Clinics in Respiratory Medicine

Review Article
Published: 08 Jan, 2020

Respiratory Function Testing in the Era of Precision Medicine

*Milanese M[1], Viegi G[2], Sposato B[3] and Dal Negro RW[4]**

[1]Azienda Sanitaria Locale 2, Italy

[2]Institutes of Biomedicine and Molecular Immunology, National Research Council, Italy

[3]Misericordia Hospital Grosseto, Italy

[4]National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology, Italy

Abstract

Precision medicine aims to deliver treatments tailored to the individual patient with the most appropriate and the best management possible, and with a balance between patients' outcomes and socio-economic savings. In this scenario, what is the role of respiratory function testing delivered by Lung Units within the different National Health Systems? In our personal view, we believe that respiratory function testing should be considered a pillar proceeding to Precision medicine.

After underscoring the mandatory role of respiratory function testing for the diagnosis of a significant group of respiratory diseases (i.e. Asthma, COPD, IPF, OSAS), we describe its major contribute in the "phenotypic" recognition of treatable traits of airway obstructive disease. But we point out also that the selection of patients for advanced therapies (omalizumab, pirfenidone, nintedanib) or approaches (i.e. lung volume reduction, bronchial thermoplasty) strongly depends on data derived from Respiratory Function Testing. Finally, we highlight that new technologies or applications in respiratory pathophysiology are opening new horizons for a precision medicine approach.

Introduction

Precision Medicine (PM) aims to deliver "a treatment targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" [1]. PM products should be tailored to the individual patient with the most appropriate and the best management possible, and with a balance between patients' outcomes and socio-economic savings [2-4]. It requires the use of the stratification process, such as the discrimination of patients according to a specified disease into subgroups based on particular characteristics: of patients who respond more frequently (or better) to a particular treatment, and with a decreased risk of side effects. It also implies new diagnostic tools [5-8], rapidly evolving. Usually, the PM approach provides substantial benefits in well-characterized patients with severe disease, and in a specialized setting [1,4,9-11].

The Role of Lung Function in Patients' Phenotyping

When proceeding to PM, one should ask what is the role of respiratory function testing, intended as the global evaluation of respiratory function which can be delivered by Lung Units within the different national health systems.

Asthma

In Respiratory Medicine, the functional approach is mandatory for the diagnosis and the follow-up of different diseases (Table 1). Indeed, UK NICE (National Institute for Health and Care Excellence) guideline on asthma diagnosis and monitoring recommended routine spirometry (with reversibility testing when obstruction is detected) for all individuals with suspected asthma, based on health economic modeling as this is the most cost-effective clinical strategy [12]. When assessing the bronchial response to inhaled β2-agonist and/or anticholinergic drugs, an increase in FEV_1 >400 mL *vs.* baseline is strongly suggestive of asthma [13]. Monitoring asthmatic patients by spirometry is a key element of the "future risk" assessment, and the unique possibility to detect the "accelerated decline" (>30 ml/yr) phenotype, or the "fixed obstruction" phenotype, and their response to inhaled corticosteroids [14,15].

OPEN ACCESS

Correspondence:
Dal Negro RW, National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology, Verona, Italy, E-mail: robertodalnegro@gmail.com

Received Date: *03 Dec 2019*
Accepted Date: *02 Jan 2020*
Published Date: *08 Jan 2020*

Citation:
Milanese M, Viegi G, Sposato B, Dal Negro RW. Respiratory Function Testing in the Era of Precision Medicine. Clin Respirat Med. 2020; 2(1): 1009.

Table 1: Characteristic of pulmonary diseases for which Respiratory Function Testing is mandatory for their diagnosis [14,16-17,24-26,57-59].

Disease	Prevalence	Mandatory for diagnosis	Appropriate treatment	Single cost of treatment, €/yr	Estimated global cost of treatment*, Million €/yr
Asthma	8% to 10%	FEV_1/FVC<LLN, FEV_1 Variability, PD_{20}	GINA 3-4 (50% of asthma) at least LABA/ICS	700	28-35
COPD (ERS/ATS 2005)	5% to 10%	FEV_1/VC <LLN	GOLD 2-4 (85% of COPD) at least LABA or LAMA	600	25-51
COPD (GOLD 2016)	10% to 22%	FEV_1/FVC<0.70	GOLD 2-4 (85% of COPD) at least LABA or LAMA	600	35-72**
Respiratory Failure	0.10%	$PaO_2 \leq 55$ mmHg $PaCO_2 \geq 45$ mmHg	LTOT	3000-6000	3-6

Estimated for every million of habitants, based on prevalence

** Estimated by multiplying 25-51 for 1, 41 [25]

Legend: LABA: Long Acting Beta Agonist; ICS: Inhaled Corticosteroids; LAMA: Long Acting Muscarinic Antagonist; LTOT: Long Term O2 Therapy; AHI: Apnea Hypopnea Index

Chronic obstructive pulmonary disease (COPD)

In addition, COPD diagnosis is linked to the detection of chronic airflow limitation (or better, airway obstruction). Performing spirometry is the first step to calculate the FEV_1/FVC (VC) ratio, whatever the threshold selected, either the FEV_1/VC Lower Limit of Normal (LLN) by the ERS/ATS document on spirometry interpretation [16], or the post-bronchodilator FEV_1/FVC <0.7 fixed ratio by the GOLD document [17]. However, in the PM era, it should be pointed out that the FEV_1/FVC fixed ratio leads to underestimate the prevalence of airflow limitation in younger people, and to overestimate it in subjects older than 45 years, yielding a 75% to 80% of false positive rate in 80-year-old healthy subjects [18-21]. Scholes et al. [22] reported a different prevalence of airway obstruction in 40 years to 95 years old in England and Wales by selecting the FEV_1/FVC <0.7 *vs.* LLN criteria (22.2% *vs.* 13.1%). Recently, Miller and Levy [23] demonstrated that up to 13% of people who received a diagnosis of COPD based on FEV_1/FVC fixed ratio have been found to be misdiagnosed. Moreover, Luoto et al. [24] found an incidence of airflow limitation per 1000 person-year of 18.1 using the fixed ratio and 11.7 with the LLN, corresponding to a 1.41-fold higher incidence rate using the first criterion. Nevertheless, COPD is largely under diagnosed [25] and spirometry largely underused [26], particularly among people with early stages of the disease, when preventive strategies are requested.

Once the diagnosis of COPD is established, the FEV_1 represents the first and the most used variable adopted for the mortality risk assessment [27]. When combined with other variable in a multidimensional graded system as the BODE index [28], the survival prediction accuracy improves. And when combined with hospitalizations and exacerbations in the BODECOST Index, an implementation of del BODE Index, it is useful also in predicting the economic impact of COPD [29].

Agusti et al. [30] have recently proposed an intriguing precision medicine strategy for the management of patients with chronic airway obstruction disease based on the identification of "*treatable traits*" in each patient [9].

These traits can be "*treatable*" based on "*phenotypic*" recognition, or on deep understanding of the critical causal pathways (e.g. true "endotypes"). In this approach, respiratory function testing has, again, a central role to define different "traits of treatable diseases": 1) airflow limitation due to smooth muscle contraction; 2) airflow limitation due to emphysema; 3) chronic bronchitis, and 4) chronic respiratory failure. In the first case, the documentation of airway calibre variability, spontaneously o pharmacologically-induced, defines the role of airway smooth muscle. In the second case, measuring lung volumes and CO diffusing capacity is the best cost-effective procedure to detect emphysema [16]. In the third case, measuring lung volumes allows to detect an isolated Residual Volume increase (RV), considered as an early airway impairment, that can be present in chronic bronchitis otherwise not included in the COPD definition [17,31]. An increased RV may be the earliest functional abnormality in heavy smokers with chronic bronchitis [32] without any significant changes in FEV_1 and FEV_1/FVC ratio [33]. In a recent series of 1000 patients with a clinical diagnosis of COPD, almost 14% could not be classified as obstructed based on a FEV_1/FVC ratio within the normal range, despite having a reduced FEV_1 [31]. This pattern may occur in early-stage COPD, due to an isolated increase in RV, and needs to be differentiated from restriction by lung volume measurements [16]. Finally, in the fourth case, it is well-known that chronic respiratory failure is defined only by another respiratory function test, i.e. arterial blood gas analysis. Therefore, respiratory function testing still represents the "core" of the recently proposed PM strategy in patients with chronic airway obstructive disease [30].

An outstanding example of "*phenotypic*" recognition, useful for a PM approach in COPD, was reported by Pellegrino et al. [34]. During the expiratory effort requested for the FVC manoeuvre, part of Thoracic Gas Volume (TGV) is compressed and the amount varies depending on airway resistance and absolute lung volume [35]. In healthy subjects the difference between FEV_1 measured at the mouth ($FEV_{1\text{-mo}}$) and the simultaneous changes in the chest wall volume derived from body plethysmography ($FEV_{1\text{-pleth}}$) is small (4%, the amount of Thoracic Gas Compression Volume: TGCV). But, in obstructive lung disease, such a difference is large, being 100% or more in the case of high airway resistance and/or large total lung capacity, as occurs in emphysema [35]. Pellegrino et al. [34] reported, for a given airway resistance that $FEV_{1\text{-mo}}$ overestimate the magnitude of airflow limitation in subjects with dominant emphysema compared with those with dominant bronchitis: this may confound severity classification and prognosis [35]. Patients with predominant emphysema may be unnecessarily over-treated with inhaled bronchodilators and steroids simply because of the large effect of TGCV on FEV_1. Therefore, body plethysmography represents a useful tool in COPD phenotyping, severity grading, and therapy establishing [36].

Severe asthma

Lung volume measurement is also part of severe asthma

Table 2: Threshold originated by Respiratory Function Testing for approved targeted treatment in Respiratory Medicine [24,37,44-46,57,59-61].

	Cut off value for Targeted Therapy	Targeted treatment	Prevalence	Cost of single intervention, €/yr	Estimated Cost of global intervention*, million €/yr
Uncontrolled Severe Asthma	FEV_1<80%	Omalizumab§	0,05%	7200-57600	3,6-28
COPD	FEV_1<80%	LABA/LAMA combination§	5%**	720	36
Uncontrolled Severe Asthma	ΔFEV$_1$ variability FEV_1>55% to 60%	Bronchial Thermoplasty	NA	21000	NA
Heterogeneous Emphysema	TLC>100%, RV>180% FEV_1<40%	Bronchoscopic Lung Volume Reduction	NA	9500-14000	NA
Moderate-to-severe OSAS	AHI>15	CPAP	1%	300-400	3-4
IPF	FVC ≥ 50%, DLCO 35% to 79%,	Pirfenidone§ Nintedanib§	0,01% to 0.3%	33,000	NA

*Estimated for every million of habitants, based on prevalence; **based on FEV1/VC LLN COPD prevalence; §In Italy prescription is strictly monitored
NA: Not Available

evaluation [37], as the severity of asthma appears to be linked to enhanced air trapping rather than the level of airflow obstruction. The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) study, comparing severe asthma with mild-to-moderate asthma, found that RV increased (parallel to a reduction in FVC) in severe asthmatic patients as compared with mild-to-moderate ones [38]. Again, the Severe Asthma Research Network (SARP) showed that severe asthmatic patients had prominent air trapping (detected as increased RV/TLC) over the entire range of airflow obstruction severity and that non-severe asthmatic patients did not exhibit significant air trapping, even at the more severe stage of airflow obstruction expressed as FEV_1/FVC ratio [39].

PM for advanced therapies and in other respiratory conditions

It is noteworthy that respiratory function testing supports the selection of patients for advanced therapies or approaches with a high social burden (Table 2). It is the case of Omalizumab and Bronchial thermoplasty in severe uncontrolled asthma [40,41], or bronchoscopic lung volume reduction in heterogeneous emphysema with pulmonary hyperinflation [42,43], or Pirfenidone and Nintedanib in Idiopathic Pulmonary Fibrosis (IPF) [44-46], or Continuous Positive Airway Pressure (CPAP) in moderate-to-severe Obstructive Sleep Apnea Syndrome (OSAS) [47,48]. Indices of pulmonary function, such as FVC and CO diffusion capacity, are considered mandatory in IPF for the selection of candidate patients for pirfenidone or nintedanib [44-46], while the ≥ 10% FVC decline is now accepted by regulatory agencies as the standard to evaluate their inefficacies [49-50]. Furthermore, as part of respiratory function testing, overnight polysomnography is mandatory for the diagnosis and severity assessment of OSAS that is a common and under diagnosed health-care consuming and eminently treatable condition [47,48,51].

As part of respiratory function testing, cardiopulmonary exercise testing is a useful tool in order to select advanced therapeutic strategies in severe-to-moderate heart failure and for the pre-operative assessment in thoracic surgery [52,53].

Finally, oscillation mechanics and partitioning of CO diffusion lung components are opening new horizons for clinical applications. In asthma, day-to-day variability of respiratory resistance by Forced Oscillatory Technique proves to be a good predictor of functional deterioration, and DL_{NO}/V_A has demonstrated a higher sensitivity than DL_{CO}/V_A to detect emphysema or pulmonary fibrosis [54-61].

Conclusion

In conclusion, Respiratory Function Testing is mandatory for the diagnosis of a significant group of respiratory diseases (i.e. asthma, COPD, IPF, OSAS) and represents a major contribute to "phenotyping" patients for different targeted treatments and to monitor their effects. Thus, Respiratory Function Testing should be now considered and emphasized a crucial pillar in the use of PM in favor of respiratory patients.

References

1. Jameson JL, Longo DL. Precision medicine - personalized, problematic, and promising. N Engl J Med. 2015;372(23):2229-34.
2. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372(9):793-5.
3. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010;363(4):301-4.
4. Bousquet J, Jorgensen C, Dauzat M, Cesario A, Camuzat T, Bourret R, et al. System medicine approaches for the definition of complex phenotypes in chronic diseases and ageing. From concept to implementation and policies. Cur Pharm Dis. 2014;20(38):5928-44.
5. Agusti A, Anto JM, Auffray C, Barbé F, Barreiro E, Dorca J, et al. Personalized respiratory medicine: exploring the horizon, addressing the issues. Am J Respir Crit Care Med. 2015;191(4):391-401.
6. Agusti A, Sobradillo P, Celli B. Addressing the complexity of chronic obstructive pulmonary disease: from phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. Am J Respir Crit Care Med. 2011;183(9):1129-37.
7. Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56-68.
8. Diez D, Agusti A, Wheelock CE. Network analysis in the investigation of chronic respiratory diseases: from basics to application. Am J Respir Crit Care Med. 2014;190(9):981-8.
9. Agusti A. Phenotypes and disease characterization in chronic obstructive pulmonary disease. Toward the extinction of phenotypes? Ann Am Thorac Soc. 2013;10 Suppl:S125-30.
10. Ritchie MD, de Andrade M, Kuivaniemi H. The foundation of precision medicine: integration of electronic health records with genomics through basic, clinical, and translational research. Front Genet. 2015;6:104.
11. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. N Engl J Med. 2012;366(6):489-91.
12. National Institute for Health and Care Excellence (NICE). Asthma: diagnosis, monitoring and chronic asthma management. 2017.
13. National Institute for Health and Clinical Excellence (NICE) Clinical

Guideline 101. Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010:1-62.

14. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2016.
15. Sposato B. Could FEV1 decline have a role in daily clinical practice for asthma monitoring. Curr Med Res Opin. 2013;29(10):1371-81.
16. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function test. Eur Respir J. 2005;26(5):948-68.
17. Global Initiative for Chronic Obstructive Lung Disease. (GOLD). Global strategy for the diagnosis, management and prevention of COPD. 2016.
18. Brusasco V, Pellegrino R, Miller MR. Arbitrary thresholds of natural variability and severity should not be used to diagnose chronic obstructive pulmonary disease. BMJ. 2016;352:i393.
19. Quanjer PH, Ruppel G, Brusasco V, Pérez-Padilla R, Fragoso CA, Culver BH, et al. COPD (confusion over proper diagnosis) in the zone of maximum uncertainty. Eur Res J. 2015;46(5):1523-4.
20. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95 age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.
21. Hansen JE, Sun X-G, Wasserman K. Spirometric criteria for airway obstruction: Use percentage of FEV1/FVC ratio below the fifth percentile, not <70%. Chest. 2007;131(2):349-55.
22. Scholes S, Moody A, Mindell JS. Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales. BMJ Open. 2104;4(7):e005685.
23. Miller MR, Levy ML. Chronic obstructive pulmonary disease: missed diagnosis versus misdiagnosis. BMJ. 2015;351:h3021.
24. Luoto JA, Elmsthal S, Wollmer P, Pihlsgard M. Incidence of airflow limitation in subjects 65-100 years of age. Eur Respir J. 2016;47(2):461-72.
25. Nacul L, Soliak M, Samarasundera E, Hopkinson NS, Lacerda E, Indulkar T, et al. COPD in England: a comparison of expected, model-based prevalence and observed prevalence from general practice data. J Public Health (Oxf). 2011;33(1):108-16.
26. Guerriero M, Caminati M, Viegi G, Senna G, Cesana G, Pomari C. COPD prevalence in a north-eastern Italian general population. Respir Med. 2015;109(8):1040-7.
27. Traver GA, Cline MG, Burrows P. Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. Am Rev Respir Dis. 1979;119(6):895-902.
28. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005-12.
29. Dal Negro RW, Celli BR. The BODECOST Index (BCI): a composite Index for assessing the impact of COPD in real life. Multidiscip Respir Med. 2016;11:10.
30. Agusti A, Bel E, Thomas M, Thomas M, Vogelmeier C, Brusselle G, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir Dis. 2016;47(2):410-9.
31. Kholer D, Fisher J, Raschke F, Schonhofer B. Usefulness of GOLD classification of COPD severity. Thorax. 2003;58(9):825.
32. Bates DV, Woolf CR, Paul GI. A report on the first two stages of the coordinated study of chronic bronchitis in the Department of Veterans Affairs, Canada. Med Serv J Can. 1962;18:211-303.
33. Corbin RP, Loveland M, Martin RR, Macklem PT. A four-year follow-up study of lung mechanics in smokers. Am Rev Respir Dis. 1979;120(2):239-304.
34. Pellegrino R, Crimi E, Gobbi A, Torchio L, Antonelli A, Gullotta C, et al. Severity grading of chronic obstructive pulmonary disease: the confounding effect of phenotype and thoracic gas compression. J Appl Physiol. 2015;118(7):796-802.
35. Ingram RH, Schilder DP. Effect of thoracic gas compression on the flow-volume curve of the forced vital capacity. Am Rev Respir Dis. 1966;94(1):56-63.
36. Barisione G, Pellegrino R. Body Plethysmography is helpful for COPD diagnosis, determination of severity, phenotyping, and response of therapy. COPD. 2015;12(6):591-4.
37. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.
38. The ENFUMOSA Study Group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. Eur Respir J. 2003;22(3):470-7.
39. Sorness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilatation. J Appl Physiol. 2008;104(2):394-403.
40. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy. 2005;60(3):302-8.
41. Zafari Z, Sadatsafavi M, Marra CA, Chen W, FitzGerald JM. Cost-effectiveness of bronchial termoplasty, omalizumab, and standard therapy for moderate-to-severe allergic asthma. PLoS One. 2016;11(1):e0146003.
42. Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet. 2015;386(9998):1066-73.
43. Pietzsch JB, Garner A, Herth FJ. Cost-effectiveness of endobronchial valve therapy for severe emphysema: a model-based projection based on the VENT study. Respiration. 2014;88(5):389-98.
44. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016;14:18.
45. Rangarajan S, Locy ML, Luckhardt TR, Thannickal VJ. Targeted therapy for idiopathic pulmonary fibrosis: where to now? Drugs. 2016;76(3):291-300.
46. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2017-82.
47. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnea. Cochrane Database Syst Rev. 2006;1(324):CD001106.
48. Mar J, Rueda JR, Duràn-Cantolla J, Schechter C, Chilcott J. The cost-effectiveness of n-CPAP treatment in patients with moderate-to-severe obstructive sleep apnea. Eur Respir J. 2003;21(3):515-22.
49. Collard HR, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168(5):538-42.
50. Karimi-shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis –FDA review of pirfenidone and nintedanib. N Engl J Med. 2015;372(13):1189-91.

51. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597-619.

52. Corrà U, Piepoli MF, Adamopoulos S, Agostoni P, Coats AJ, Conraads V, et al. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the committee on exercise physiology and training of the heart failure association of the ESC. Eur J Heart Fail. 2014;16(9):929-41.

53. Brunelli A, Charloux A, Bollinger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical Guidelines on fitness for radical therapy (surgery and chemo-radiotherapy) in lung cancer surgery. Eur Respir J. 2009;34(1):17-41.

54. Gulotta C, Suki B, Brusasco V, Pellegrino R, Gobbi A, Pedotti A, et al. Monitoring the temporal changes of respiratory resistance: a novel test for the management of asthma. Am J Respir Crit Care Med. 2012;185(12):1330-1.

55. van der Lee I, Gietema HA, Zanen P, van Klaveren RJ, Prokop M, Lammers J-WJ, et al. Nitric oxide diffusing capacity versus spirometry in the early diagnosis of emphysema in smokers. Respir Med. 2009;103(12):1892-7.

56. Barisione G, Brusasco C, Garlaschi A, Baroffio M, Brusasco V. Lung diffusing capacity for nitric oxide as a marker for fibrotic changes in idiopathic interstitial pneumonias. J Appl Physiol (1958). 2016:120(9):1029-38.

57. Dal Negro RW, Bonadinam L, Turco P, Tognella S, Iannazzo S. Cost of illness analysis in Italian patients with chronic obstructive disease (COPD). Clinicoecon Outcomes Res. 2015;7:153-9.

58. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis or emphysema. Lancet. 1981;1(8222):681-6.

59. Foo J, Landis SH, Maskell J, Oh Y-M, van der Molen T, Han MK, et al. Continuing to confront COPD international Survey: Economic Impact of COPD in 12 countries. Plos One. 2016;11(4):e01522618.

60. Fernandez Perez ER, Daniels CE, Schroeder DR, St. Sauver J, Hartman TE, Bartholmaj BE, et al. Incidence, prevalence and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest. 2010;137(1):129-37.

61. Raghu J, Weycker D, Edelsberg J, Brandford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(7):810-6.