The Use of Computed Tomography Densitometry for the Assessment of Emphysema in Clinical Trials

A Position Paper from the Fleischner Society

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Abstract

Emphysema's significant morbidity and mortality underscore the need for reliable outcome metrics in clinical trials. However, commonly accepted chronic obstructive pulmonary disease outcome measures do not adequately capture emphysema severity or progression. Computed tomography (CT) metrics have been validated as accurate indicators of pathological emphysema and predictors of chronic obstructive pulmonary disease progression, exacerbations, and mortality. This position paper reviews the evidence supporting CT densitometry as a biomarker for emphysema, establishes implementation standards, and highlights areas for future research. A systematic literature review addressed three key questions: whether CT densitometry can be used as a diagnostic biomarker of emphysema, whether CT densitometry can be used as a prognostic biomarker, and whether longitudinal change in densitometry can be used as a disease progression monitoring biomarker. Emphysema metrics, such as the percentage of low attenuation areas below −950 Hounsfield units, are validated, highly reproducible diagnostic and prognostic biomarkers. Volume-adjusted lung density is recommended for disease monitoring. Both metrics demonstrate a scan–rescan intraclass correlation coefficient of 0.99 with proper technique. The paper also discusses relevant CT physics, techniques, and sources of variation, including technical factors, physiological changes, and software analysis. Key recommendations for clinical trials include using standardized CT techniques, proper subject selection, and longitudinal evaluation with volume-adjusted lung density.

Keywords: computed tomography; emphysema; lung densitometry; clinical trials

Chronic obstructive pulmonary disease (COPD) encompasses a range of conditions characterized by airflow limitation and is influenced by multiple functional trajectories. Emphysema, a critical pathological component of COPD, involves abnormal permanent enlargement of airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis and contributes significantly to the disease's progression. The etiology of emphysema is diverse, influenced by factors such as susceptibility to cigarette smoke exposure, alpha-1 antitrypsin deficiency (AATD), and a combination of environmental and genetic contributors. Despite this, its pathobiology remains only partially understood (1). Although emphysema is commonly associated with airflow obstruction, this relationship is variable; in one cohort of 3,171 individuals who had smoked, emphysema was visible in about 43% of individuals who did not have airflow obstruction (2). Emphysema can manifest early in an emphysema-predominant pathway or later in an airway-predominant pathway of COPD (3).

Over the past 40 years, numerous studies have demonstrated that emphysema can be measured quantitatively using

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A data supplement for this article is available via the Supplements tab at the top of the online article.

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Contents

computed tomography (CT) imaging of the chest and that these measurements are associated with clinical outcomes in COPD (4–6) and in the general population without COPD (7–9). CT densitometric measures are consistently associated with clinically significant outcomes such as perioperative morbidity and mortality, lung function decline, incident airflow limitation, hospitalizations, and death (10–13). However, they are not currently used in clinical settings despite increasing CT use for lung cancer screening or other indications (14). The lack of uptake of densitometry hinders its use in identifying therapies and other interventions that directly modify emphysema progression. Currently, the only generally accepted measure of COPD progression is FEV_1, but this is not a direct measure of emphysema itself. Additionally, because the correlation between FEV_1 and emphysema severity is relatively weak (15, 16), a direct measure of emphysema progression would be important in determining the therapeutic effect of specific treatments for emphysema. Other patient-important endpoints such as exercise capacity, respiratory exacerbations, and mortality are confounded by comorbid diseases such as cardiovascular disease, osteoporosis, and diabetes, which are common in patients with emphysema and can limit the understanding of the ability of a treatment to modify the disease (17, 18).

The purpose of this paper is to summarize the evidence base for the validity of CT densitometry in observational studies and clinical trials of emphysema, define standards for its implementation, and identify areas for future development.

Methods

We followed a prospective protocol in performing this systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (or, PRISMA) 2020 statement (19). The systematic search was conducted by a specialized medical librarian (L.K.) across

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from their inception until December 2022, with an update in January 2024 utilizing the same databases and search strategies. The search incorporated both controlled vocabulary terms and keywords that were relevant to pulmonary emphysema and CT densitometry. (For the complete search strategy and terms for MEDLINE, *see* Section E1 in the online supplement).

After the search, all identified citations were imported into EndNote 20 for deduplication. Screening and full-text review processes were facilitated using Covidence systematic review software. Two reviewers (D.A.L. and R.S.J.E.) independently screened the titles and abstracts. Subsequently, the full texts of potentially relevant studies were thoroughly reviewed by our review team. Inclusion criteria specified publications in English, studies with a sample size exceeding 50 participants, and the utilization of CT scanners with more than 16 detector rows, without imposing restrictions on the publication period.

The search strategy resulted in 2,350 unique citations after the removal of duplicates, supplemented by an additional 45 citations identified through manual search efforts. Upon screening, 294 articles were deemed suitable for full-text review, with 199 publications ultimately meeting our inclusion criteria (Figure 1; for included articles sorted by publication date, *see* Section E2). A *post hoc* topic analysis of the selected publications was conducted using natural-language processing (for details, *see* Section E3). Publications were assigned to key questions based on their cosine similarity to the questions (*see* Table E1), and relationships between references across key question groups were visualized (*see* Figure E1). Additionally, unsupervised topic modeling of the titles and abstracts identified five distinct topics (*see* Figure E2 and Table E2).

Background

Physics of CT Densitometry

CT measures the X-ray attenuation that results from interactions between photons and tissue as the beam passes from X-ray source to detector. The interactions of photons with lung tissue depend on tissue characteristics (including average atomic number and density of constituent materials) and photon energy. In the simple case of a monoenergetic X-ray beam passing through a homogenous tissue of thickness x, the number of monoenergetic photons detected,

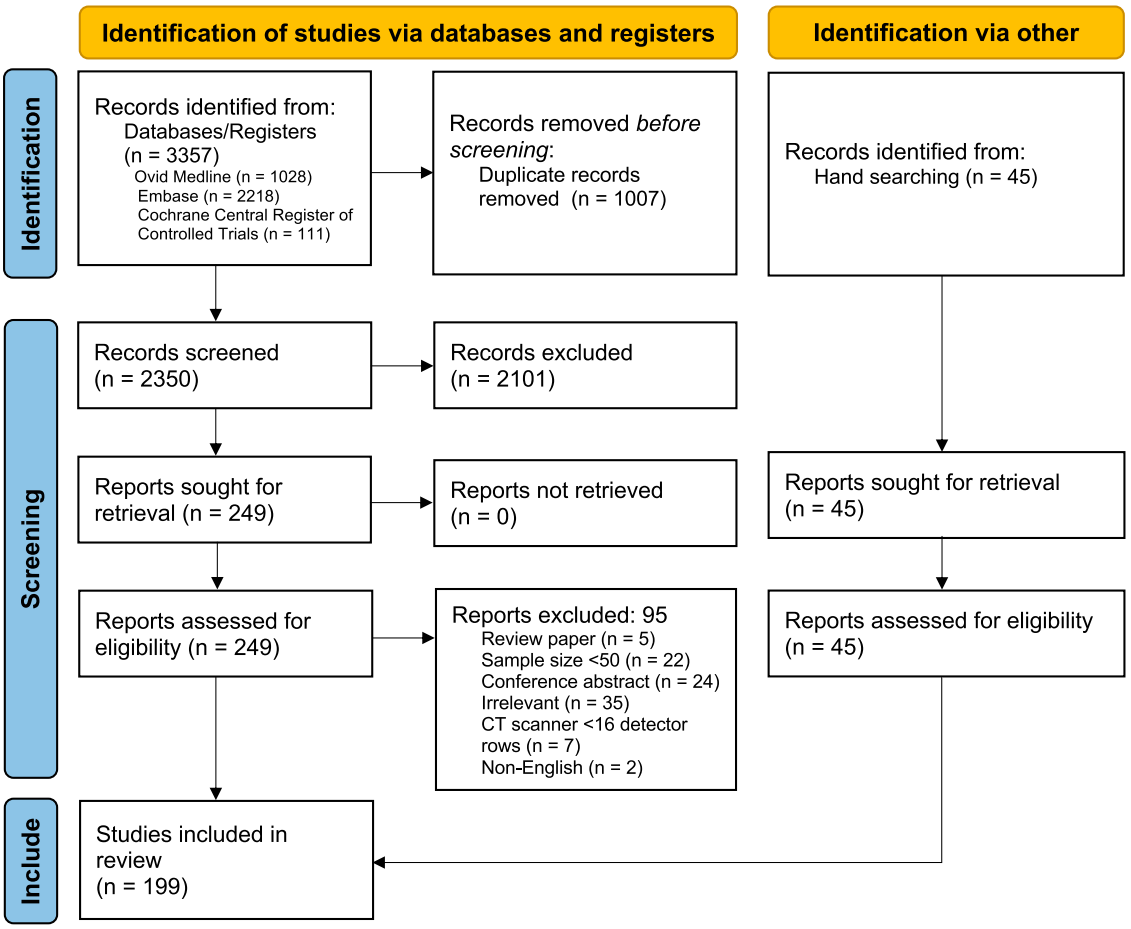

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (or, PRISMA) flow diagram depicting the systematic literature search process for lung densitometry studies. A total of 3,357 records were identified through database searches, and an additional 45 records were identified by hand searching. After the removal of 1,007 duplicate records, 2,350 records were screened. The diagram further details the assessment of 249 reports for eligibility, which resulted in 201 studies being included in the review. CT = computed tomography.

N, follows an exponential decay formula: $N = N_0 e^{-\mu x}$, where x is the thickness of the tissue, μ is the linear X-ray attenuation coefficient for the tissue for a given photon energy, and N_0 is the initial quantity of photons (20). The linear attenuation coefficient μ quantifies a material's ability to attenuate the intensity of the X-rays by absorption and scattering processes. μ is a constant for a given material and photon energy and depends on the properties and density of atoms in the material. Because X-ray beams consist of a spectrum of photon energies that vary with equipment and change as the beam passes through a material, effective linear attenuation is, in practice, a composite of interactions between tissue and photons of different energies. This is an important source of variation discussed later in the paper.

The voxels of a CT image are based on estimates of local linear attenuation coefficients in each voxel, expressed on the Hounsfield unit (HU) scale. The HU value of a particular tissue type in a CT image is derived from its linear attenuation coefficient (μ_x) relative to water (μ_{water}), using the formula:

$$CT\ number\ [HU] = \frac{\mu_x - \mu_{water}}{\mu_{water}} \times 1,000.$$

By convention, the nominal CT number of air lies near −1,000 HU, and water is calibrated to be 0 HU. The CT number of normal lungs is approximately −850 HU (21). Focal within-subject decrease in CT attenuation in the lung under idealized conditions usually reflects reduced tissue density due to emphysematous tissue loss, increased air content and lung hyperexpansion, and decreased perfusion, or some combination of all three.

CT Density Metrics

Emphysema, characterized by the destruction of lung tissue and enlargement of air spaces, results in a decrease in tissue density that explicitly affects the lower tail of the histogram of CT attenuation histogram values within the lungs (Figure 2). A summary of commonly used densitometry metrics for emphysema is provided in Table 1. Among these metrics, the percentage of emphysema-like lung, defined by low attenuation areas (LAAs), quantifies the percentage of lung voxels with CT attenuations below a given threshold (4). Of various thresholds proposed, typically ranging from −900 to −970 HU, the percentage of low attenuation areas below −950 HU (LAA_{-950}) remains the most widely used current metric: It correlates with microscopic emphysema severity (22) and has empirically served as a reliable metric for quantifying disease extent in contemporary high-resolution inspiratory CT scans, validated through correlation with human lung tissue (15, 23–26). LAA_{-910} and LAA_{-970} (the percentages of lung voxels below −910 HU

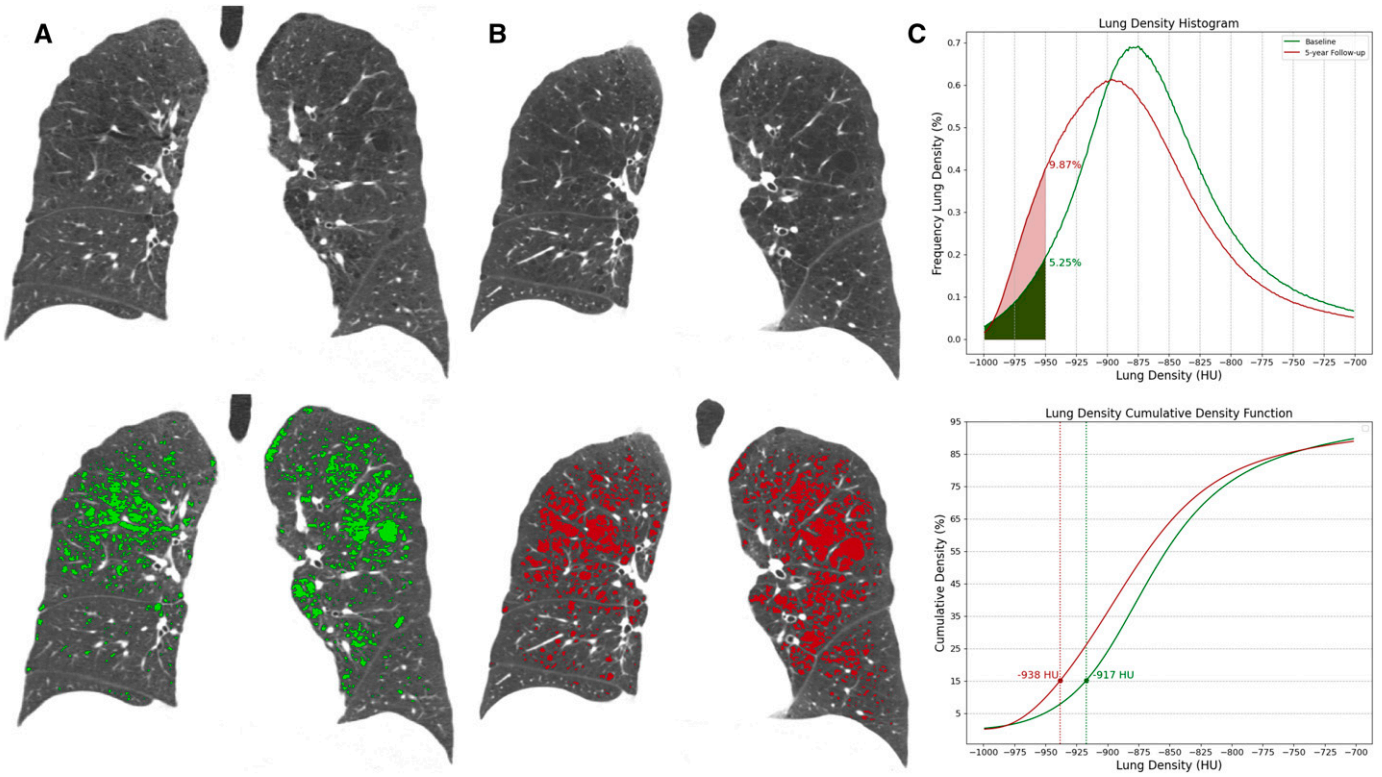

Figure 2. Baseline and follow-up images of a COPDGene participant showing emphysema progression. (*A*) Coronal view of the baseline inspiratory computed tomography (CT) scan with the emphysema region highlighted in green for voxels below −950 Hounsfield units (HU). (*B*) Coronal view of the 5-year follow-up inspiratory CT scan, with emphysema progression similarly highlighted in red for voxels below −950 HU. (*C*) Derivation of lung densitometry metrics for emphysema, depicted through lung CT attenuation histogram (top) and cumulative distribution (bottom) for both baseline and follow-up scans. The distribution of lung densities undergoes a change in the low-attenuation region that is due to the progression of emphysema. The emphysema index, defined as the percentage of low-attenuation area below −950 HU (shaded region in the lung CT attenuation histogram), increased from 5.25% to 9.87% over 5 years, indicating emphysema progression. The 15th percentile of lung attenuation shifted from −917 HU to –938 HU, reflecting a decrease in lung density. Additionally, the volume-adjusted Perc15 ($VALD_{PERC15}$) with respect to the baseline lung volume decreased by 21.6 g/L over the interval period of 2,038 days.

Table 1. CT Metrics of Emphysema

Metric	Abbreviation	Definition	Strengths	Weaknesses
Percent emphysema	LAA_{-950}	Lung voxels with CT attenuation ⩽−950 HU as a percentage of total lung voxels	• Well-validated • Intuitively interpretable Widely used in cross-sectional studies • Predictive of events	• Skewed distribution • More complex to evaluate longitudinally • Sensitive to variation in lung volume, CT dose and reconstruction kernel
15th Percentile lung attenuation	Perc15 (also denoted as PD15)	CT attenuation at the 15th percentile point of the cumulative CT histogram	• In an idealized setting, it can provide a measure of physical lung density • Can be adjusted for inspired lung volume • More normal distribution and, therefore, potentially more robust for longitudinal analysis	• Less well evaluated in cross-sectional studies • Sensitive to variation in lung volume, CT dose and reconstruction kernel
Volume-adjusted lung density	$VALD_{PERC15}$ (also denoted as volume-adjusted Perc15 in lung density units)	Perc15 lung attenuation, converted to lung density, and adjusted for inspired lung volume based on predicted or observed lung volume	• Has been used for longitudinal analysis in several large studies, including as endpoint in clinical trials of AAT	• Increased lung volume due to airflow obstruction and/or emphysema may reduce $VALD_{PERC15}$

Definition of abbreviations: AAT = alpha-1 antitrypsin; CT = computed tomography; HU = Hounsfield units; LAA_{-950} = percentage of low-attenuation area below −950 HU; VALD = volume-adjusted lung density.

and −970 HU) also correlate well with emphysema on pathology (22, 27).

The lowest percentiles of the cumulative HU value-frequency distribution have also been used to capture the degree of emphysema on CT (Figure 2C). Ranges from the fifth to the 15th percentile point of the lung attenuation distribution (Perc5–Perc15) are commonly used to reflect the attenuation of lung tissue, where 5–15% of lung voxels have lower attenuation (22, 28). Of these, Perc15 is the widely used (29). Like LAA, this metric holds physical meaning, as tissue loss results in a decrement of lung attenuation corresponding to the lowest percentiles, and it has been shown to correlate with quantitative pathological scores of emphysema detected on single-slice (30) and contemporary multislice CT scanners (27).

Emphysema quantification should be performed using coached full inspiratory CT scans and presupposes a nominal airspace size that may vary with height, weight, sex, smoking status, and lung inflation degree, potentially leading to variability in lung density metrics (31). Normative equations for LAA and total lung volume (TLV) distributions in healthy individuals, including by sex, race, age, body mass index (BMI), and current smoking have been developed (32), although the value of this approach to define normality is controversial, the equations do not provide a metric of a full inspiration for quality control (QC) purposes, and adjusting for race may introduce population biases. To account for deviations in lung volume from the target TLV, lung density metrics have been adjusted for inspiratory lung volume using a sponge model based on the ratio of CT-derived lung volume to reference values for physiologically predicted TLV or observed TLV (33, 34). Volume-adjusted lung density of the Perc15 ($VALD_{PERC15}$) is commonly used in emphysema progression studies to compensate for longitudinal changes in inspiratory lung volume between repeated scans (35–38).

Beyond density-based metrics, alternative metrics such as low attenuation cluster size and normalized join counts have been proposed to capture the heterogeneity of airspace sizes and distribution (39–41). However, the value of these metrics remains unclear (42). Advanced image analysis techniques, such as texture analysis and deep learning, have also been used to quantify emphysema. Texture analysis involves the characterization of patterns in CT pixel intensity and spatial distribution to detect and quantify emphysema. Approaches such as the adaptive multiple feature method, the local histogram, hidden Markov measure field modeling, and other machine-learning approaches (43–47) may provide more robust volume percentage metrics and resolve different pathologically defined emphysema patterns. Deep-learning approaches have also been proposed to quantify the qualitative description of emphysema and its progression on the basis of categories using the Fleischner criteria (48–50). In general, these approaches show promise in detecting subtle disease patterns, potentially enhancing diagnostic accuracy and prognostic capabilities with respect to densitometry measurements but require further validation.

Metrology of CT Biomarkers

Understanding the technical performance of imaging biomarkers, including their precision and bias, is vital for their effective clinical application and for designing robust clinical trials (51). Precision denotes the ability of a biomarker to produce consistent measurement values across repeated assessments, quantified by indicators such as the within-subject SD or the within-subject coefficient of variation, which are each expressed as a percentage of the biomarker's overall magnitude. Bias, conversely, assesses the measure's capacity to align, on average, with the true value of what is being measured. It is often assumed that the measured and true values of a biomarker will

exhibit a linear relationship with a slope of 1, implying minimal or consistent bias across the spectrum of disease severity. Any deviations from this model can significantly affect the accuracy of disease progression assessments and the evaluation of treatment efficacy in clinical trials (52).

The distinction between real changes attributable to disease progression and variations due to measurement error is fundamental. Precision enables this differentiation, facilitating accurate diagnosis and disease prognostication and ensuring that clinical studies are sufficiently powered. Moreover, a deep understanding of both precision and bias is indispensable for optimizing clinical trial designs, such as by enriching study populations, calculating the required sample size, and estimating treatment effects (52, 53). Technical performance studies of a biomarker are a fundamental aspect of understanding its performance; for example, meta-analyses of published studies have shown that, in subjects with emphysema, a decrease in $VALD_{PERC15}$ by 11 HU or more, or an increase in LAA_{-950} by 3.7% or more, confidently indicates a progression of emphysema with 95% certainty (54–59). However, interpreting these measurements, especially the reproducibility coefficient derived from test–retest experiments, requires caution. Rather than using it as a sensitivity threshold for change detection, it should be viewed as a demarcation point for its specificity, where changes exceeding this limit are likely due to genuine physiological changes rather than measurement variance.

Sources of Variation

Quantitative lung densitometry is influenced by multiple factors that can introduce variability into measurements, impacting their reliability and interpretability. Understanding these sources of variation is essential for standardizing protocols and ensuring robust results in both clinical and research settings. Table 2 provides a detailed summary of the common sources of variation.

Scanner-related Factors

Variations in HU values between imaging exams due to differences in CT equipment and protocols can present challenges for longitudinal densitometric assessment of emphysema (60–64). Factors affecting HU calibration, image spatial resolution, or noise may alter lung attenuation histograms (38, 65). Lung densitometry is sensitive to local errors in CT numbers, especially factors that increase systematic error and stochastic noise. Balancing the need to appropriately minimize radiation dose while maintaining image quality presents a particular challenge in CT densitometry because of the sensitivity of density measures to structured artifacts and random noise.

CT equipment and protocols impact various scanner-related factors. The X-ray tube and filtration system affect the X-ray energy spectrum, which, in turn, influences scatter and beam hardening. System detector configuration contributes to artifacts from scatter, beam hardening, and electronic noise. These physical properties, together with proprietary correction software, vary significantly between CT manufacturers and models, leading to differences in densitometry metrics (66, 67). Scanner modifications, such as major hardware or software updates, are likely to affect performance and operation for longitudinal studies.

Acquisition parameters, particularly those that are dose related, impact densitometric measures (68). Technologies such as tube current modulation (automatic exposure control) can lower radiation dose while stabilizing CT number variability across the lung field and preserving image quality for visual and quantitative evaluations, but imaging with reduced dose increases noise, which may overestimate emphysema severity (69, 70). Other acquisition parameters—including table speed, rotation time, collimation, and pitch—affect lung coverage, helical artifact, and breath-hold time. Loss of breath-hold is a significant source of variability that can be controlled by careful coaching and a balanced CT protocol that is designed to keep breath-hold to under 10 seconds.

Reconstruction parameters also play a significant role in quantitative CT (71–75). Smaller reconstruction field of view and/or

Table 2. Common Sources of Variation in CT Densitometry

Source of Variation	Approach to Mitigation
Scanner related	
Calibration	Regular calibration Regular phantom measurements to detect scanner deviations from their nominal behavior
Image noise	Standardized, consistent protocol (slice thickness, reconstruction algorithm)
Beam hardening	Avoid substantial metal artifacts (e.g., scoliosis rods)
Patient related	
Inspired lung volume	Technologist is trained to coach the patient in breath holding to maximal inspiration, using standardized breathing instructions. Rehearse breath hold at least once before scan. Consider adjusting lung density measurement for inspired lung volume. Consider excluding scans with >10% change in inspired lung volume
Motion artifact	Emphasize importance of breath holding during scan
Current smoking	Consider exclusion of current smokers or stratify for smoking status. Consider exclusion of those who change smoking status during study. Consider exclusion of individuals who have not smoked <1 yr
COPD exacerbation	Avoid scanning within 4–6 wk of exacerbation
Analysis software	
Segmentation/airway removal	Use consistent analysis software throughout the study

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography.

slice thickness may improve the ability to resolve airway and parenchymal texture structures, but at the expense of increased noise if the dose is not adjusted. Higher spatial frequency reconstruction algorithms can improve visualization of subtle details, but they tend to increase image noise and typically alter the brightness profile at the edge of structures, reducing the quantitative accuracy of lung density (73, 76) and confounding training for texture characterization (77). Iterative reconstruction (IR) algorithms can reduce noise due to CT dose reduction and BMI and improve image quality, reducing emphysema estimates that are typically overestimated because of the impact of noise in the density histogram (78), but the characteristics of IR vary notably between manufacturers' and software versions (69, 79, 80). More recent versions of IR methods are better at preserving structural details, rather than merely smoothing the image, while also incorporating enhanced corrections for beam hardening and other common artifacts such as streaking due metals implants, photon starvation, and scattering (81).

CT technology continues to improve, offering noninvasive assessment of emphysema at decreased radiation dose (82, 83), but the improvement presents challenges in comparing new images with legacy data. For instance, the recent adoption of photon-counting CT enables improved image contrast and reduced electronic noise with a lower radiation dose, promising to improve quantitative CT capabilities substantially. However, the decreased noise may change emphysema measurements when compared with historical scans (84). Work to harmonize quantitative metrics across generations of CT equipment will be increasingly important.

Participant-related Factors: Breath-Holding

Age, sex, BMI, and cigarette smoking affect emphysema metrics in both participants with COPD and those without (32, 78, 85–91). However, in longitudinal studies using the same scanner, the primary sources of variation in quantitative CT (QCT) measures for a given patient are the lung volume at acquisition (91, 92) and smoking status (93–96). These will be addressed separately.

Unlike CT scanning of other body parts, lung imaging is sensitive to the level of inspiration at acquisition of the scan. Lung densitometry is an effort-dependent test and, given its thresholding at the extreme of the attenuation histogram, is particularly sensitive to incomplete inhalation by the participant to total lung capacity. Some studies have used a volume controller to physically determine the lung volume at which the patient is holding their breath (97–99). However, these systems are not widely available, and, in their absence, careful patient coaching to achieve consistency of breath-holding at the desired lung volume before beginning the scan is critical (100).

Coaching of breath-holding is challenging for several reasons, more so in the CT suite than in the pulmonary function testing (PFT) laboratory. Challenges include the use of CT technologists who are not used to pulmonary function testing–style coaching, the distance between the technologist and the participant during test acquisition, the acquisition of a single test, and the inability to repeat the test in general because of radiation safety concerns. Recommended scripts for standardized coaching should be used (101). Ideally, for longitudinal evaluation, a difference in lung inflation smaller than 10% of baseline lung inflation volume should be achieved. As discussed earlier, volume adjustment of percentile-based lung density is recommended for monitoring the progression of emphysema in patients who have smoked and in patients with alpha-1 antitrypsin deficiency (34, 35, 37, 102, 103).

Participant-related Factors: Smoking and Exacerbations

Smoking status is a known confounder of the densitometric assessment of the lung parenchyma. Several studies showed that patients who are currently smoking appear to have significantly less quantitative emphysema on CT than those who quit smoking (94–96, 104–109). CT lung density related to current smoking appears to be associated with cellular concentration on BAL. The inflammatory consequences of particle deposition and subclinical smoking-related interstitial lung disease (110, 111) lead to increased lung density on CT images and may partly mask the presence of emphysema on QCT. In fact, smoking cessation results in a decrease in lung density (95). This decrease, which mimics rapid progression of emphysema, is probably due to reduced inflammation after smoking cessation. This phenomenon was observed in two studies that included individuals with a history of current or former smoking (105, 112). In the first study, the differences in lung density declined during the first and second years after smoking cessation (105). In the second study, the difference in mean lung density and 15th percentile density of the lung density histogram observed at baseline between individuals who were actively smoking and those who had quit was maintained for 1 year in recent quitters and for at least 4 years in long-term quitters (107). Hence, current smoking status and time since cessation or relapse should be considered when assessing emphysema severity.

Exacerbations of COPD have also been shown to alter CT lung density in inconsistent directions. In a *post hoc* analysis of the RAPID study measuring CT density change (113), a larger variance from the slope of decline was found when a scan was performed within 6 weeks after an exacerbation: The effect of an exacerbation was most significant in the first 2 weeks after the exacerbation (114). It is interesting that CT density declined in some participants, which indicated more air trapping, and increased in others, which suggested more lung inflammation during the exacerbation event. The recommendation is to avoid CT acquisition in clinical trials until the patient fully recovers from a pulmonary exacerbation, typically 4–6 weeks.

Analysis Software

Densitometry of emphysema involves measuring the volume fraction of low attenuation areas of the total extracted lung area, resulting in relatively limited variation caused by the analysis software. There are three main sources of variation: extracted whole lung volume, definition of mediastinal borders, and associated central airway and vessel removal. In addition, the threshold for low attenuation areas will clearly affect the quantitation of emphysema. Most software programs segment lung areas with an initial step of selecting voxels with CT numbers below a certain threshold, which varies between −400 HU and −500 HU (115). More advanced methods utilizing deep-learning approaches have evolved to identify lung fissures (116) and to differentiate lung borders against the chest wall in the presence of consolidation and fibrosis (117). In cases where software has an additional function of airway segmentation, airway areas may be removed from the lung area. If airway segmentation is not performed, the airway volume is included in the total lung volume.

Although differences may occur between software approaches when defining the lung borders at the mediastinal borders, a study comparing different software analysis packages suggests that reproducibility was comparable for software tools generated by academic-based groups and commercial vendors, and segmentation variations had negligible impact on measurement variability between software tools (118).

Using analysis software, efforts have been made to minimize measurement variations caused by CT factors. Several correction or calibration methods of CT values of the lung using measured air and water from the same images have been proposed (119, 120). More recently, studies have shown that CT histogram harmonization (121) and CT image conversion using deep learning–based style transfer methods (122, 123) can help reduce measurement variations caused by reconstruction kernel or radiation dose. In general, variations caused by software are relatively small compared with those caused by the CT protocol or patient factors and can be controlled more easily.

Use of CT Densitometry in Interventional (Drug) Clinical Trials

The first use of CT densitometry as a primary outcome in a prospective, randomized, double-blind clinical trial was by Dirksen and colleagues (124), who studied the effectiveness of α-1 augmentation therapy (with α-1 proteinase inhibitor [A1PI]) in 56 individuals with severe AATD due to the ZZ genotype, or PiZZ AATD. Subsequently, many similar trials have been performed in AATD because of the emphysema endotype that characterizes this genetic cause of COPD. Important to this body of work is an underappreciated concept that emphysema progression often does not affect pulmonary airways and, by inference, has a poor correlation with lung function outcomes such as FEV_1 (113, 124). Furthermore, emphysema is slowly progressive, and correlation with other outcomes such as mortality, exercise capacity, or health status requires long study intervals.

The effect of inhaled budesonide compared with placebo was studied in 137 patients with COPD over 4 years, showing a significantly slower decline in emphysema as assessed with LAA_{-910} ($P = 0.02$) (125). However, the study did not meet its primary endpoint of Perc15 percent difference ($P = 0.09$), although trends were directionally consistent. In a pilot study of the impact of all-*trans*-retinoic acid on emphysema progression, no overall difference in the emphysema extent also defined by LAA_{-910} was observed in a comparison before and after all-*trans*-retinoic acid treatment (126).

Success in using CT densitometry for a primary clinical trial outcome relies on several factors. First, the intervention must target molecular pathways associated with the development or progression of emphysema. The most successful clinical trial demonstrating the utility of change in inspiratory CT densitometry assessed the effects of A1PI relative to placebo. The RAPID study enrolled 180 participants with AATD and included five scans performed over 2 years to get accurate slope measurements for the rate of change (113, 127). The absolute mean difference between A1PI and placebo was a slope difference of 0.74 g/L per year, highlighting that the technical aspects of CT density must be robust to detect changes of this magnitude. The change in slope between the placebo and A1PI groups before versus after treatment was further confirmed in the open-label extension to the RAPID study, in which a difference of 1.00 g/L per year was seen (Figure 3) (128).

In cigarette smoking–related COPD, a trial of losartan or placebo did not demonstrate a difference in CT density over 48 weeks, either because losartan did not have an effect on emphysema or because the observational time was too short (129). In a larger 52-week placebo-controlled study of a γ-selective retinoid agonist (130), 262 participants with AATD were randomized, but no statistical difference was observed in the placebo-corrected lung density slope ($P = 0.94$). However, in contrast to studies in AATD, these studies did not enrich for COPD subsets that would demonstrate a risk for accelerated progression of emphysema (131).

Regulatory bodies have responded to these data in different ways. COPD associated with cigarette smoking often presents as mixed airway disease and emphysema. As such, COPD progression is usually assessed using spirometric measures of airflow obstruction that are expected to be colinear with emphysema (132). However, the relationship between emphysema and airflow obstruction is relatively weak, and spirometry has high variability (15). In contrast, CT lung density measures the density of lung tissue present. As lung tissue is lost over time, patients with nonobstructive emphysema may change lung density without having correlative loss of other lung function measures until much later in the disease course. Using the proper test to measure the progression of emphysema in COPD, regardless of its etiology, is important in supporting therapies targeting lung destruction pathways or regenerative medicine.

Key Questions

In At-Risk Individuals, Can CT Densitometry Be Used to Identify Individuals with Emphysema (i.e., Can CT Densitometry Be Used as a Diagnostic Biomarker)?

Pulmonary emphysema is defined anatomically as the chronic, irreversible dilation and destruction of the distal airspaces (133). Emphysema was historically defined at autopsy, and many cross-sectional studies—including one of over 1,800 specimens (134)—described the pathological changes of emphysema.

Investigations in the 1980s demonstrated that densitometrically defined emphysema on CT scan reflected histopathologic remodeling of the lung parenchyma on excised tissue (4, 135). Several subsequent reports demonstrated that various contemporary definitions of emphysema on CT scan, including LAA_{-950}, LAA_{-910}, and histogram percentile of lung attenuation, are correlated with emphysema as defined on pathology (27, 136–140). Hence, alterations in CT densitometry accurately reflect the underlying pathological tissue destruction of emphysema (141). Additionally, CT densitometry correlates with symptoms of dyspnea (142), spirometric airflow obstruction (15, 143–147), lung diffusing capacity (148–150), reduced oxygen saturation (151), and with exercise capacity (152). However, the relationship between CT densitometry and physiology in COPD is nonlinear because of the heterogeneity of the disease (153) and the indirectness of spirometry as an index of morphologic emphysema.

CT densitometry, therefore, has the potential to provide a noninvasive and

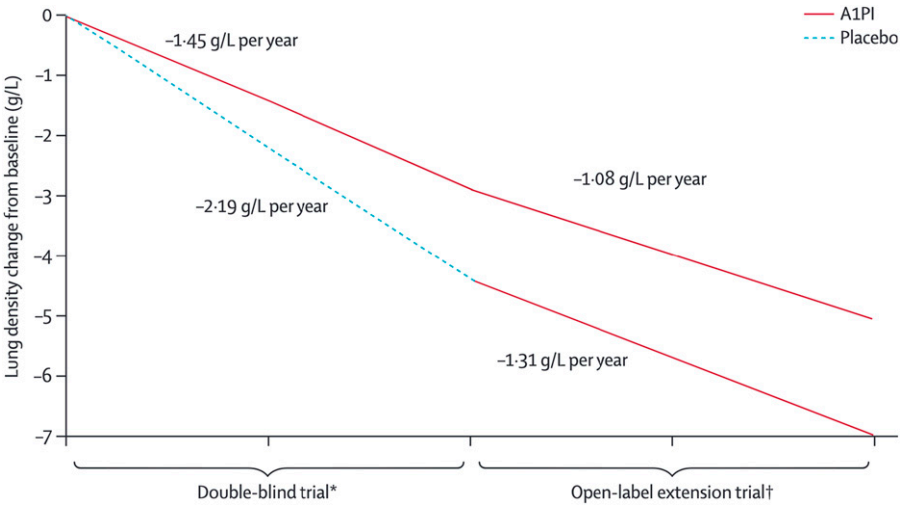

Figure 3. Data from the RAPID double-blind clinical trial of α1 proteinase inhibitor in subjects with α1 antitrypsin deficiency and airflow obstruction. The graph shows that the rate of lung density decline in the treated group (pink solid line) was significantly slower than in the placebo group (dotted blue line). During an open-label extension where the placebo group was treated with α1 proteinase inhibitor, the rate of decline of lung density decreased in this group. Markings along the *x*-axis correspond to years. Reproduced by permission from Reference 113. *A1PI $n = 92$; placebo $n = 85$. †A1PI $n = 50$; placebo $n = 47$.

efficient method to diagnose pulmonary emphysema. CT densitometry measures are also precise, being highly repeatable and reliable in controlled research settings with standardized protocols and centralized QC by a CT reading center. Recent results from the SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS) demonstrate excellent short-term (2–6 wk) scan–rescan precision of several measures, including an intraclass correlation coefficient of 0.99 for LAA_{-950} and $VALD_{PERC15}$ before QC and an intraclass correlation coefficient of 0.99 for most densitometry measures after QC (Figure 4) (154), which is superior to that of spirometry (155). These results build on and are superior to earlier efforts (54, 55, 59, 156–160). Furthermore, even in the general population at lower risk, the longitudinal trajectory of CT densitometry measures is consistent in individuals over intervals of up to 16 years (161). Hence, densitometry has the potential to establish an accurate and precise diagnosis of emphysema on standardized research CT scans. However, current variability in scan protocols in clinical settings means that densitometry-based diagnosis in the research setting is not yet fully translatable to clinical settings.

An additional caveat to the use of CT densitometry as a diagnostic biomarker might be continued uncertainty about the correct threshold for diagnosis (75) (similar to thresholds for spirometry, which have been long debated and the calculation for one of which was just changed) (162). Hoffman and colleagues provided a threshold definition that was based on the upper limit of normal, derived among healthy, nonsmoking participants (32). In a study of incident events in two disease-based prospective studies, a threshold LAA_{-950} of more than 5% appeared to be associated with an increased incidence of exacerbations and

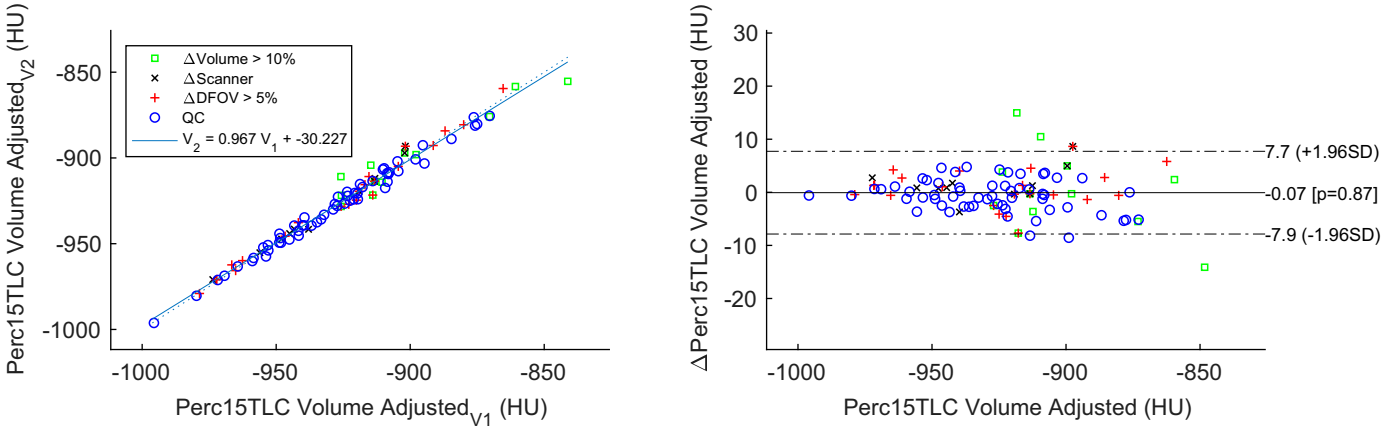

Figure 4. Analysis of repeatability for volume-adjusted Perc15 ($VALD_{PERC15}$) in the SPIROMICS substudy over a 6-week follow-up (154). Left: The relationship between first- and second-visit (V1 and V2, respectively) volume-adjusted lung density measurements, indicating a strong linear correlation. Right: A Bland–Altman plot to assess agreement between measurements across visits. The plot indicates a minimal bias (−0.07 HU) and a repeatability coefficient of 7.01, demonstrating consistent measurement precision over time. HU = Hounsfield units.

increased mortality (6). However, participants with mild emphysema on visual evaluation may have LAA_{-950} values less than 5% (163, 164), and the best threshold for dichotomizing quantitative lung density remains unclear. Visual CT assessment of emphysema can be a useful complement or substitute for densitometry in determining entry into clinical trials for emphysema treatment, as supported by the association of visible emphysema with mortality, progressive emphysema, and progressive airflow obstruction (2, 165, 166).

Can CT Densitometry Be Used to Predict Emphysema-related Clinical Outcomes in At-Risk Individuals (i.e., Can CT Densitometry Be Used as a Prognostic Biomarker)?

Lung densitometry has been incorporated into numerous observational studies and clinical cohorts from which investigators have been examining the prognostic value of low attenuating tissue. Common clinical outcomes used for these prognostic studies include rate of decline in lung function, acute respiratory exacerbations, and mortality.

Multiple studies have demonstrated that densitometrically detected emphysema on CT scans is associated with subsequent decline in spirometric measures of lung function and development of incident expiratory airflow obstruction. This has been reported in observational studies, in cohorts of people undergoing CT screening for lung cancer, and in population-based investigations ranging in size from hundreds to thousands of individuals (8, 165, 167–171). Additional work has demonstrated that lung densitometry remains a statistically significant predictor of accelerated loss of lung function (165). Individuals with upper-lobe predominant emphysema have a higher rate of progression of emphysema, gas trapping, and dyspnea (172).

Densitometrically detected emphysema also predicted acute respiratory events or exacerbations. In a cohort of 380 patients with COPD undergoing clinical care at one of sixteen hospitals in Korea, Oh and colleagues found that the subset of frequent exacerbators ($\geq$2 per year; $n = 77$) had greater emphysema on CT scans than the subgroups of infrequent ($n = 54$) and nonexacerbators ($n = 171$) (173). A subsequent smaller study ($n = 65$) reported that lower lobe-specific measures of emphysema were prognostic for respiratory events (174). Among 521 older participants eligible for lung cancer screening, densitometry independently predicted acute episodes of care (13).

These same CT metrics are associated with an increased risk of death, even after multivariable adjustment. In an early study of AATD, densitometric measures were shown to be the strongest independent predictors of mortality (175). Several disease-based studies, including ECLIPSE, the Hokkaido COPD cohort, and the Norwegian GenKOLS reported that densitometrically detected emphysema was associated with an increased risk of death during longitudinal follow-up (24, 176, 177). In their principal-component analysis of COPDGene study data, Yuan and colleagues found that CT-derived features, including lung densitometry, were the strongest predictor of loss of lung function, respiratory exacerbations, and mortality during longitudinal follow-up (178). A *post hoc* analysis of the COPDGene and SPIROMICS studies also replicated the association of LAA_{-950} with mortality and exacerbations (6). These findings extend to the general population; Oelsner and colleagues demonstrated that lung densitometry independently predicted respiratory and all-cause mortality in the population-based Multi-Ethnic Study of Atherosclerosis (or, MESA) Lung Study (7, 179). In two lung cancer screening cohorts, densitometry was an independent predictor of overall mortality and cardiovascular mortality (9, 180). Additionally, a meta-analysis showed that densitometry on thin-section CT was associated with lung cancer risk (181).

In At-Risk Individuals, Does a Decrease in Lung Attenuation over Time Indicate Clinically Significant Emphysema Progression (i.e., Can CT Densitometry Be Used as a Monitoring Biomarker)?

While initial investigations of emphysema have focused on the histopathologic and clinical correlates of low attenuating lung parenchyma on CT scans, efforts have grown to include an examination of longitudinal progression. Such data have been put forth as a stand-alone metric of disease progression and, increasingly, as both a cause of worsening in clinical indices of disease severity as well as a consequence of exogenous exposures such as tobacco smoke, environmental exposures such as ambient air pollution, and acute exacerbations (104, 161, 182, 183).

Some of the first studies to rigorously use CT to measure loss of lung tissue were performed in people with AATD (36, 130, 184–186). In a pooled analysis of two cohorts including 119 people, Stockley and colleagues demonstrated that augmentation therapy slowed the loss of lung tissue by almost 40% (36). In a U.K. AATD registry study, the rate of decline in lung density in the lower lungs was associated with survival (187). Several studies in AATD showed that CT densitometry is more sensitive for disease progression than physiology (108, 188), and a decline in lung density was associated with a decline in FEV_1 (189). More recent interventional studies such as the RAPID study and its open-label extension echoed these results, where augmentation therapy again slowed the radiologic loss of lung tissue but did not impact other clinical indices (113, 128). A disease progression model based on the RAPID study suggested that higher doses of augmentation might yield greater reduction in lung density decline (190). Although CT density allows the most practical assessment of emphysema change in AATD because of the smaller sample sizes needed for prospective clinical trials (113), other nonrandomized studies have shown differences in other outcomes such as change as measured with the St. George's Respiratory Questionnaire (191) and mortality (192).

Recent studies have also shown that CT densitometry can detect short-term progression in severe COPD (193). In a multicenter study of 144 subjects with COPD, the signal-to-noise ratio for the detection of change in Perc15 at 30 months was 3.2, compared with only 1.3 for FEV_1 and D_{LCO} (194). Larger observational studies in non-AATD COPD have provided a more extensive exploration of the relationship between serial densitometry and clinical outcomes such as decline in lung function and death. Using 5-year interval clinical and radiologic data from 4,143 COPDGene study participants, Pompe and colleagues reported that only a small fraction ($<$10%) of the loss of lung density over 5 years could be explained by the changes in FEV_1 (195). Other studies have shown either weak or absent correlation between change in lung attenuation and change in FEV_1 (104, 146, 196). A further study from COPDGene suggested that the correlation between change in FEV_1 and lung density decline was predominantly in subjects with COPD that meets the criteria of Global Initiative for Obstructive Lung

Disease Stages III and IV (197). It is interesting that the rate of progression of emphysema appeared to be slower in individuals using angiotensin-receptor blockers or angiotensin-converting enzyme inhibitors (198, 199), aspirin (200), and metformin (201).

The definition of normal lung density decline across the lifespan is not well established. However, people with emphysema have faster rates of parenchymal destruction progression (165, 202). Evidence supporting the clinical relevance of emphysema progression on CT comes from Ash and colleagues, using data from the COPDGene and ECLIPSE studies. A total of 5,143 people from the COPDGene cohort and 1,549 people from the ECLIPSE cohort were evaluated with 5.5 $\pm$ 0.6 years and 3.0 $\pm$ 0.2 years of follow-up, respectively. For every 1 g/L per year of faster rate of decline in $VALD_{PERC15}$, all-cause mortality increased by 8% in the COPDGene cohort and 6% in the ECLIPSE cohort. Furthermore, in the COPDGene study, this rate of $VALD_{PERC15}$ decline was associated with a 22% increase in respiratory-specific mortality (11).

To assess the bias and precision of lung density metrics, the Quantitative Imaging Biomarkers Alliance (QIBA) Lung Density Biomarker Committee performed a meta-analysis of six studies published between 2007 and 2012 in which subjects underwent two chest CT scans at an interval of 4 months or less (100). All six studies evaluated LAA_{-950}, and four also included Perc15. The meta-analysis showed that a longitudinal increase in LAA_{-950} and a decrease in Perc15 measurements of 3.7% and 18 HU, respectively, were required to detect an increase in the extent of emphysema with 95% confidence (without volume adjustment). Volume adjustment using a physical sponge model that conserves total mass (35) improved the repeatability coefficient by nearly 10 HU (Perc15 reduced from 18 to 11 HU after adjustment). A study in two lung cancer screening populations confirmed that the limits of agreement of Perc15 are improved by volume adjustment (58). The more recent SPIROMICS study, which evaluated the repeatability of CT metrics in 96 participants who underwent repeat scanning at seven centers after a mean interval of 29 days, found that the repeatability coefficient for $VALD_{PERC15}$ was 7.01 HU (154); these measurements, obtained on more modern scanners with standardized technique, are likely more representative of current practice.

Volume adjustment of Perc15 has been almost universally used in longitudinal densitometric studies of emphysema (11, 36, 108, 113, 195, 196, 202, 203). Although volume adjustment could theoretically reduce sensitivity to change if lung volume increases with progression of emphysema, longitudinal studies have not shown significant increase in lung volume over time (202). Careful attention to maintaining consistent lung inflation during CT acquisition is crucial for obtaining reliable longitudinal measurements.

Because of interscanner variations, only longitudinal claims are currently supported in the QIBA CT Lung Densitometry Profile, assuming that the same scanner make, model, imaging protocol and analysis software are used in following a given patient. However, studies have focused on reducing variability for repeated measures with the potential to eventually allow interscanner corrections and harmonization (67, 121).

Current Status and Recommendation on the Use of CT Densitometry in Clinical Trials

The context of use for CT densitometry in clinical trials is primarily as a monitoring biomarker in individuals with alpha-1 antitrypsin deficiency and those with COPD and emphysema. Table 3 summarizes some recommendations on the use of CT densitometry in interventional clinical trials. In longitudinal studies using lung densitometry, a prospectively defined standardized scanning protocol that includes manufacturer-specific acquisition and reconstruction parameters is critical for obtaining accurate and reliable measurements over time. A standardized approach to longitudinal CT densitometry has been provided by QIBA CT Lung Densitometry Profile (100). The QIBA guidelines provide generalizable image acquisition and image quality specifications that can be adapted for different vendor architectures, reconstruction algorithms, and analysis software. The QIBA guidelines provide generalizable image acquisition and

Table 3. Recommendations for Use of CT Densitometry in Clinical Trials

CT technique	Technique is based on QIBA CT lung densitometry profile. Use same CT scanner (or same make and model) and consistent breath-hold instructions for baseline and follow-up examinations.
Patient selection	Eligibility criteria will depend on the specifics of the trial but could include either visual identification of emphysema using the Fleischner criteria and/or LAA_{-950} greater than a specified threshold (typically 5%). Either exclude individuals who currently smoke or stratify analysis by smoking status. Expand visit windows to avoid CT scans during current COPD exacerbations.
CT interval	The interval between CT scans should range from 12 to 24 mo, with shorter intervals (6–12 mo) considered for high-risk populations or adaptive trial designs requiring frequent anchoring.
Treatment efficacy	
CT metric	Longitudinal evaluation uses volume-adjusted lung density (sponge model) using measured (e.g., baseline) lung volume.
Statistical adjustment factors	Potential adjustment factors may include lung volume differences (if sponge model is not used), scanner make and model, smoking status, sex, age, height, body mass index, image field of view, and image noise measurement.

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; LAA_{-950} = percentage of low-attenuation area below −950 HU; QIBA = Quantitative Imaging Biomarkers Alliance.

image quality specifications that can be adapted for different vendor architectures, reconstruction algorithms, and analysis software. They recommend using a standardized phantom to ensure baseline calibration and monitor longitudinal differences in scanner performance. To further reduce variations resulting from equipment-specific factors, the same scanner (or, at least, the same scanner model) should be used at each time point in a study. Before the study, the subjects should ideally rest for several minutes to avoid dynamic hyperinflation related to hyperventilation (204).

For image acquisition, the following parameters should be met: total collimation width, ⩾16 mm; image thickness, ⩽1 mm; scan duration, ⩽10-second breath-hold; CT dose for an average-sized patient, a CT dose index volume of ⩽3 mGy, with adjustment based on patient size and shape, an image thickness ⩽1 mm, an in-plane resolution ⩽1 mm, and edge enhancement of ⩽3%. Longitudinal imaging should also ensure that breath-hold volume is consistent and that the difference in lung inflation is less than 10% of the baseline volume. In addition, reconstruction parameters can impact the lung density histogram and should be consistent between baseline and follow-up image acquisitions (70, 80). Image analysis software packages should be tested on a reference set of CT images and compared with the consensus mean measurements provided in the Profile to qualify and be consistent between baseline and follow-up (118).

Standardized imaging protocols, such as those provided by the QIBA CT Lung Densitometry Profile, are essential for ensuring accurate and reliable measurements in emphysema progression studies. In addition, rigorous attention to breath-holding and quality control are essential (101). Dose modulation is helpful in mitigating the effect of image noise. By following these guidelines, researchers and clinicians can minimize sources of variability, effectively track the progression of emphysema, and assess the impact of treatments on disease progression.

Several approaches have been proposed to reduce the important effect of image noise simulating emphysema using filtering and frequency decomposition techniques (46, 205). More recently, directly measured image noise was incorporated into a statistical adjustment model to estimate longitudinal change in emphysema (202) and a lung density histogram deconvolution approach to account for changes in noise, volume, and bias has also been proposed (121). Ongoing improvements—likely, leveraging advances in deep learning—are needed to address continuing scanner evolution.

Patient Selection

Given the relatively slow rate of progression, emphysema treatment trials should be enriched for patients at greater likelihood of progression. Visual evidence of emphysema on CT at baseline is associated with increased progression of emphysema over time, and the degree of progression increases with increasing visual grade of emphysema (165). Thus, the inclusion of participants with mild or moderate visual emphysema using the Fleischner criteria (206) may help enrich a trial for those with increased likelihood of progression. Alternatively, QCT could be used as a criterion for study entry, with a threshold for LAA_{-950} of 5% or greater (6).

Lung cancer screening CTs offer a valuable opportunity to identify patients with emphysema who may be suitable candidates for clinical trials. Although these scans are typically acquired at lower radiation doses, they have been shown to provide reliable quantitative assessments of emphysema using validated software algorithms (58, 59). Leveraging lung cancer screening programs for patient selection in emphysema trials requires careful consideration of imaging standardization, particularly ensuring consistent lung volume during acquisition. Additionally, integrating automated tools for emphysema quantification and harmonizing imaging protocols across screening programs could enhance the utility of these scans.

CT Interval

We recommend CT evaluation intervals of 12 to 24 months for lung densitometry in most studies, as these intervals are practical for detecting meaningful changes in emphysema progression. However, shorter intervals (6–12 mo) may be appropriate for populations at higher risk of rapid progression, such as individuals with AATD or those with high baseline FEV_1 decline rates. Evidence from studies such as the RAPID trial (113) suggests that more frequent scans (e.g., at 6-mo intervals) early and late in the study can anchor longitudinal slope measurements, facilitating adaptive trial designs. For most interventional studies, a minimum of three scans is preferred to ensure reliable slope measurements. Although optimal trial designs may vary, incorporating frequent, early, and late measurements may offer advantages, whereas intervals shorter than 6 months may be generally impractical, except in specific circumstances.

Defining Progression

A key challenge to the application of biomarkers such as Perc15 in clinical trials is consensus on the powering of studies, as minimal detectable differences may depend on the COPD endotype (underlying pathobiology), severity of disease, and duration of study. Because of the strong correlation of Perc15 with mortality, some would argue that population standards are not needed when two comparable populations receive an intervention that shows differences (207). Additionally, lost lung tissue detected by CT cannot be regenerated by any known interventions at this time; therefore, preservation of lung tissue for long-term health is important.

On the basis of pooled healthy, never-smoking participants who had longitudinal imaging data from the COPDGene and ECLIPSE cohorts (11), a minimal clinically important difference for emphysema progression was defined as a decline in volume-adjusted Perc15 emphysema progression of at least 1.22 g/L per year. Compared with those without progression by this definition, the hazard ratios for mortality in those with progression were 1.76 (95% confidence interval = 1.25–2.48) in the COPDGene cohort and 1.63 (95% confidence interval = 1.18–2.24) in the ECLIPSE cohort.

Radiation Dose Considerations

Among the concerns related to the application of CT in longitudinal clinical trials is participant exposure to ionizing radiation. The effective radiation dose that a patient receives from a lung CT using the QIBA protocol parameters is comparable with the annual dose from naturally occurring background radiation sources and is associated with a very low risk of long-term effects. To mitigate concerns over the use of ionizing radiation in CT, all manufacturers of CT technology continue to make extensive efforts to reduce radiation exposure while maintaining or enhancing image quality through the use of automatic exposure control and advanced reconstruction techniques, and this is particularly important for participants undergoing repeated measurements (69, 81–83).

Statistical Analysis

As outlined in the Metrology of CT Biomarkers section, key considerations for evaluating change of lung density in an individual are the bias and precision of the CT densitometry measure. Establishing negligible bias and high precision reduces the sample size needed to establish individual response to an intervention (e.g., increase or decrease in lung density using either Perc15 or LAA_{-950} as an endpoint). Bias and precision are typically determined through meta-analysis using a random effects model (208). In transitioning from individual assessments to groupwise comparisons in clinical and observational studies, the statistical approach shifts toward linear mixed-effect models. These models are favored for their ability to handle intra- and intersubject variations, which is crucial for understanding lung density changes in response to treatments or risk factors (113, 129, 195, 196, 209). They adeptly manage the complexities of longitudinal data, accounting for both fixed treatment effects and random individual variations, thereby offering a more comprehensive analysis of treatment impacts on lung density. Large sample sizes can address lower precision and nominal bias, leveraging the central limit theorem, as long as both groups are comparably affected by CT densitometry's bias and precision. This is supported by a SPIROMICS substudy's Bland–Altman analysis, indicating that bias and precision are mostly independent of disease severity (154).

Research Priorities

Evolving CT Technology

In the diagnostic CT energy range, physical sources that contribute to error in the CT number include the X-ray photon energy spectrum of the beam source, scatter, electronic noise, and reconstruction filter (kernel). Advanced CT architectures and reconstruction methods have improved performance of modern CT systems. Important examples include adaptive X-ray source tube current modulation (automatic exposure control) along the table axis (z-axis) and azimuthally (x-axis and y-axis) to improve the consistency of noise behavior on the basis of patient size and anatomic location. Further advances using patient model-based IRs that also account for the physics of attenuation specific to the patient reduce noise and enable more accurate measures of density at lower CT doses than previously possible (81, 82). IR methods have limitations in the realm of low-contrast resolution structures such as the lung. This has limited their application in assessing subtle changes in tissue density over large scales, such as emphysema and liver density. Deep-learning methods of CT reconstruction may overcome this limitation and still provide the other benefits of IR, such as dose reduction and decreased image noise (210). However, they may also cause problems with the standardization of lung density measures, because they are orientated to visual rather than quantitative results. Photon-counting CT scanners that are just becoming available for clinical work may provide another way forward in reducing patient dose, decreasing image noise and providing more accurate CT density measurements of lung tissue (84). Although photon-counting CT may substantively improve the sensitivity and accuracy of emphysema detection, further work is necessary to understand the differences between photon-counting CT and conventional CT. Photon-counting CT could be optimized for quantitative assessment of lung density if appropriate validation studies confirm its accuracy. Designing a study that mixes CT technologies is not recommended until extensive comparative studies are performed.

Accounting for Smoking-related Inflammatory Changes and Comorbidities

As mentioned earlier, cigarette smoking results in a substantial increase in lung attenuation, and smoking cessation results in an abrupt decrease in attenuation, simulating progression of emphysema (95, 96). Although sequential evaluation of lung attenuation in individuals who are currently smoking cigarettes may be subject to variation, these individuals have a higher rate of progressive emphysema than those who have quit smoking (202, 211) and, therefore, may enrich a clinical trial population.

Approximately 8% of older individuals who smoke cigarettes have evidence of interstitial lung abnormality, which may progress slowly over time, resulting in increased lung attenuation (212). These individuals may need to be excluded from clinical trials. However, quantitative assessment might permit statistical adjustment for the confounding effect of progressive interstitial lung abnormality as a cause of increasing attenuation (50). A further potential cause of decreased lung attenuation, which has not been well evaluated, is hyperinflation due to nonemphysematous small airway obstruction (204). Volume-adjusted lung density metrics can partially mitigate the impact of hyperinflation, which may otherwise mimic accelerated emphysema progression by increasing lung volumes.

Virtual Clinical Trials

Virtual clinical trials using computational simulation approaches can provide a novel way to validate and assess emphysema progression in CT scans. These trials consider the impact of various acquisition parameters, such as BMI, radiation dose, and reconstruction algorithms, on the accuracy of lung density biomarkers used to quantify emphysema. Recent works by Abadi and colleagues demonstrate the potential of virtual trials to systematically validate scanning protocols, which are crucial for standardizing density-based emphysema measurements and reducing variability (60). The simulation framework can also evaluate emerging CT technologies and deep-learning reconstruction methods. Regulatory agencies are increasingly acknowledging the value of these computational experiments for validation, providing new alternatives for image-based biomarker validation. This evolution in approach is particularly beneficial for addressing specific disease stages and adapting to the varied anatomical structures encountered in clinical settings. Such advancements underscore the progress toward a more accurate and unified approach in evaluating emphysema as a biomarker, enhancing the reliability and applicability of these measures in clinical research.

Emerging Approaches for Lung Density Harmonization and Deep Learning

In the rapidly evolving landscape of CT technology, harmonization of lung densitometry may improve precision and be critical for integrating emphysema monitoring into clinical trials. Recent advancements have seen the development of sophisticated statistical models that adeptly adjust for variabilities in lung density measurements, considering both

biological and technical factors impacting CT readings (56, 61, 67, 202, 209, 213–216). These models have been instrumental in identifying optimal confounders that are crucial for standardizing measurements across various CT scanners and protocols. Alongside these, alternative signal models are gaining traction, addressing changes in lung density histograms and factoring in imaging confounders such as image noise; scanner discrepancies; and physiological variations, including volume shifts and inflammatory status (46, 70, 121, 205, 217–219). These methods are integral in providing harmonized metrics tailored to individual patients. They are particularly effective in addressing discrepancies arising from different section thicknesses, kernels, and reconstruction methods in CT imaging, thereby aiding in maintaining measurement consistency across various scanning technologies.

Additionally, the integration of image processing and deep learning into CT reconstructions and emphysema densitometry is gaining traction. Initiatives utilizing deep-learning architectures are underway, with a focus on normalizing the effects of reconstruction kernels and correcting artifacts in CT images (123, 220–223). Artificial intelligence–based approaches hold significant promise for enhancing image processing and introducing more refined automation and precision in emphysema quantification. The anticipated development of models capable of converting raw CT data into accurate, standardized lung density measurements could mark a notable improvement in emphysema monitoring and management, potentially leading to more effective strategies for understanding and addressing this condition, but further development and careful validation of those approaches are needed before its adoption.

Conclusions

CT densitometry-based metrics reflect pathologic emphysema and predict the progression of COPD, COPD exacerbations, and mortality, serving as a surrogate endpoint. Longitudinal decreases in $VALD_{PERC15}$ are associated with increased mortality. Clinical trials involving subjects with alpha-1 antitrypsin deficiency have demonstrated that treatment slows the rate of decrease in $VALD_{PERC15}$ compared with control groups, indicating reduced tissue loss. Key sources of variation in lung density are inspired lung volume, CT reconstruction algorithms, and inflammatory abnormalities, including smoking-related lung injury. With the appropriate technique, the reproducibility coefficient of volume-adjusted lung CT attenuation is about 7 HU, and the intraclass correlation coefficient is extremely high at 0.99. To mitigate sources of variation in the context of clinical trials, a standardized CT acquisition technique should be used, and the same scanner should be used for each subject throughout the trial. Researchers may need to exclude individuals who quit or resume smoking during the trial. Important areas for future research include better adjustment for image noise and adapting CT densitometry methods for scanner evolution, including new technology such as photon-counting CT. With careful accounting for its potential limitations and performed properly as described, CT densitometry is appropriate for use as a monitoring biomarker in clinical trials for individuals with alpha-1 antitrypsin deficiency and those with COPD and emphysema. ■

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