those living in isolated areas or without access to transportation. However, to date, there is limited evidence of the benefit of these technologies in pulmonary rehabilitation. New technologies that may be applicable to pulmonary rehabilitation in the future include cell phone–based, monitored, home exercise training programs (246), videoconferencing (247), telemonitoring (248), and activity counseling delivered via telehealth (249, 250).

Program Duration, Structure, and Staffing

Since the previous Statement, there remains no consensus on the optimal duration of pulmonary rehabilitation (251). However, longer programs are thought to produce greater gains and maintenance of benefits, with a minimum of 8 weeks required to achieve a substantial effect on exercise performance and quality of life (251–254).

Program Enrollment and Adherence

A sizeable percentage of individuals referred for pulmonary rehabilitation do not enroll or fail to complete the program. Major barriers to enrollment include disruption to the patient's routine, distance and transportation problems, influence of the patient's health care provider, lack of perceived benefit from the program, and inconvenient timing of the program (255). The major issues for noncompletion include illness and comorbidities, travel, transportation, lack of perceived benefits, smoking, depressive symptoms, lack of support, deprivation, and perceived impairment (256–258). Moreover, the provider's support for enrollment can influence patient attendance and adherence. Addressing these major barriers may increase enrollment and graduation rates. For example, Graves and colleagues reported positive effects of a "group opt-in session" on the uptake and graduation rates for a pulmonary rehabilitation program for patients with COPD in an observational study using historical controls (259).

HEALTH CARE USE

Several studies comparing health care use before and after pulmonary rehabilitation found significant reductions in the number of hospital admissions, hospital days, and emergency room visits (260–265). Randomized controlled trials comparing pulmonary rehabilitation with usual care found a significant reduction in hospitalizations (266) or a trend in the same direction (160, 267, 268). A 2011 Cochrane review showed a positive impact of pulmonary rehabilitation on readmissions after COPD exacerbations (163). There are four full economic evaluations of pulmonary rehabilitation that included both program costs and total costs of health care use during and after rehabilitation (171, 269–271), with varying results because of differences in country, setting, target group, and comparator treatment.

MOVING FORWARD

The science and application of pulmonary rehabilitation have grown considerably since the previous Statement. This Task Force identifies the following major areas that need to be addressed further in the coming years:

1. Increasing the scope of pulmonary rehabilitation: This includes further defining its efficacy in patients with diseases other than COPD, in those hospitalized for exacerbations, and in those with critical illness. Furthermore, it is important to explore the disease-modifying potential of pulmonary rehabilitation in those with milder chronic respiratory disease.
2. Increasing the accessibility to pulmonary rehabilitation: This includes developing robust models for alternative forms of delivery, defining the role of telehealth and other new technologies, advocating for funding to ensure viability of existing pulmonary rehabilitation programs, fostering the creation of new programs, increasing clinician and patient awareness of the benefits of pulmonary rehabilitation, and identifying and overcoming barriers to participation.
3. Optimizing pulmonary rehabilitation components to influence meaningful and sustainable behavior change: This includes further developing collaborative self-management

strategies and ways to translate gains in exercise capacity into increased physical activity.

4. Further understanding and addressing the heterogeneity and multisystem complexity of COPD and other forms of chronic respiratory disease: This includes defining phenotypes and using this information in optimizing the impact of the pulmonary rehabilitation.

This official statement was prepared by an *ad hoc* subcommittee of the ATS Assembly on Pulmonary Rehabilitation and the ERS Scientific Group 01.02 "Rehabilitation and Chronic Care."

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References

1. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, *et al.*; ATS/ERS Pulmonary Rehabilitation Writing Committee. American Thoracic Society/ European Respiratory Society Statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390–1413.
2. Nici L, ZuWallack R; American Thoracic Society Subcommittee on Integrated Care of the COPD Patient. An official American Thoracic Society workshop report: the integrated care of the COPD patient. *Proc Am Thorac Soc* 2012;9:9–18.
3. Wagg K. Unravelling self-management for COPD: what next? *Chron Respir Dis* 2012;9:5–7.
4. Gröne O, Garcia-Barbero M; WHO European Office for Integrated Health Care Services. Integrated care: a position paper of the WHO European Office for Integrated Health Care Services. *Int J Integr Care* 2001;1:e21.
5. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP; American College of Sports Medicine. American College of Sports Medicine position stand: quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43:1334–1359.
6. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.
7. Hill K, Dolmage TE, Woon L, Coutts D, Goldstein R, Brooks D. Comparing peak and submaximal cardiorespiratory responses during field walking tests with incremental cycle ergometry in COPD. *Respirology* 2012;17:278–284.
8. Sillen MJ, Vercoulen JH, van't Hul AJ, Klijn PH, Wouters EF, van Ranst D, Peters JB, van Keimpema AR, Franssen FM, Otten HJ, *et al.* Inaccuracy of estimating peak work rate from six-minute walk distance in patients with COPD. *COPD* 2012;9:281–288.
9. Holland AE, Hill K, Alison JA, Luxton N, Mackey MG, Hill CJ, Jenkins SC. Estimating peak work rate during incremental cycle ergometry from the 6-minute walk distance: differences between reference equations. *Respiration* 2011;81:124–128.
10. Luxton N, Alison JA, Wu J, Mackey MG. Relationship between field walking tests and incremental cycle ergometry in COPD. *Respirology* 2008;13:856–862.

11. Spruit MA, Vanderhoven-Augustin I, Janssen PP, Wouters EF. Integration of pulmonary rehabilitation in COPD. *Lancet* 2008;371:12–13.
12. Leung RW, Alison JA, McKeough ZJ, Peters MJ. Ground walk training improves functional exercise capacity more than cycle training in people with chronic obstructive pulmonary disease (COPD): a randomised trial. *J Physiother* 2010;56:105–112.
13. Breyer MK, Breyer-Kohansal R, Funk GC, Dornhofer N, Spruit MA, Wouters EF, Burghuber OC, Hartl S. Nordic walking improves daily physical activities in COPD: a randomised controlled trial. *Respir Res* 2010;11:112.
14. Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J* 2002;20:12–19.
15. Puhan MA, Schünemann HJ, Buesching G, vanOort E, Spaar A, Frey M. COPD patients' ability to follow exercise influences short-term outcomes of rehabilitation. *Eur Respir J* 2008;31:304–310.
16. Puhan MA, Büsching G, Schünemann HJ, VanOort E, Zaugg C, Frey M. Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2006;145:816–825.
17. Vogiatzis I, Simoes DC, Stratakos G, Kourepini E, Terzis G, Manta P, Athanasopoulos D, Roussos C, Wagner PD, Zakynthinos S. Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. *Eur Respir J* 2010;36:301–310.
18. Arnardóttir RH, Boman G, Larsson K, Hedenström H, Emtner M. Interval training compared with continuous training in patients with COPD. *Respir Med* 2007;101:1196–1204.
19. Mador MJ, Krawza M, Alhajhusian A, Khan AI, Shaffer M, Kufel TJ. Interval training versus continuous training in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev* 2009;29:126–132.
20. Varga J, Porszasz J, Boda K, Casaburi R, Somfay A. Supervised high intensity continuous and interval training vs. self-paced training in COPD. *Respir Med* 2007;101:2297–2304.
21. Nasis IG, Vogiatzis I, Stratakos G, Athanasopoulos D, Koutsoukou A, Daskalakis A, Spetsioti S, Evangelodimou A, Roussos C, Zakynthinos S. Effects of interval-load versus constant-load training on the BODE Index in COPD patients. *Respir Med* 2009;103:1392–1398.
22. Vogiatzis I, Terzis G, Nanas S, Stratakos G, Simoes DC, Georgiadou O, Zakynthinos S, Roussos C. Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest* 2005;128:3838–3845.
23. Vogiatzis I, Terzis G, Stratakos G, Cherouveim E, Athanasopoulos D, Spetsioti S, Nasis I, Manta P, Roussos C, Zakynthinos S. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* 2011;140:744–752.
24. Beauchamp MK, Nonoyama M, Goldstein RS, Hill K, Dolmage TE, Mathur S, Brooks D. Interval versus continuous training in individuals with chronic obstructive pulmonary disease—a systematic review. *Thorax* 2010;65:157–164.
25. Zainuldin R, Mackey MG, Alison JA. Optimal intensity and type of leg exercise training for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;11:CD008008.
26. American College of Sports Medicine. American College of Sports Medicine position stand: progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009;41:687–708.
27. O'Shea SD, Taylor NF, Paratz JD. Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: a systematic review. *Chest* 2009;136:1269–1283.
28. Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, Gulanick M, Laing ST, Stewart KJ. Resistance exercise in individuals with and without cardiovascular disease: 2007 update. A scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2007;116:572–584.
29. Seymour JM, Spruit MA, Hopkinson NS, Natanek SA, Man WD, Jackson A, Gosker HR, Schols AM, Moxham J, Polkey MI, *et al*. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J* 2010;36:81–88.
30. Verhage TL, Heijdra Y, Molema J, Vercoulen J, Dekhuijzen R. Associations of muscle depletion with health status: another gender difference in COPD? *Clin Nutr* 2011;30:332–338.
31. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J* 2002;19:1072–1078.
32. Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Bérubé C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:896–901.
33. Ortega F, Toral J, Cejudo P, Villagomez R, Sánchez H, Castillo J, Montemayor T. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:669–674.
34. Probst VS, Troosters T, Pitta F, Decramer M, Gosselink R. Cardiopulmonary stress during exercise training in patients with COPD. *Eur Respir J* 2006;27:1110–1118.
35. Spruit MA, Pennings HJ, Janssen PP, Does JD, Scroyen S, Akkermans MA, Mostert R, Wouters EF. Extra-pulmonary features in COPD patients entering rehabilitation after stratification for MRC dyspnea grade. *Respir Med* 2007;101:2454–2463.
36. Troosters T, Probst VS, Crul T, Pitta F, Gayan-Ramirez G, Decramer M, Gosselink R. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;181:1072–1077.
37. Spruit MA, Wouters EF. New modalities of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. *Sports Med* 2007;37:501–518.
38. Janaudis-Ferreira T, Hill K, Goldstein R, Wadell K, Brooks D. Arm exercise training in patients with chronic obstructive pulmonary disease: a systematic review. *J Cardiopulm Rehabil Prev* 2009;29:277–283.
39. Costi S, Crisafulli E, Antoni FD, Beneventi C, Fabbri LM, Clini EM. Effects of unsupported upper extremity exercise training in patients with COPD: a randomized clinical trial. *Chest* 2009;136:387–395.
40. Janaudis-Ferreira T, Hill K, Goldstein RS, Robles-Ribeiro P, Beauchamp MK, Dolmage TE, Wadell K, Brooks D. Resistance arm training in patients with COPD: a randomized controlled trial. *Chest* 2011;139:151–158.
41. Sillen MJ, Speksnijder CM, Eterman RM, Janssen PP, Wagers SS, Wouters EF, Uszko-Lencer NH, Spruit MA. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest* 2009;136:44–61.
42. Vivodtzev I, Lacasse Y, Maltais F. Neuromuscular electrical stimulation of the lower limbs in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev* 2008;28:79–91.
43. Sillen MJ, Janssen PP, Akkermans MA, Wouters EF, Spruit MA. The metabolic response during resistance training and neuromuscular electrical stimulation (NMES) in patients with COPD, a pilot study. *Respir Med* 2008;102:786–789.
44. Sillen MJ, Wouters EF, Franssen FM, Meijer K, Stakenborg KH, Spruit MA. Oxygen uptake, ventilation, and symptoms during low-frequency versus high-frequency NMES in COPD: a pilot study. *Lung* 2011;189:21–26.
45. Neder JA, Sword D, Ward SA, Mackay E, Cochrane LM, Clark CJ. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2002;57:333–337.
46. Abdellaoui A, Préfaut C, Gouzi F, Couillard A, Coisy-Quivy M, Hugon G, Molinari N, Lafontaine T, Jonquet O, Laoudj-Chenivesse D, *et al*. Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. *Eur Respir J* 2011;38:781–788.
47. Giavedoni S, Deans A, McCaughey P, Drost E, MacNee W, Rabinovich RA. Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. *Respir Med* 2012;106:1429–1434.
48. O'Brien K, Geddes EL, Reid WD, Brooks D, Crowe J. Inspiratory muscle training compared with other rehabilitation interventions in chronic obstructive pulmonary disease: a systematic review update. *J Cardiopulm Rehabil Prev* 2008;28:128–141.
49. Gosselink R, De Vos J, van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J* 2011;37:416–425.
50. Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005;127:809–817.

51. Franssen FM, Spruit MA, Wouters EF. Determinants of polypharmacy and compliance with GOLD guidelines in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2011;6:493–501.
52. Lewis MI, Fournier M, Storer TW, Bhasin S, Porszasz J, Ren SG, Da X, Casaburi R. Skeletal muscle adaptations to testosterone and resistance training in men with COPD. *J Appl Physiol* 2007;103: 1299–1310.
53. Nonoyama ML, Brooks D, Lacasse Y, Guyatt GH, Goldstein RS. Oxygen therapy during exercise training in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;2:CD005372.
54. Héraud N, Préfaut C, Durand F, Varray A. Does correction of exercise-induced desaturation by O_2 always improve exercise tolerance in COPD? A preliminary study. *Respir Med* 2008;102:1276–1286.
55. Marciniuk DD, Butcher SJ, Reid JK, MacDonald GF, Eves ND, Clemens R, Jones RL. The effects of helium-hyperoxia on 6-min walking distance in COPD: a randomized, controlled trial. *Chest* 2007;131:1659–1665.
56. Scorsone D, Bartolini S, Saporiti R, Braido F, Baroffio M, Pellegrino R, Brusasco V, Crimi E. Does a low-density gas mixture or oxygen supplementation improve exercise training in COPD? *Chest* 2010; 138:1133–1139.
57. Eves ND, Sandmeyer LC, Wong EY, Jones LW, MacDonald GF, Ford GT, Petersen SR, Bibeau MD, Jones RL. Helium-hyperoxia: a novel intervention to improve the benefits of pulmonary rehabilitation for patients with COPD. *Chest* 2009;135:609–618.
58. Corner E, Garrod R. Does the addition of non-invasive ventilation during pulmonary rehabilitation in patients with chronic obstructive pulmonary disease augment patient outcome in exercise tolerance? A literature review. *Physiother Res Int* 2010;15:5–15.
59. Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. *Respir Med* 2009;103:117–123.
60. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, Arizono S. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. *Chest* 2005;127:2028–2033.
61. Spruit MA, Thomeer MJ, Gosselink R, Troosters T, Kasran A, Debrock AJ, Demedts MG, Decramer M. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. *Thorax* 2005;60:32–38.
62. Kilgour RD, Vigano A, Trutschnigg B, Hornby L, Lucar E, Bacon SL, Morais JA. Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. *J Cachexia Sarcopenia Muscle* 2010;1:177–185.
63. Coups EJ, Park BJ, Feinstein MB, Steingart RM, Egleston BL, Wilson DJ, Ostroff JS. Correlates of physical activity among lung cancer survivors. *Psychooncology* 2009;18:395–404.
64. Coups EJ, Park BJ, Feinstein MB, Steingart RM, Egleston BL, Wilson DJ, Ostroff JS. Physical activity among lung cancer survivors: changes across the cancer trajectory and associations with quality of life. *Cancer Epidemiol Biomarkers Prev* 2009;18:664–672.
65. Feinstein MB, Krebs P, Coups EJ, Park BJ, Steingart RM, Burkhalter J, Logue A, Ostroff JS. Current dyspnea among long-term survivors of early-stage non–small cell lung cancer. *J Thorac Oncol* 2010;5:1221–1226.
66. Hung R, Krebs P, Coups EJ, Feinstein MB, Park BJ, Burkhalter J, Ostroff JS. Fatigue and functional impairment in early-stage non–small cell lung cancer survivors. *J Pain Symptom Manage* 2011;41: 426–435.
67. Krebs P, Coups EJ, Feinstein MB, Burkhalter JE, Steingart RM, Logue A, Park BJ, Ostroff JS. Health behaviors of early-stage non–small cell lung cancer survivors. *J Cancer Surviv* 2012;6:37–44.
68. Ostroff JS, Krebs P, Coups EJ, Burkhalter JE, Feinstein MB, Steingart RM, Logue AE, Park BJ. Health-related quality of life among early-stage, non–small cell, lung cancer survivors. *Lung Cancer* 2011;71: 103–108.
69. Tejero García S, Giráldez Sánchez MA, Cejudo P, Quintana Gallego E, Dapena J, García Jiménez R, Cano Luis P, Gómez de Terreros I. Bone health, daily physical activity, and exercise tolerance in patients with cystic fibrosis. *Chest* 2011;140:475–481.
70. Troosters T, Langer D, Vrijsen B, Segers J, Wouters K, Janssens W, Gosselink R, Decramer M, Dupont L. Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. *Eur Respir J* 2009;33:99–106.
71. Lee AL, Button BM, Ellis S, Stirling R, Wilson JW, Holland AE, Denehy L. Clinical determinants of the 6-minute walk test in bronchiectasis. *Respir Med* 2009;103:780–785.
72. Koulouris NG, Retsou S, Kosmas E, Dimakou K, Malagari K, Mantzikopoulos G, Koutsoukou A, Milic-Emili J, Jordanoglou J. Tidal expiratory flow limitation, dyspnoea and exercise capacity in patients with bilateral bronchiectasis. *Eur Respir J* 2003;21:743–748.
73. Bradley J, Moran F, Greenstone M. Physical training for bronchiectasis. *Cochrane Database Syst Rev* 2002;3:CD002166.
74. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, *et al.*; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–2537.
75. Smith G, Reyes JT, Russell JL, Humpl T. Safety of maximal cardiopulmonary exercise testing in pediatric patients with pulmonary hypertension. *Chest* 2009;135:1209–1214.
76. Novoa N, Varela G, Jiménez MF, Aranda JL. Influence of major pulmonary resection on postoperative daily ambulatory activity of the patients. *Interact Cardiovasc Thorac Surg* 2009;9:934–938.
77. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007;132:207–213.
78. de Kleijn WP, De Vries J, Lower EE, Elfferich MD, Baughman RP, Drent M. Fatigue in sarcoidosis: a systematic review. *Curr Opin Pulm Med* 2009;15:499–506.
79. De Kleijn WP, Drent M, Vermunt JK, Shigemitsu H, De Vries J. Types of fatigue in sarcoidosis patients. *J Psychosom Res* 2011;71:416–422.
80. Marcellis RG, Lenssen AF, Elfferich MD, De Vries J, Kassim S, Foerster K, Drent M. Exercise capacity, muscle strength and fatigue in sarcoidosis. *Eur Respir J* 2011;38:628–634.
81. Spruit MA, Janssen DJ, Franssen FM, Wouters EF. Rehabilitation and palliative care in lung fibrosis. *Respirology* 2009;14:781–787.
82. Rochester CL. Pulmonary rehabilitation for patients who undergo lung-volume-reduction surgery or lung transplantation. *Respir Care* 2008; 53:1196–1202.
83. Maury G, Langer D, Verleden G, Dupont L, Gosselink R, Decramer M, Troosters T. Skeletal muscle force and functional exercise tolerance before and after lung transplantation: a cohort study. *Am J Transplant* 2008;8:1275–1281.
84. Spruit MA, Thomeer MJ, Gosselink R, Wuyts WA, Van Herck E, Bouillon R, Demedts MG, Decramer M. Hypogonadism in male outpatients with sarcoidosis. *Respir Med* 2007;101:2502–2510.
85. McCollister DH, Beutz M, McLaughlin V, Rumsfeld J, Masoudi FA, Tripputi M, Yaeger T, Weintraub P, Badesch DB. Depressive symptoms in pulmonary arterial hypertension: prevalence and association with functional status. *Psychosomatics* 2010;51:339–339, e338.
86. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, *et al*. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010;137:376–387.
87. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, Provencher S. Effects of a rehabilitation program on skeletal muscle function in idiopathic pulmonary arterial hypertension. *J Cardiopulm Rehabil Prev* 2010;30:319–323.
88. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, Provencher S. Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. *Thorax* 2010;65:113–117.
89. Pugh ME, Buchowski MS, Robbins IM, Newman JH, Hemnes AR. Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. *Chest* 2012;142:1391–1398.
90. Mainguy V, Provencher S, Maltais F, Malenfant S, Saey D. Assessment of daily life physical activities in pulmonary arterial hypertension. *PLoS One* 2011;6:e27993.
91. Korenromp IH, Grutters JC, van den Bosch JM, Heijnen CJ. Post-inflammatory fatigue in sarcoidosis: personality profiles, psychological symptoms and stress hormones. *J Psychosom Res* 2012;72:97–102.

92. Korenromp IH, Heijnen CJ, Vogels OJ, van den Bosch JM, Grutters JC. Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. *Chest* 2011;140:441–447.
93. Hill K, Mangovski-Alzamora S, Blouin M, Guyatt G, Heels-Ansdell D, Bragaglia P, Tamari I, Jones K, Goldstein R. Disease-specific education in the primary care setting increases the knowledge of people with chronic obstructive pulmonary disease: a randomized controlled trial. *Patient Educ Couns* 2010;81:14–18.
94. Bourbeau J, Nault D, Dang-Tan T. Self-management and behaviour modification in COPD. *Patient Educ Couns* 2004;52:271–277.
95. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;4:CD003793.
96. Velloso M, Jardim JR. Study of energy expenditure during activities of daily living using and not using body position recommended by energy conservation techniques in patients with COPD. *Chest* 2006;130:126–132.
97. Bischoff EW, Hamd DH, Sedeno M, Benedetti A, Schermer TR, Bernard S, Maltais F, Bourbeau J. Effects of written action plan adherence on COPD exacerbation recovery. *Thorax* 2011;66:26–31.
98. Rice KL, Dewan N, Bloomfield HE, Grill J, Schult TM, Nelson DB, Kumari S, Thomas M, Geist LJ, Beaner C, *et al.* Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med* 2010;182:890–896.
99. Effing T, Monninkhof EM, van der Valk PD, van der Palen J, van Herwaarden CL, Partidge MR, Walters EH, Zielhuis GA. Self-management education for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;4:CD002990.
100. Trappenburg JC, Monninkhof EM, Bourbeau J, Troosters T, Schrijvers AJ, Verheij TJ, Lammers JW. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax* 2011;66:977–984.
101. Effing T, Kerstjens H, van der Valk P, Zielhuis G, van der Palen J. (Cost)-effectiveness of self-treatment of exacerbations on the severity of exacerbations in patients with COPD: the COPE II study. *Thorax* 2009;64:956–962.
102. Fried TR, Van Ness PH, Byers AL, Towle VR, O'Leary JR, Dubin JA. Changes in preferences for life-sustaining treatment among older persons with advanced illness. *J Gen Intern Med* 2007;22:495–501.
103. Janssen DJ, Engelberg RA, Wouters EF, Curtis JR. Advance care planning for patients with COPD: past, present and future. *Patient Educ Couns* 2012;86:19–24.
104. Janssen DJ, Spruit MA, Schols JM, Cox B, Nawrot TS, Curtis JR, Wouters EF. Predicting changes in preferences for life-sustaining treatment among patients with advanced chronic organ failure. *Chest* 2012;141:1251–1259.
105. Janssen DJ, Spruit MA, Schols JM, Wouters EF. A call for high-quality advance care planning in outpatients with severe COPD or chronic heart failure. *Chest* 2011;139:1081–1088.
106. Silveira MJ, Kim SY, Langa KM. Advance directives and outcomes of surrogate decision making before death. *N Engl J Med* 2010;362:1211–1218.
107. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ* 2010;340:c1345.
108. Teno JM, Gruneir A, Schwartz Z, Nanda A, Wetle T. Association between advance directives and quality of end-of-life care: a national study. *J Am Geriatr Soc* 2007;55:189–194.
109. Curtis JR. Palliative and end-of-life care for patients with severe COPD. *Eur Respir J* 2008;32:796–803.
110. van Wetering CR, Hoogendoorn M, Broekhuizen R, Geraerts-Keeris GJ, De Munck DR, Rutten-van Mölken MP, Schols AM. Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. *J Am Med Dir Assoc* 2010;11:179–187.
111. Pison CM, Cano NJ, Chérion C, Caron F, Court-Fortune I, Antonini MT, Gonzalez-Bermejo J, Meziane L, Molano LC, Janssens JP, *et al.*; IRAD Investigators. Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomised controlled trial. *Thorax* 2011;66:953–960.
112. Al-Ghimlas F, Todd DC. Creatine supplementation for patients with COPD receiving pulmonary rehabilitation: a systematic review and meta-analysis. *Respirology* 2010;15:785–795.
113. Deacon SJ, Vincent EE, Greenhaff PL, Fox J, Steiner MC, Singh SJ, Morgan MD. Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;178:233–239.
114. Velasco R, Pirraglia PA, Casserly B, Nici L. Influence of body mass index on changes in disease-specific quality of life of veterans completing pulmonary rehabilitation. *J Cardiopulm Rehabil Prev* 2010;30:334–339.
115. Sava F, Laviolette L, Bernard S, Breton MJ, Bourbeau J, Maltais F. The impact of obesity on walking and cycling performance and response to pulmonary rehabilitation in COPD. *BMC Pulm Med* 2010;10:55.
116. Ramachandran K, McCusker C, Connors M, Zuwallack R, Lahiri B. The influence of obesity on pulmonary rehabilitation outcomes in patients with COPD. *Chron Respir Dis* 2008;5:205–209.
117. Greening NJ, Evans RA, Williams JE, Green RH, Singh SJ, Steiner MC. Does body mass index influence the outcomes of a Waking-based pulmonary rehabilitation programme in COPD? *Chron Respir Dis* 2012;9:99–106.
118. Dreher M, Kabitz HJ. Impact of obesity on exercise performance and pulmonary rehabilitation. *Respirology* 2012;17:899–907.
119. Waschki B, Spruit MA, Watz H, Albert PS, Shrikrishna D, Groenen M, Smith C, Man WD, Tal-Singer R, Edwards LD, *et al.* Physical activity monitoring in COPD: compliance and associations with clinical characteristics in a multicenter study. *Respir Med* 2012;106:522–530.
120. Hernandes NA, Teixeira DdeC, Probst VS, Brunetto AF, Ramos EM, Pitta F. Profile of the level of physical activity in the daily lives of patients with COPD in Brazil. *J Bras Pneumol* 2009;35:949–956.
121. Vorrink SN, Kort HS, Troosters T, Lammers JW. Level of daily physical activity in individuals with COPD compared with healthy controls. *Respir Res* 2011;12:33.
122. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;171:972–977.
123. Pitta F, Breyer MK, Hernandes NA, Teixeira D, Sant'Anna TJ, Fontana AD, Probst VS, Brunetto AF, Spruit MA, Wouters EF, *et al.* Comparison of daily physical activity between COPD patients from Central Europe and South America. *Respir Med* 2009;103:421–426.
124. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006;61:772–778.
125. Ringbaek TJ, Lange P. Outdoor activity and performance status as predictors of survival in hypoxaemic chronic obstructive pulmonary disease (COPD). *Clin Rehabil* 2005;19:331–338.
126. Waschki B, Kirsten A, Holz O, Müller KC, Meyer T, Watz H, Magnussen H. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011;140:331–342.
127. Garcia-Rio F, Rojo B, Casitas R, Lores V, Madero R, Romero D, Galera R, Villasante C. Prognostic value of the objective measurement of daily physical activity in patients with COPD. *Chest* 2012;142:338–346.
128. Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM; EFRAM Investigators. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003;58:100–105.
129. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. *Chest* 2006;129:536–544.
130. Seidel D, Cheung A, Suh ES, Raste Y, Atakhorrami M, Spruit MA. Physical inactivity and risk of hospitalisation for chronic obstructive pulmonary disease [review article]. *Int J Tuberc Lung Dis* 2012;16:1015–1019.
131. Mercken EM, Hageman GJ, Schols AM, Akkermans MA, Bast A, Wouters EF. Rehabilitation decreases exercise-induced oxidative stress in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:994–1001.
132. Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with COPD more active after pulmonary rehabilitation? *Chest* 2008;134:273–280.

133. Sewell L, Singh SJ, Williams JE, Collier R, Morgan MD. Can individualized rehabilitation improve functional independence in elderly patients with COPD? *Chest* 2005;128:1194–1200.
134. Walker PP, Burnett A, Flavahan PW, Calverley PM. Lower limb activity and its determinants in COPD. *Thorax* 2008;63:683–689.
135. Coronado M, Janssens JP, de Muralt B, Terrier P, Schutz Y, Fitting JW. Walking activity measured by accelerometry during respiratory rehabilitation. *J Cardiopulm Rehabil* 2003;23:357–364.
136. Dallas MI, McCusker C, Haggerty MC, Rochester CL, Zuwallack R; Northeast Pulmonary Rehabilitation Consortium. Using pedometers to monitor walking activity in outcome assessment for pulmonary rehabilitation. *Chron Respir Dis* 2009;6:217–224.
137. Mador MJ, Patel AN, Nadler J. Effects of pulmonary rehabilitation on activity levels in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev* 2011;31:52–59.
138. Steele BG, Belza B, Cain KC, Coppersmith J, Lakshminarayan S, Howard J, Haselkorn JK. A randomized clinical trial of an activity and exercise adherence intervention in chronic pulmonary disease. *Arch Phys Med Rehabil* 2008;89:404–412.
139. Steele BG, Belza B, Hunziker J, Holt L, Legro M, Coppersmith J, Buchner D, Lakshminaryan S. Monitoring daily activity during pulmonary rehabilitation using a triaxial accelerometer. *J Cardiopulm Rehabil* 2003;23:139–142.
140. Ng LWC, Mackney J, Jenkins S, Hill K. Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis. *Chron Respir Dis* 2012;9:17–26.
141. Casaburi R. Activity promotion: a paradigm shift for chronic obstructive pulmonary disease therapeutics. *Proc Am Thorac Soc* 2011;8:334–337.
142. Troosters T, Gosselink R, Janssens W, Decramer M. Exercise training and pulmonary rehabilitation: new insights and remaining challenges. *Eur Respir Rev* 2010;19:24–29.
143. Egan C, Deering BM, Blake C, Fullen BM, McCormack NM, Spruit MA, Costello RW. Short term and long term effects of pulmonary rehabilitation on physical activity in COPD. *Respir Med* 2012;106: 1671–1679.
144. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. *Eur Respir J* 2006;27:1040–1055.
145. Gimeno-Santos E, Frei A, Dobbels F, Rüdell K, Puhan MA, Garcia-Aymerich J; PROactive Consortium. Validity of instruments to measure physical activity may be questionable due to a lack of conceptual frameworks: a systematic review. *Health Qual Life Outcomes* 2011;9:86.
146. Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, Marciniuk DD, Denberg T, Schünemann H, Wedzicha W, *et al.*; American College of Physicians; American College of Chest Physicians; American Thoracic Society; European Respiratory Society. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011;155:179–191.
147. Huijsmans RJ, de Haan A, ten Hacken NN, Straver RV, van't Hul AJ. The clinical utility of the GOLD classification of COPD disease severity in pulmonary rehabilitation. *Respir Med* 2008;102:162–171.
148. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. *Eur Respir J* 2009;33:262–272.
149. Graat-Verboom L, van den Borne BE, Smeenk FW, Spruit MA, Wouters EF. Osteoporosis in COPD outpatients based on bone mineral density and vertebral fractures. *J Bone Miner Res* 2011;26: 561–568.
150. Spruit MA, Watkins ML, Edwards LD, Vestbo J, Calverley PM, Pinto-Plata V, Celli BR, Tal-Singer R, Wouters EF; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study Investigators. Determinants of poor 6-min walking distance in patients with COPD: the ECLIPSE cohort. *Respir Med* 2010; 104:849–857.
151. Hernandes NA, Wouters EF, Meijer K, Annegarn J, Pitta F, Spruit MA. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J* 2011;38:261–267.
152. van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Mölken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010;65:7–13.
153. Zanotti E, Felicetti G, Maini M, Fracchia C. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. *Chest* 2003;124:292–296.
154. Gerovasili V, Stefanidis K, Vitzilaios K, Karatzanos E, Politis P, Koroneos A, Chatzimichail A, Routsi C, Roussos C, Nanas S. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. *Crit Care* 2009;13:R161.
155. Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, Bouillon R, Decramer M. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003;58:752–756.
156. Behnke M, Jorres RA, Kirsten D, Magnussen H. Clinical benefits of a combined hospital and home-based exercise programme over 18 months in patients with severe COPD. *Monaldi Arch Chest Dis* 2003; 59:44–51.
157. Carr SJ, Hill K, Brooks D, Goldstein RS. Pulmonary rehabilitation after acute exacerbation of chronic obstructive pulmonary disease in patients who previously completed a pulmonary rehabilitation program. *J Cardiopulm Rehabil Prev* 2009;29:318–324.
158. Clini EM, Crisafulli E, Costi S, Rossi G, Lorenzi C, Fabbri LM, Ambrosino N. Effects of early inpatient rehabilitation after acute exacerbation of COPD. *Respir Med* 2009;103:1526–1531.
159. Kirsten DK, Taube C, Lehnigk B, Jörres RA, Magnussen H. Exercise training improves recovery in patients with COPD after an acute exacerbation. *Respir Med* 1998;92:1191–1198.
160. Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ* 2004;329:1209.
161. Murphy N, Bell C, Costello RW. Extending a home from hospital care programme for COPD exacerbations to include pulmonary rehabilitation. *Respir Med* 2005;99:1297–1302.
162. Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. *Arch Phys Med Rehabil* 1998;79:849–854.
163. Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;10: CD005305.
164. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality—a systematic review. *Respir Res* 2005;6:54.
165. Seymour JM, Moore L, Jolley CJ, Ward K, Creasey J, Steier JS, Yung B, Man WD, Hart N, Polkey MI, *et al*. Outpatient pulmonary rehabilitation following acute exacerbations of COPD. *Thorax* 2010;65:423–428.
166. Ko FW, Dai DL, Ngai J, Tung A, Ng S, Lai K, Fong R, Lau H, Tam W, Hui DS. Effect of early pulmonary rehabilitation on health care utilization and health status in patients hospitalized with acute exacerbations of COPD. *Respirology* 2011;16:617–624.
167. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, Hermans G, Decramer M, Gosselink R. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009;37:2499–2505.
168. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, Ross A, Anderson L, Baker S, Sanchez M, *et al*. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238–2243.
169. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, *et al*. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373: 1874–1882.
170. O'Neill B, McKevitt A, Rafferty S, Bradley JM, Johnston D, Bradbury I, McMahon J. A comparison of twice- versus once-weekly supervision during pulmonary rehabilitation in chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2007;88: 167–172.

171. Waterhouse JC, Walters SJ, Oluboyede Y, Lawson RA. A randomised 2×2 trial of community versus hospital pulmonary rehabilitation, followed by telephone or conventional follow-up. *Health Technol Assess* 2010;14:i–v, vii–xi, 1–140.
172. Spruit MA, Troosters T, Trappenburg JC, Decramer M, Gosselink R. Exercise training during rehabilitation of patients with COPD: a current perspective. *Patient Educ Couns* 2004;52:243–248.
173. du Moulin M, Taube K, Wegscheider K, Behnke M, van den Bussche H. Home-based exercise training as maintenance after outpatient pulmonary rehabilitation. *Respiration* 2009;77:139–145.
174. Spencer LM, Alison JA, McKeough ZJ. Maintaining benefits following pulmonary rehabilitation: a randomised controlled trial. *Eur Respir J* 2010;35:571–577.
175. Ringbaek T, Brondum E, Martinez G, Thogersen J, Lange P. Long-term effects of 1-year maintenance training on physical functioning and health status in patients with COPD: a randomized controlled study. *J Cardiopulm Rehabil Prev* 2010;30:47–52.
176. Ries AL, Kaplan RM, Myers R, Prewitt LM. Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. *Am J Respir Crit Care Med* 2003;167:880–888.
177. Hill K, Bansal V, Brooks D, Goldstein RS. Repeat pulmonary rehabilitation programs confer similar increases in functional exercise capacity to initial programs. *J Cardiopulm Rehabil Prev* 2008;28:410–414.
178. Romagnoli M, Dell'Orso D, Lorenzi C, Crisafulli E, Costi S, Lugli D, Clini EM. Repeated pulmonary rehabilitation in severe and disabled COPD patients. *Respiration* 2006;73:769–776.
179. Coventry PA. Does pulmonary rehabilitation reduce anxiety and depression in chronic obstructive pulmonary disease? *Curr Opin Pulm Med* 2009;15:143–149.
180. Harrison SL, Greening NJ, Williams JE, Morgan MD, Steiner MC, Singh SJ. Have we underestimated the efficacy of pulmonary rehabilitation in improving mood? *Respir Med* 2012;106:838–844.
181. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–654.
182. Dodd JW, Hogg L, Nolan J, Jefford H, Grant A, Lord VM, Falzon C, Garrod R, Lee C, Polkey MI, *et al*. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. *Thorax* 2011;66:425–429.
183. Dodd JW, Marns PL, Clark AL, Ingram KA, Fowler RP, Canavan JL, Patel MS, Kon SS, Hopkinson NS, Polkey MI, *et al*. The COPD Assessment Test (CAT): short- and medium-term response to pulmonary rehabilitation. *COPD* 2012;9:390–394.
184. Jones PW, Harding G, Wiklund I, Berry P, Tabberer M, Yu R, Leidy NK. Tests of the responsiveness of the COPD Assessment Test following acute exacerbation and pulmonary rehabilitation. *Chest* 2012;142:134–140.
185. Hyland ME, Jones RC, Hanney KE. The Lung Information Needs Questionnaire: development, preliminary validation and findings. *Respir Med* 2006;100:1807–1816.
186. White R, Walker P, Roberts S, Kalisky S, White P. Bristol COPD Knowledge Questionnaire (BCKQ): testing what we teach patients about COPD. *Chron Respir Dis* 2006;3:123–131.
187. Jones RC, Wang X, Harding S, Bott J, Hyland M. Educational impact of pulmonary rehabilitation: Lung Information Needs Questionnaire. *Respir Med* 2008;102:1439–1445.
188. Garrod R, Marshall J, Jones F. Self efficacy measurement and goal attainment after pulmonary rehabilitation. *Int J Chron Obstruct Pulmon Dis* 2008;3:791–796.
189. Scherer YK, Schmieder LE. The effect of a pulmonary rehabilitation program on self-efficacy, perception of dyspnea, and physical endurance. *Heart Lung* 1997;26:15–22.
190. Vincent E, Sewell L, Wagg K, Deacon S, Williams J, Singh S. Measuring a change in self-efficacy following pulmonary rehabilitation: an evaluation of the PRAISE tool. *Chest* 2011;140:1534–1539.
191. Robles PG, Mathur S, Janaudis-Fereira T, Dolmage TE, Goldstein RS, Brooks D. Measurement of peripheral muscle strength in individuals with chronic obstructive pulmonary disease: a systematic review. *J Cardiopulm Rehabil Prev* 2011;31:11–24.
192. Annegarn J, Spruit MA, Savelberg HH, Willems PJ, van de Bool C, Schols AM, Wouters EF, Meijer K. Differences in walking pattern during 6-min walk test between patients with COPD and healthy subjects. *PLoS One* 2012;7:e37329.
193. Roig M, Eng JJ, MacIntyre DL, Road JD, FitzGerald JM, Burns J, Reid WD. Falls in people with chronic obstructive pulmonary disease: an observational cohort study. *Respir Med* 2011;105:461–469.
194. Beauchamp MK, Hill K, Goldstein RS, Janaudis-Ferreira T, Brooks D. Impairments in balance discriminate fallers from non-fallers in COPD. *Respir Med* 2009;103:1885–1891.
195. Beauchamp MK, O'Hoski S, Goldstein RS, Brooks D. Effect of pulmonary rehabilitation on balance in persons with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2010;91:1460–1465.
196. Leung RW, McKeough ZJ, Peters MJ, Alison JA. Short-form Sun-style t'ai chi as an exercise training modality in people with COPD. *Eur Respir J* 2013;41:1051–1057.
197. Camillo CA, Pitta F, Possani HV, Barbosa MV, Marques DS, Cavalheri V, Probst VS, Brunetto AF. Heart rate variability and disease characteristics in patients with COPD. *Lung* 2008;186:393–401.
198. van Gestel AJ, Kohler M, Steier J, Sommerwerck U, Teschler S, Russi EW, Teschler H. Cardiac autonomic function and cardiovascular response to exercise in patients with chronic obstructive pulmonary disease. *COPD* 2012;9:160–165.
199. Van Gestel AJ, Kohler M, Steier J, Teschler S, Russi EW, Teschler H. Cardiac autonomic dysfunction and health-related quality of life in patients with chronic obstructive pulmonary disease. *Respirology* 2011;16:939–946.
200. Gale NS, Duckers JM, Enright S, Cockcroft JR, Shale DJ, Bolton CE. Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? *BMC Pulm Med* 2011;11:20.
201. Vivodtzev I, Minet C, Wuyam B, Borel JC, Vottero G, Monneret D, Baguet JP, Lévy P, Pépin JL. Significant improvement in arterial stiffness after endurance training in patients with COPD. *Chest* 2010;137:585–592.
202. Camillo CA, Laburu VdeM, Gonçalves NS, Cavalheri V, Tomasi FP, Hernandes NA, Ramos D, Marquez Vanderlei LC, Cipulo Ramos EM, Probst VS, *et al*. Improvement of heart rate variability after exercise training and its predictors in COPD. *Respir Med* 2011;105:1054–1062.
203. Marquis K, Maltais F, Lacasse Y, Lacourciere Y, Fortin C, Poirier P. Effects of aerobic exercise training and irbesartan on blood pressure and heart rate variability in patients with chronic obstructive pulmonary disease. *Can Respir J* 2008;15:355–360.
204. Borghi-Silva A, Arena R, Castello V, Simões RP, Martins LE, Catai AM, Costa D. Aerobic exercise training improves autonomic nervous control in patients with COPD. *Respir Med* 2009;103:1503–1510.
205. Kiley JP, Sri Ram J, Croxton TL, Weinmann GG. Challenges associated with estimating minimal clinically important differences in COPD—the NHLBI perspective. *COPD* 2005;2:43–46.
206. Pepin V, Laviolette L, Brouillard C, Sewell L, Singh SJ, Revill SM, Lacasse Y, Maltais F. Significance of changes in endurance shuttle walking performance. *Thorax* 2011;66:115–120.
207. Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. *Thorax* 2008;63:775–777.
208. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk Test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;155:1278–1282.
209. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2010;91:221–225.
210. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schünemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *Eur Respir J* 2008;32:637–643.
211. Puhan MA, Chandra D, Mosenifar Z, Ries A, Make B, Hansel NN, Wise RA, Sciurba F; National Emphysema Treatment Trial (NETT) Research Group. The minimal important difference of exercise tests in severe COPD. *Eur Respir J* 2011;37:784–790.
212. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Sahn SA, Szwarcberg J,

et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am J Respir Crit Care Med* 2012;183:1231–1237.

213. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;186:428–433.
214. Brooks D, Sottana R, Bell B, Hanna M, Laframboise L, Selvanayagarajah S, Goldstein R. Characterization of pulmonary rehabilitation programs in Canada in 2005. *Can Respir J* 2007;14:87–92.
215. Yohannes A, Stone R, Lowe D, Pursey N, Buckingham R, Roberts C. Pulmonary rehabilitation in the United Kingdom. *Chron Respir Dis* 2011;8:193–199.
216. Annegarn J, Meijer K, Passos VL, Stute K, Wiechert J, Savelberg HH, Schols AM, Wouters EF, Spruit MA; CIRO+ Rehabilitation Network. Problematic activities of daily life are weakly associated with clinical characteristics in COPD. *J Am Med Dir Assoc* 2012;13: 284–290.
217. Ambrosino N, Venturelli E, Vagheggini G, Clini E. Rehabilitation, weaning and physical therapy strategies in chronic critically ill patients. *Eur Respir J* 2012;39:487–492.
218. Baltzan MA, Kamel H, Alter A, Rotaple M, Wolkove N. Pulmonary rehabilitation improves functional capacity in patients 80 years of age or older. *Can Respir J* 2004;11:407–413.
219. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999;160:1248–1253.
220. Couser JI Jr, Guthmann R, Hamadeh MA, Kane CS. Pulmonary rehabilitation improves exercise capacity in older elderly patients with COPD. *Chest* 1995;107:730–734.
221. Vogelmeier C, Worth H. [COPD—a historical review, current management and research perspectives]. *Pneumologie* 2010;64: 550–554.
222. Cazzola M, Bettoncelli G, Sessa E, Cricelli C, Biscione G. Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration* 2010;80:112–119.
223. Graat-Verboom L, Spruit MA, van den Borne BE, Smeenk FW, Martens EJ, Lunde R, Wouters EF; CIRO Network. Correlates of osteoporosis in chronic obstructive pulmonary disease: an underestimated systemic component. *Respir Med* 2009;103:1143–1151.
224. Graat-Verboom L, Wouters EF, Smeenk FW, van den Borne BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J* 2009;34:209–218.
225. Hanania NA, Müllerova H, Locantore NW, Vestbo J, Watkins ML, Wouters EF, Rennard SI, Sharafkhaneh A; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study Investigators. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med* 2011;183:604–611.
226. Incalzi RA, Corsonello A, Pedone C, Battaglia S, Paglino G, Bellia V; Extrapulmonary Consequences of COPD in the Elderly Study Investigators. Chronic renal failure: a neglected comorbidity of COPD. *Chest* 2010;137:831–837.
227. Janssen DJ, Spruit MA, Leue C, Gijsen C, Hameleers H, Schols JM, Wouters EF; CIRO Network. Symptoms of anxiety and depression in COPD patients entering pulmonary rehabilitation. *Chron Respir Dis* 2010;7:147–157.
228. Lee R, McNicholas WT. Obstructive sleep apnea in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* 2011;17:79–83.
229. Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005;128:2068–2075.
230. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;128:2099–2107.
231. Terada K, Muro S, Ohara T, Kudo M, Ogawa E, Hoshino Y, Hirai T, Niimi A, Chin K, Mishima M. Abnormal swallowing reflex and COPD exacerbations. *Chest* 2010;137:326–332.
232. Yohannes AM, Ershler WB. Anemia in COPD: a systematic review of the prevalence, quality of life, and mortality. *Respir Care* 2011;56: 644–652.
233. Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. *Eur Respir J* 2010;35:913–922.
234. Vanfleteren LE, Franssen FM, Uszko-Lencer NH, Spruit MA, Celis M, Gorgels AP, Wouters EF. Frequency and relevance of ischemic electrocardiographic findings in patients with chronic obstructive pulmonary disease. *Am J Cardiol* 2011;108:1669–1674.
235. Janssen DJ, Spruit MA, Uszko-Lencer NH, Schols JM, Wouters EF. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. *J Palliat Med* 2011;14:735–743.
236. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;33:1165–1185.
237. Wouters EFM, Celis MPM, Breyer MK, Rutten EPA, Graat-Verboom L, Spruit MA. Co-morbid manifestations in COPD. *Respir Med COPD Update* 2007;3:135–151.
238. Watz H, Waschki B, Kirsten A, Müller KC, Kretschmar G, Meyer T, Holz O, Magnussen H. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009;136: 1039–1046.
239. Crisafulli E, Costi S, Luppi F, Cirelli G, Cilione C, Coletti O, Fabbri LM, Clini EM. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. *Thorax* 2008;63:487–492.
240. Crisafulli E, Gorgone P, Vagaggini B, Pagani M, Rossi G, Costa F, Guarriello V, Paggiaro P, Chetta A, de Blasio F, *et al*. Efficacy of standard rehabilitation in COPD outpatients with comorbidities. *Eur Respir J* 2010;36:1042–1048.
241. Maltais F, Bourbeau J, Shapiro S, Lacasse Y, Perrault H, Baltzan M, Hernandez P, Rouleau M, Julien M, Parenteau S, *et al*.; Chronic Obstructive Pulmonary Disease Axis of Respiratory Health Network, Fonds de Recherche en Santé du Québec. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008;149:869–878.
242. Güell MR, de Lucas P, Gáldiz JB, Montemayor T, Rodríguez González-Moro JM, Gorostiza A, Ortega F, Bellón JM, Guyatt G. [Home vs hospital-based pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: a Spanish multicenter trial]. *Arch Bronconeumol* 2008;44:512–518.
243. Mendes de Oliveira JC, Studart Leitão Filho FS, Malosa Sampaio LM, Negrinho de Oliveira AC, Hirata RP, Costa D, Donner CF, de Oliveira LVF. Outpatient vs. home-based pulmonary rehabilitation in COPD: a randomized controlled trial. *Multidiscip Respir Med* 2010;5:401–408.
244. Fernández AM, Pascual J, Ferrando C, Arnal A, Vergara I, Sevila V. Home-based pulmonary rehabilitation in very severe COPD: is it safe and useful? *J Cardiopulm Rehabil Prev* 2009;29:325–331.
245. Albores J, Marolda C, Haggerty M, Gerstenhaber B, Zuwallack R. The use of a home exercise program based on a computer system in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev* 2013;33:47–52.
246. Liu WT, Huang CD, Wang CH, Lee KY, Lin SM, Kuo HP. A mobile telephone–based interactive self-care system improves asthma control. *Eur Respir J* 2011;37:310–317.
247. Stickland M, Jourdain T, Wong EY, Rodgers WM, Jendzjowsky NG, Macdonald GF. Using Telehealth technology to deliver pulmonary rehabilitation in chronic obstructive pulmonary disease patients. *Can Respir J* 2011;18:216–220.
248. Lewis KE, Annandale JA, Warm DL, Rees SE, Hurlin C, Blyth H, Syed Y, Lewis L. Does home telemonitoring after pulmonary rehabilitation reduce healthcare use in optimized COPD? A pilot randomized trial. *COPD* 2010;7:44–50.
249. Wewel AR, Gellermann I, Schwertfeger I, Morfeld M, Magnussen H, Jörres RA. Intervention by phone calls raises domiciliary activity and exercise capacity in patients with severe COPD. *Respir Med* 2008;102:20–26.
250. Hospes G, Bossenbroek L, Ten Hacken NH, van Hengel P, de Greef MH. Enhancement of daily physical activity increases physical fitness of outclinic COPD patients: results of an exercise counseling program. *Patient Educ Couns* 2009;75:274–278.
251. Beauchamp MK, Janaudis-Ferreira T, Goldstein RS, Brooks D. Optimal duration of pulmonary rehabilitation for individuals with

chronic obstructive pulmonary disease—a systematic review. *Chron Respir Dis* 2011;8:129–140.

252. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:19–38.
253. Rossi G, Florini F, Romagnoli M, Bellantone T, Lucic S, Lugli D, Clini E. Length and clinical effectiveness of pulmonary rehabilitation in outpatients with chronic airway obstruction. *Chest* 2005;127:105–109.
254. Solanes I, Güell R, Casan P, Sotomayor C, Gonzalez A, Feixas T, Gonzalez M, Guyatt G. Duration of pulmonary rehabilitation to achieve a plateau in quality of life and walk test in COPD. *Respir Med* 2009;103:722–728.
255. Keating A, Lee A, Holland AE. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. *Chron Respir Dis* 2011;8:89–99.
256. Garrod R, Marshall J, Barley E, Jones PW. Predictors of success and failure in pulmonary rehabilitation. *Eur Respir J* 2006;27:788–794.
257. Hogg L, Garrod R, Thornton H, McDonnell L, Bellas H, White P. Effectiveness, attendance, and completion of an integrated, system-wide pulmonary rehabilitation service for COPD: prospective observational study. *COPD* 2012;9:546–554.
258. Selzler AM, Simmonds L, Rodgers WM, Wong EY, Stickland MK. Pulmonary rehabilitation in chronic obstructive pulmonary disease: predictors of program completion and success. *COPD* 2012;9:538–545.
259. Graves J, Sandrey V, Graves T, Smith DL. Effectiveness of a group opt-in session on uptake and graduation rates for pulmonary rehabilitation. *Chron Respir Dis* 2010;7:159–164.
260. Cecins N, Geelhoed E, Jenkins SC. Reduction in hospitalisation following pulmonary rehabilitation in patients with COPD. *Aust Health Rev* 2008;32:415–422.
261. Hui KP, Hewitt AB. A simple pulmonary rehabilitation program improves health outcomes and reduces hospital utilization in patients with COPD. *Chest* 2003;124:94–97.
262. California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. *J Cardiopulm Rehabil* 2004;24:52–62.
263. Rasekaba TM, Williams E, Hsu-Hage B. Can a chronic disease management pulmonary rehabilitation program for COPD reduce acute rural hospital utilization? *Chron Respir Dis* 2009;6:157–163.
264. Raskin J, Spiegler P, McCusker C, ZuWallack R, Bernstein M, Busby J, DiLauro P, Griffiths K, Haggerty M, Hovey L, *et al*. The effect of pulmonary rehabilitation on healthcare utilization in chronic obstructive pulmonary disease: the Northeast Pulmonary Rehabilitation Consortium. *J Cardiopulm Rehabil* 2006;26:231–236.
265. Cote CG, Celli BR. Pulmonary rehabilitation and the BODE Index in COPD. *Eur Respir J* 2005;26:630–636.
266. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Ionescu AA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362–368.
267. Eaton T, Young P, Fergusson W, Moodie L, Zeng I, O'Kane F, Good N, Rhodes L, Poole P, Kolbe J. Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. *Respirology* 2009;14:230–238.
268. Güell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, Sanchis J. Long-term effects of outpatient rehabilitation of COPD: a randomized trial. *Chest* 2000;117:976–983.
269. Goldstein RS, Gort EH, Guyatt GH, Feeny D. Economic analysis of respiratory rehabilitation. *Chest* 1997;112:370–379.
270. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001;56:779–784.
271. Hoogendoorn M, van Wetering CR, Schols AM, Rutten-van Mölken MP. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? *Eur Respir J* 2010;35:79–87.
272. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax* 2008;63:549–554.
273. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008;13:394–399.
274. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, Behr J, Kenn K. Effects of in-patient pulmonary rehabilitation in patients with interstitial lung disease. *Eur Respir J* 2012.
275. Holland A, Hill C. Physical training for interstitial lung disease. *Cochrane Database Syst Rev* 2008;4:CD006322.
276. Kozu R, Senjyu H, Jenkins SC, Mukae H, Sakamoto N, Kohno S. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. *Respiration* 2011;81:196–205.
277. Yorke J, Jones PW, Swigris JJ. Development and validity testing of an IPF-specific version of the St George's Respiratory Questionnaire. *Thorax* 2010;65:921–926.
278. Newall C, Stockley RA, Hill SL. Exercise training and inspiratory muscle training in patients with bronchiectasis. *Thorax* 2005;60:943–948.
279. Ong HK, Lee AL, Hill CJ, Holland AE, Denehy L. Effects of pulmonary rehabilitation in bronchiectasis: a retrospective study. *Chron Respir Dis* 2011;8:21–30.
280. Murray MP, Turnbull K, MacQuarrie S, Pentland JL, Hill AT. Validation of the Leicester Cough Questionnaire in non–cystic fibrosis bronchiectasis. *Eur Respir J* 2009;34:125–131.
281. Cerny FJ. Relative effects of bronchial drainage and exercise for in-hospital care of patients with cystic fibrosis. *Phys Ther* 1989;69:633–639.
282. Schneiderman-Walker J, Pollock SL, Corey M, Wilkes DD, Canny GJ, Pedder L, Reisman JJ. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. *J Pediatr* 2000;136:304–310.
283. Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. *Pediatr Pulmonol* 2002;33:194–200.
284. Klijn PH, Oudshoorn A, van der Ent CK, van der Net J, Kimpen JL, Helders PJ. Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. *Chest* 2004;125:1299–1305.
285. Moorcroft AJ, Dodd ME, Morris J, Webb AK. Individualised unsupervised exercise training in adults with cystic fibrosis: a 1 year randomised controlled trial. *Thorax* 2004;59:1074–1080.
286. Hebestreit H, Kieser S, Junge S, Ballmann M, Hebestreit A, Schindler C, Schenk T, Posselt HG, Kriemler S. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. *Eur Respir j* 2010;35:578–583.
287. Bradley J, Moran F. Physical training for cystic fibrosis. *Cochrane Database Syst Rev* 2008;1:CD002768.
288. Dwyer TJ, Alison JA, McKeough ZJ, Daviskas E, Bye PT. Effects of exercise on respiratory flow and sputum properties in patients with cystic fibrosis. *Chest* 2011;139:870–877.
289. Saiman L, Siegel J; Cystic Fibrosis Foundation. Infection control recommendations for patients with cystic fibrosis: microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. *Infect Control Hosp Epidemiol* 2003;24(5, Suppl):S6–S52.
290. Gee L, Abbott J, Conway SP, Etherington C, Webb AK. Development of a disease specific health related quality of life measure for adults and adolescents with cystic fibrosis. *Thorax* 2000;55:946–954.
291. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* 2005;128:2347–2354.
292. Ram FS, Robinson SM, Black PN, Picot J. Physical training for asthma. *Cochrane Database Syst Rev* 2005;4:CD001116.
293. Mendes FA, Gonçalves RC, Nunes MP, Saraiva-Romanholo BM, Cukier A, Stelmach R, Jacob-Filho W, Martins MA, Carvalho CR. Effects of aerobic training on psychosocial morbidity and symptoms in patients with asthma: a randomized clinical trial. *Chest* 2010;138:331–337.
294. Turner S, Eastwood P, Cook A, Jenkins S. Improvements in symptoms and quality of life following exercise training in older adults with moderate/severe persistent asthma. *Respiration* 2011;81:302–310.

295. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, *et al*. Guidelines for methacholine and exercise challenge testing—1999. *Am J Respir Crit Care Med* 2000;161:309–329.
296. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992; 47:76–83.
297. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, *et al*. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 2006;114:1482–1489.
298. Grünig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, Opitz CF, Klose H, Wilkens H, Rosenkranz S, *et al*. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. *Respiration* 2011;81:394–401.
299. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herrerias C. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest* 2007;131(5, Suppl):4S–42S.
300. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res* 2006;15:103–115.
301. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE; American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126 (1, Suppl):14S–34S.
302. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–483.
303. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Qual Life Res* 1999;8:209–224.
304. Jones LW, Peddle CJ, Eves ND, Haykowsky MJ, Courneya KS, Mackey JR, Joy AA, Kumar V, Winton TW, Reiman T. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer* 2007;110:590–598.
305. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, Carbognani P, Rusca M, Olivieri D. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non–small cell lung cancer. *Eur J Cardiothorac Surg* 2008;33:95–98.
306. Cesario A, Ferri L, Galetta D, Pasqua F, Bonassi S, Clini E, Biscione G, Cardaci V, di Toro S, Zarzana A, *et al*. Post-operative respiratory rehabilitation after lung resection for non–small cell lung cancer. *Lung Cancer* 2007;57:175–180.
307. Jones LW, Eves ND, Peterson BL, Garst J, Crawford J, West MJ, Mabe S, Harpole D, Kraus WE, Douglas PS. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. *Cancer* 2008;113:3430–3439.
308. Spruit MA, Janssen PP, Willemsen SC, Hochstenbag MM, Wouters EF. Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. *Lung Cancer* 2006;52:257–260.
309. Jones LW, Eves ND, Kraus WE, Potti A, Crawford J, Blumenthal JA, Peterson BL, Douglas PS. The Lung Cancer Exercise Training Study: a randomized trial of aerobic training, resistance training, or both in postsurgical lung cancer patients: rationale and design. *BMC Cancer* 2010;10:155.
310. Arbane G, Tropman D, Jackson D, Garrod R. Evaluation of an early exercise intervention after thoracotomy for non–small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. *Lung Cancer* 2011;71: 229–234.
311. Granger CL, McDonald CF, Berney S, Chao C, Denehy L. Exercise intervention to improve exercise capacity and health related quality of life for patients with non–small cell lung cancer: a systematic review. *Lung Cancer* 2011;72:139–153.
312. Temel JS, Greer JA, Goldberg S, Vogel PD, Sullivan M, Pirl WF, Lynch TJ, Christiani DC, Smith MR. A structured exercise program for patients with advanced non–small cell lung cancer. *J Thorac Oncol* 2009;4:595–601.
313. Cella D. The Functional Assessment of Cancer Therapy-Lung and Lung Cancer Subscale assess quality of life and meaningful symptom improvement in lung cancer. *Semin Oncol* 2004;31(3, Suppl 9): 11–15.
314. Cella D, Eton DT, Fairclough DL, Bonomi P, Heyes AE, Silberman C, Wolf MK, Johnson DH. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) study 5592. *J Clin Epidemiol* 2002;55:285–295.
315. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995;12:199–220.
316. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003;1:79.
317. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;24:547–561.
318. Ries AL, Make BJ, Lee SM, Krasna MJ, Bartels M, Crouch R, Fishman AP; National Emphysema Treatment Trial Research Group. The effects of pulmonary rehabilitation in the National Emphysema Treatment Trial. *Chest* 2005;128:3799–3809.
319. Debigaré R, Maltais F, Whittom F, Deslauriers J, LeBlanc P. Feasibility and efficacy of home exercise training before lung volume reduction. *J Cardiopulm Rehabil* 1999;19:235–241.
320. Kaplan RM, Atkins CJ, Timms R. Validity of a quality of well-being scale as an outcome measure in chronic obstructive pulmonary disease. *J Chronic Dis* 1984;37:85–95.
321. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
322. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773–778.
323. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–1327.
324. Gloeckl R, Halle M, Kenn K. Interval versus continuous training in lung transplant candidates: a randomized trial. *J Heart Lung Transplant* 2012;31:934–941.
325. Biggar D, Trulock E, Patterson G, Cooper J. Comparisons of functional results in single versus bilateral lung transplantation in COPD patients through three years [abstract]. *Am Rev Respir Dis* 1994;149:A740.
326. Dear CL, Grossman RF, Maurer JR. Preoperative evaluation of patients awaiting lung transplant. *Chest* 1988;94(1 Suppl):30S.
327. Dear CL, Thomas J, Kesten S, Maurer JR. Impact of preoperative pulmonary rehabilitation in cystic fibrosis lung transplant recipients [abstract]. *Am J Respir Crit Care Med* 1994;149:A733.
328. Jastrzebski D, Ochman M, Ziora D, Labus L, Kowalski K, Wyrwol J, Lutogniewska W, Maksymiak M, Ksiazek B, Magner A, *et al*. Pulmonary rehabilitation in patients referred for lung transplantation. *Adv Exp Med Biol* 2013;755:19–25.
329. Stiebellehner L, Quittan M, End A, Wieselthaler G, Klepetko W, Haber P, Burghuber OC. Aerobic endurance training program improves exercise performance in lung transplant recipients. *Chest* 1998;113:906–912.
330. Munro PE, Holland AE, Bailey M, Button BM, Snell GI. Pulmonary rehabilitation following lung transplantation. *Transplant Proc* 2009; 41:292–295.
331. Wickerson L, Mathur S, Brooks D. Exercise training after lung transplantation: a systematic review. *J Heart Lung Transplant* 2010;29:497–503.