Pulmonary function testing, as chest radiography, has become an integral part of the clinical assessment of pulmonary diseases. The application of pulmonary function testing is increasing in many areas of clinical medicine, including diagnosis of airflow obstruction and lung restriction, evaluation of pulmonary impairment, preoperative assessment, assessment of environmental and occupational lung diseases, epidemiological surveys, and public health screening. The progress of pulmonary function tests in 2011 and 2012 were presented as follows:

1. Normal values and predicted equations

In common practice, the results of pulmonary function tests should be interpreted in relation to reference values, and in terms of whether or not they are considered to be within the “normal” range. Unlike the majority of biological indices in medicine, the normal range of pulmonary function varies with age, height, sex as well as ethnicity. Ethnic difference has been consistently shown to be an important determinant of pulmonary function and should be taken into account when interpreting these tests.

Braun L and his colleagues [1] demonstrated that by using the methodology of the systematic review. They searched PubMed in July 2008 and screened 10,471 titles and abstracts to identify potentially eligible articles that compared “whites” to “other racial and ethnic
groups.” Of the 226 eligible articles published between 1922 and 2008, race and/or ethnicity was defined in 17.3%, with the proportion increasing to 70% in the 2000s for those using parallel controls, indicating the increasing realization of the importance of ethnic difference in pulmonary function. In this report, most articles (83.6%) reported that “other racial and ethnic groups” have a lower lung capacity compared to “whites”. In the 189 studies that reported lower lung function in “other racial and ethnic groups”, 21.8% and 29.4% of explanations cited inherent factors and anthropometric differences, respectively, whereas 23.1% of explanations cited environmental and social factors.

Lung volumes variation in different ethnic populations has been further confirmed in a global analysis. After collecting more than 65 thousands data sets from healthy individuals aged between 3 and 95 years for Caucasians (N=57,395), African Americans (N=3,545), and North (N=4,992) and South East Asians (N=8,255), Quanjer PH et al. [2] showed that spirometry indexes such as forced expiratory volume in one second (FEV1) in Caucasians were the highest, followed by north Asians and south Asians. Among all population, FEV1 in African seems the lowest. Reference equations for these populations were derived.

Regarding to the impact of age on lung function change, it is more complex than height or sex. As a function of age, lung function increases before the adolescent period but declines after the adolescent period. Therefore, use of a unique linear equation for all ages seems impossible. To overcome this problem, a new mathematical model for establishing lung function prediction equations for all ages was reported. By using the LMS (λ, μ, σ) method, which allows simultaneous modelling of the mean (mu), the coefficient of variation (sigma) and skewness (lambda) of a distribution family, this model is able to develop equations for the age from 3 to 95 with appropriate age-dependent lower limits of normal (LLN) [2]. These equations were adopted and recommended to be used in accordance with appropriate ethnic populations by the Global Lung Initiative (GLI). The equation for Caucasian have been supported in contemporary Caucasian Australasian subjects [3].

2. Cut-off values of FEV1/FVC for determination of airflow obstruction

It is widely accepted that the presence of airflow obstruction, characterized by reduction of FEV1/forced vital capacity (FVC) ratio, is key in diagnosing COPD. Nevertheless, there is still a controversy regarding the appropriate cut-off values for FEV1/FVC. It has been argued that a fixed ratio and fixed percentage criterion result in misclassification.

A fixed FEV1/FVC <0.70 value was recommended by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee since the first consensus statement, and remained in the 2011 update version [4]. One of the objectives in introducing fixed values was to
standardize and increase the awareness of diagnosing COPD, i.e. to simplify the diagnosis. In the mean time, the GOLD committee had recognized that using a fixed value of <0.70 may lead to potential overdiagnosis in the elderly and underdiagnosis in the younger subjects.

By reviewing the currently available literature by searching MEDLINE, EMBASE and Cochrane databases and comparing the FEV1/FVC <LLN with a fixed value of FEV1/FVC <0.70, Firdaus AA et al. [5] demonstrated that the prevalence rates of airflow obstruction in subjects aged >40 years were greater when using the fixed value of FEV1/FVC than using the LLN. But based on one longitudinal study the in-between group, it appeared to have a higher risk of hospitalization (HR 2.6) and mortality (HR 1.3). The author argued that that using the LLN of FEV1/FVC might underestimates COPD. It will be necessary to determine which criterion is better and more clinically relevant by COPD longitudinal study.

Another issue for debating airflow obstruction is the reference equations used as a criterion for normality. Marks GB [6] argued that critique of FEV1/FVC <0.7 was based on a false presumption about the validity of reference equations. The flaw lied in the methods used to derive reference equations, which involved arbitrary and circular criteria for exclusion of some members of the population, used potentially non-representative reference populations and included predictive variables that were really risk factors for disease or for adverse outcomes of disease. The author argued for a new interpretative approach for the use of lung function data in clinical practice based on prognostic equations analogous to the Framingham cardiovascular risk factor equations. These interpretative equations should be based on data from cohort studies and randomised controlled trials, rather than cross-sectional studies, and if properly formulated, will prove to be valuable aids to clinical decision making.

3. FEV1/FEV6 for the diagnosis of airflow limitation

The ratio of FEV1 and forced expiratory volume in 6 s (FEV1/FEV6) has been proposed as an alternative for FEV1/FVC to diagnose obstructive diseases with less effort during spirometry; however, the significance of isolated reductions in either the FEV1/FEV6 or FEV1/FVC, as well as the prognostic value of FEV1/FEV6 are unknown. Morris ZQ and his colleagues [7] investigated the first-time adult spiromograms (n = 22,837), with concomitant lung volumes (n = 12,040), diffusion (n = 14,154), and inspiratory capacity (n = 12,480), and found that in patients with obstructed spirometry (either a reduced FEV1/FVC and/or FEV1/FEV6), 3.8% only had a reduced FEV1/FEV6, while 14.4% only had a reduced FEV1/FVC. The mean FEV1 was lower when both ratios were reduced. The group with only a reduced FEV1/FEV6, compared to only the FEV1/FVC reduced, had a lower FEV1, FVC, BMI, Expiratory Time, and IC (p values < 0.0001).
DLCO was also lower (p = 0.005), and the FEV1/FVC and RV/TLC were higher (p values < 0.0001). When the patients with only a reduced FEV1/FEV6 had a subsequent spirogram, 60% had a reduced FEV1/FVC when their mean expiratory times were 3.5 seconds longer. Ninety percent of this group had strong clinical evidence of airways obstruction. They concluded that the FEV1/FEV6 is not as sensitive as the FEV1/FVC for diagnosing airways obstruction, but in the presence of a normal FEV1/FVC, subjects have greater physiologic abnormalities than when only the FEV1/FVC is reduced. The FEV1/FEV6 ratio should not replace the FEV1/FVC as the standard for airways obstruction, but there is benefit in including this measurement to identify individuals with greater air trapping and diffusion abnormalities.

Sorino C et al. [8] evaluated whether FEV1/FEV6 could be used as a significant predictor of mortality in elderly subjects and compared its prognostic value with that of FEV1/FVC and FEV1 alone. 1971 subjects aged > 65 years were enrolled and followed up to 6 years. Results revealed that among subjects with both survival data and acceptable spirometry, including FEV6, all-cause unadjusted mortality ratio was 2.84 (95%CI: 2.12–3.84) for subjects with FEV1/FEV6 < LLN by comparison with > or = LLN. After adjustment for age, gender, FVC, smoke exposure and main comorbidities, the risk of all-cause mortality remained significantly increased in subjects with FEV1/FEV6 < LLN [hazard ratio (HR): 1.87, 95%CI: 1.35–2.58] as well as in subjects with FEV1/FVC < LLN (HR: 2.01, 95%CI: 1.51–2.90) and FEV1 < LLN (HR: 2.17, 95% CI: 1.32–3.57). Similar results were found for Cardio-Pulmonary (CP) mortality, but not for non-CP mortality. Therefore, it was concluded that a low FEV1/FEV6 is a significant predictor of mortality in older patients.

4. FEV1 decline rate in COPD.

Another important sign of COPD is an accelerated rate of decline in FEV1 which is consequently used as a measure of the severity of airflow obstruction and the progressive deterioration. But data on the variability and determinants of this change in patients who have established disease are scarce. In ECLIPSE study, Vestbo J et al. [9] observed the changes in FEV1 after administration of a bronchodilator over a 3-year period in 2163 patients by applying a random-coefficient model and evaluating possible predictors. The mean (±SE) rate of change in FEV1 was a decline of 33±2 ml /yr, with significant variation among the patients studied. The between-patient standard deviation for the rate of decline was 59 ml /yr. Over the 3-year study period, 38% of patients had an estimated decline in FEV1 of more than 40 ml /yr, 31% had a decline of 21 to 40 ml /yr, 23% had a change in FEV1 that ranged from a decrease of 20 ml /yr to an increase of 20 ml /yr, and 8% had an increase of more than 20 ml /yr. The mean rate of decline in FEV1 was 21±4 ml /yr greater in current smokers than in current non-smokers, 13±4 ml /yr greater in patients with emphysema than in those without emphysema, and 17±4 ml /yr
greater in patients with bronchodilator reversibility than in those without reversibility. They concluded that the rate of change in FEV1 among patients with COPD is highly variable, with increased rates of decline among current smokers, patients with bronchodilator reversibility, and patients with emphysema.

### 5. Bronchial provocation tests

Methacholine bronchial provocation test has been used for decades to detect the airway hyperresponsiveness, which is a key characteristic for asthma. However, in clinical practice, not all patients with asthma demonstrate the positive response, and vice versa. To determine the frequency of negative methacholine bronchoprovocation tests in adults who report physician-diagnosed asthma and to explore the clinical characteristics of subjects with negative tests, 304 adults who reported physician-diagnosed asthma were studied with methacholine challenge, spirometry, and physician assessment by McGrath et al. [10]. The clinical characteristics of methacholine-positive and -negative subjects were compared and a predictive model was tested to identify those characteristics associated with a negative test. Results showed that 27% (83/304) of subjects had a negative methacholine test, which was positively associated with an adult-onset of symptoms (P<0.001), normal FEV1 (P<0.001), and having no history of exacerbation requiring oral steroids (P = 0.03). Over half (60%) of those with a negative test reported weekly asthma-like symptoms (cough, dyspnea, chest tightness, or wheeze), while 39% reported emergency department visits for asthma-like symptoms. These subjects were characterized by diagnosis of asthma as an adult and by normal or near normal spirometry. Therefore, caution should be exercised in the assessment and diagnosis of adults presenting with asthma-like symptoms, because they may not have asthma. Further diagnostic studies including other bronchoprovocation testing and/or variation of peak flow are warranted in this patient group.

When conventional spirometry are used to measure the airway function, reproducible maneuvers throughout all stages of bronchial challenge are required, but sometimes it is difficult to be achieved, especially in some population, such as young children. The forced oscillation technique (FOT) that does not require forced or maximal maneuvers and is less cooperation-dependent than spirometry might be warranted. Spirometric and FOT indices in bronchial provocation test were compared by Schulze, J using methacholine as provocation agent [11], and by McClean MA [12] using mannitol as provocation agent. They all concluded that FOT provided a sensitive, repeatable detection of airway function for bronchoprovocation tests.
6. Vibration response imaging technology

Vibration response imaging (VRI) is the emerging technique that measures vibration energy of respiratory sounds. The turbulent air and vibration generated within the airways were captured via VRI sensors. VRI is characterized as non-invasive, safe, radiation-free and convenient approach, and has been applied for the diagnosis of respiratory diseases. Importantly, VRI has also been employed for prediction of pulmonary function after pulmonary resection. Kim HK and his colleagues [13] measured the predicted postoperative pulmonary function as determined by a perfusion lung scan and the VRI in patients who were candidates for major pulmonary resection. There were no significant differences for predicted postoperative FEV1 (ppoFEV1) and predicted postoperative diffusion capacity of the lung for carbon monoxide (ppoDLCO) between scan and VRI. Both ppoFEV1 and ppoDLCO using a scan and VRI predicted the postoperative results well, respectively. They concluded that VRI was highly predictive of postoperative FEV1 and DLCO for lung resection.

References:

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