Overview of COPD Management and the Application of Quantitative Imaging

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National Jewish Health

Disclosures

- Parexel Imaging: Consultant (Active)
- Boehringer Ingelheim: Consultant (Active)
- Genentech: Consultant (Active)
- Veracyte: Consultant (Active)
- Gilead: Consultant (Past)
- Siemens: Research Support (Past)

Outline

- Definition of COPD
  - GOLD
- Challenges with current definitions of COPD
- Quantitative imaging in COPD
  - Emphysema
  - Large airway abnormality
  - Inflammatory small airways disease
  - Obstructive small airways disease
- Longitudinal changes
- Quantitative Imaging Biomarkers Alliance

Definition of COPD

- A common, preventable and treatable disease characterized by respiratory symptoms and airflow limitation
- Airflow obstruction caused by a mixture of obstructive bronchiolitis and emphysema
- Diagnosis requires spirometry, with post-bronchodilator FEV1/FVC ratio < 0.70
- GOLD Stage 1: FEV1 ≥80% predicted
- GOLD Stage 2: FEV1 50-80% predicted
- GOLD Stage 3: FEV1 ≥30-50% predicted
- GOLD Stage 4: FEV1 <30% predicted

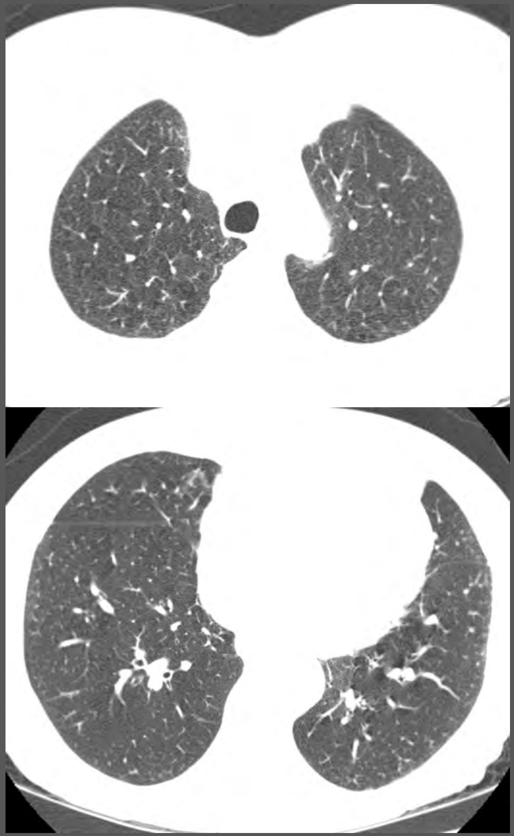
www.goldcopd.org

Challenges with current definition of COPD

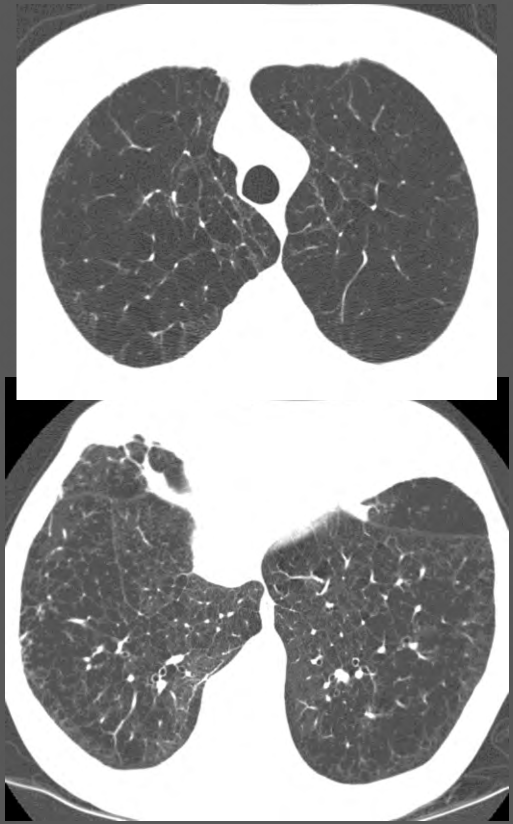
- Does not address morphologic differences within COPD
- Underemphasizes anatomic airway dropout as the early lesion of COPD
- Smokers “without” COPD have symptoms and comorbidities
- Little understanding of COPD unrelated to smoking (e.g. biomass lung)
- No basis for personalization of therapy to morphologic COPD subtypes

COPD is not one disease

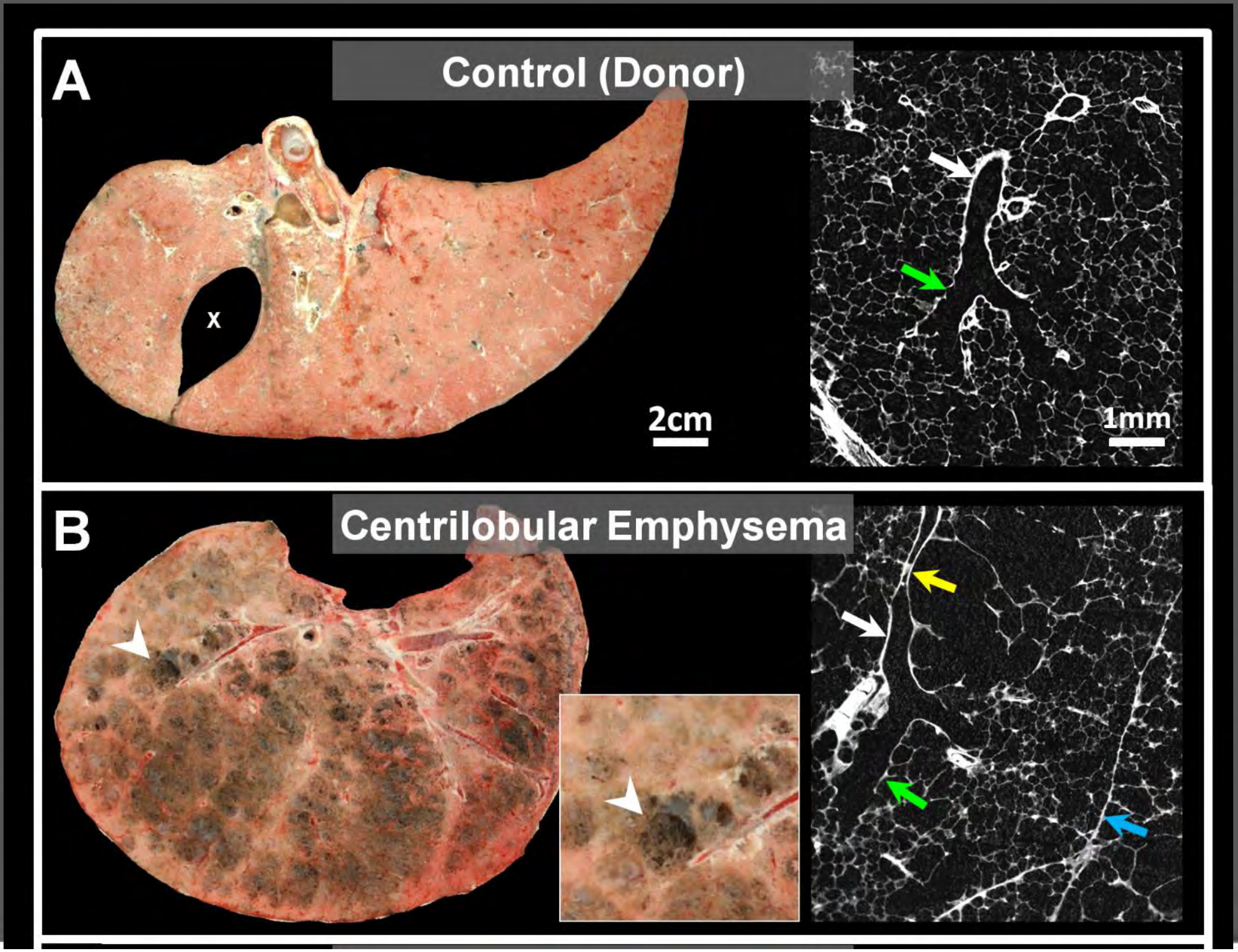
FEV1 59% predicted: GOLD Stage 2



FEV1 62% predicted: GOLD Stage 2

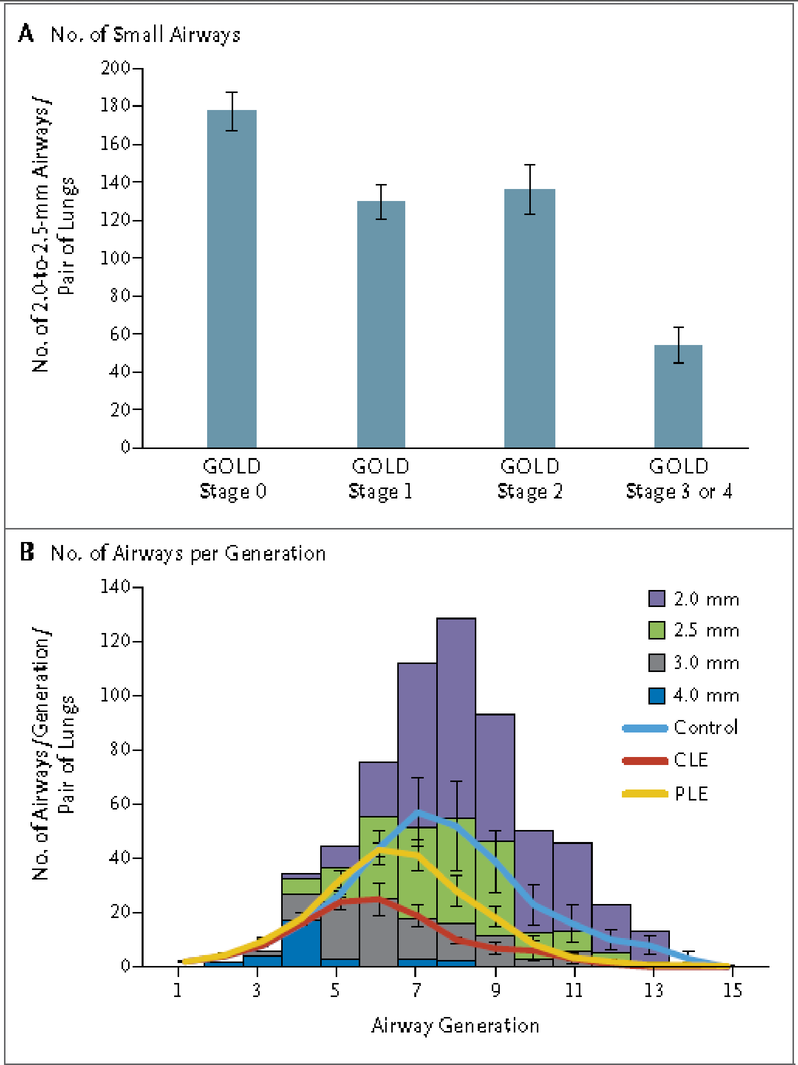


Airway narrowing is an important early marker of smoking-related lung injury



Courtesy: James Hogg, MD

Decreasing numbers of small airways on CT with increasing severity of COPD



The NEW ENGLAND JOURNAL of MEDICINE

McDonough et al.
N Engl J Med
2011;365:1567-1575

The myth of the "healthy smoker"

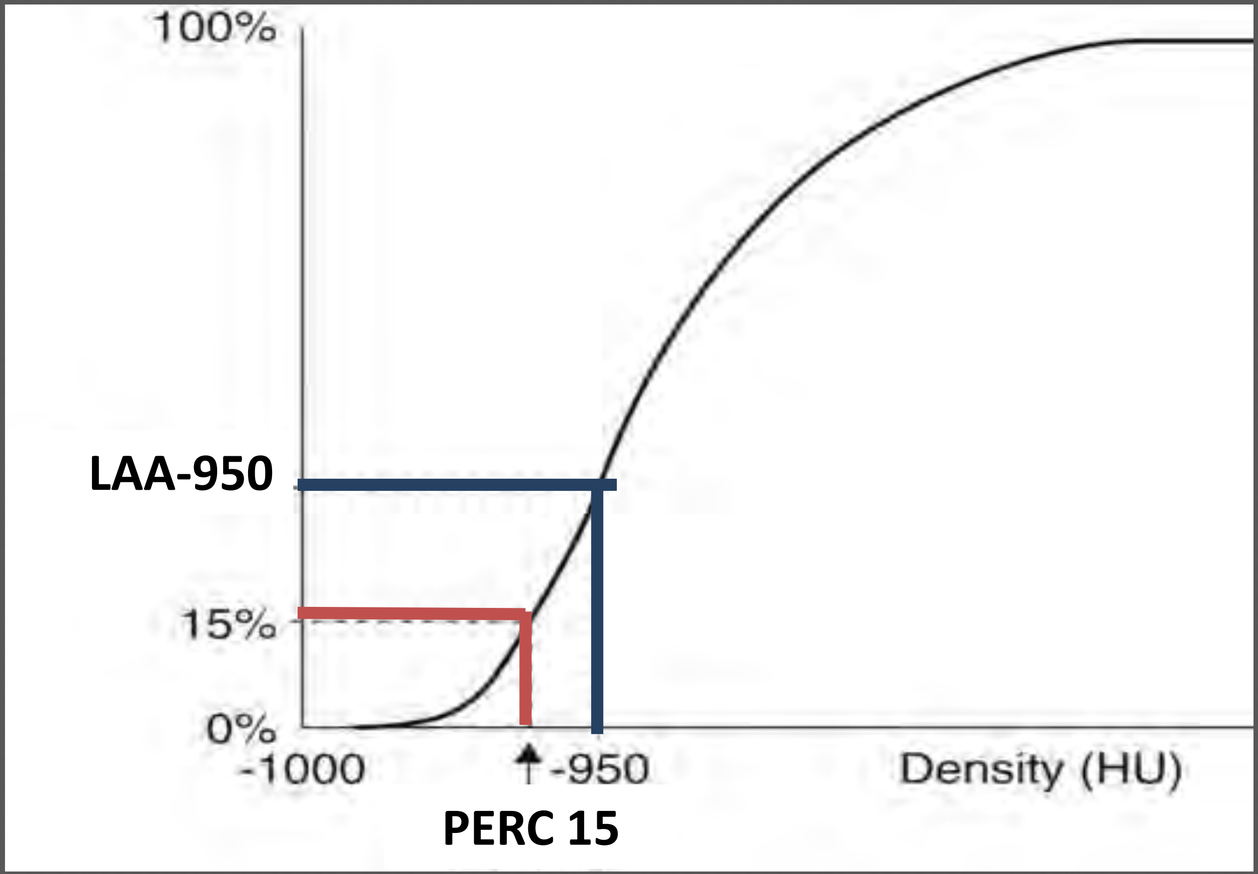
- Among smokers without COPD in COPDGene
  - 24% have significant dyspnea
  - 13% have chronic bronchitis
  - 22% have visible emphysema
  - 30% have airway wall thickening
  - 10% have quantitative evidence of emphysema
  - 11% have quantitative evidence of gas trapping
  - 32% have quantitative evidence of airway wall thickening
  - 54% have one or more respiratory impairment

Regan et al. JAMA Intern Med. 2015;175(9):1539-1549.

Approaches to emphysema quantification

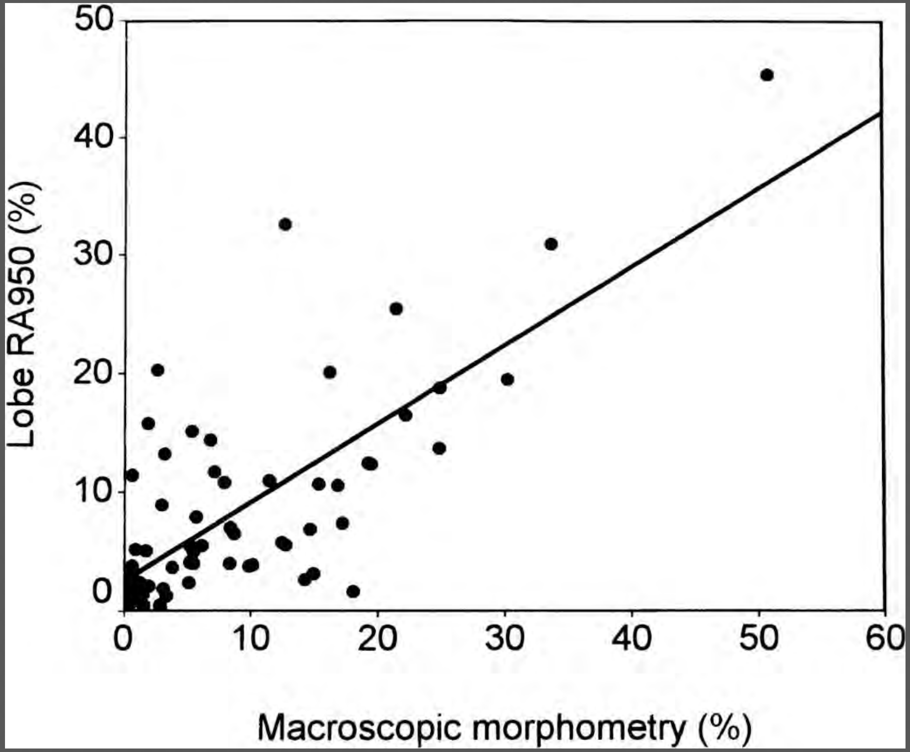
- Density mask
  - % lung area < HU threshold
- Histogram percentile
- Lung density (g/L)
- Volume-adjusted lung density
- Local histogram evaluation
- (Size of emphysematous "holes")
- (Textural evaluation)
- (Vascular evaluation)

Quantitative phenotyping: emphysema



Parr et al. Respiratory Research 2008, **9**:21

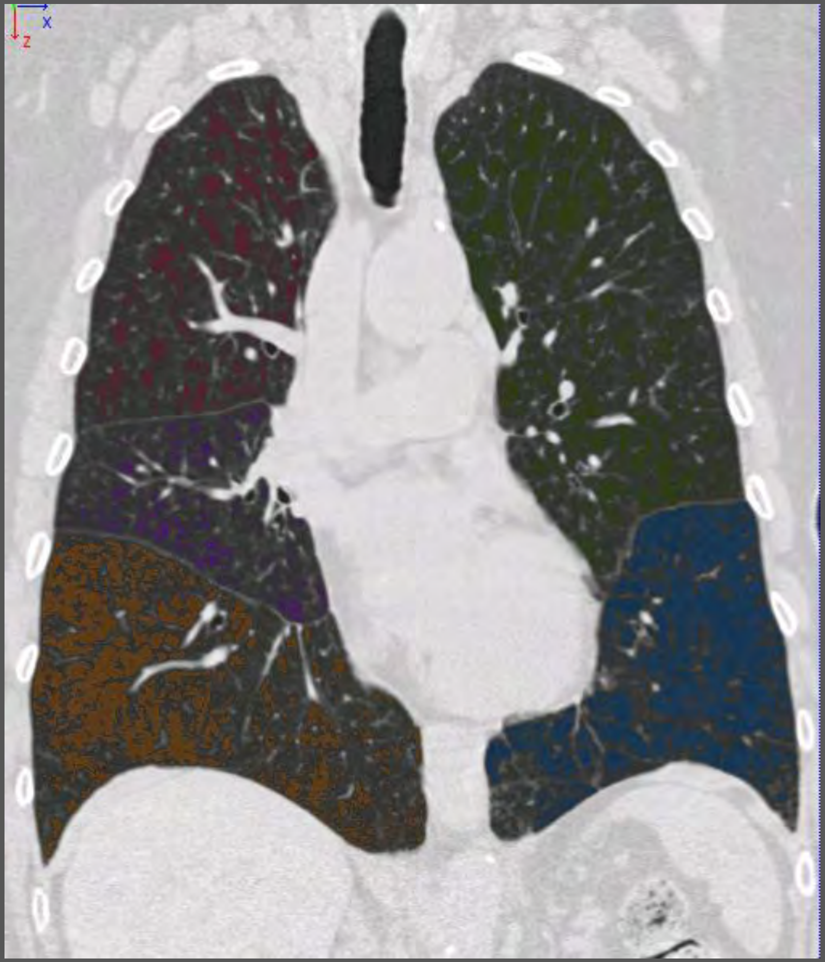
Correlation between emphysema index (threshold -950) and morphometric extent of emphysema



r= 0.623
p<0.0001

Bankier, A.A., *et al.*, 1999, Radiology 211, 851-858.

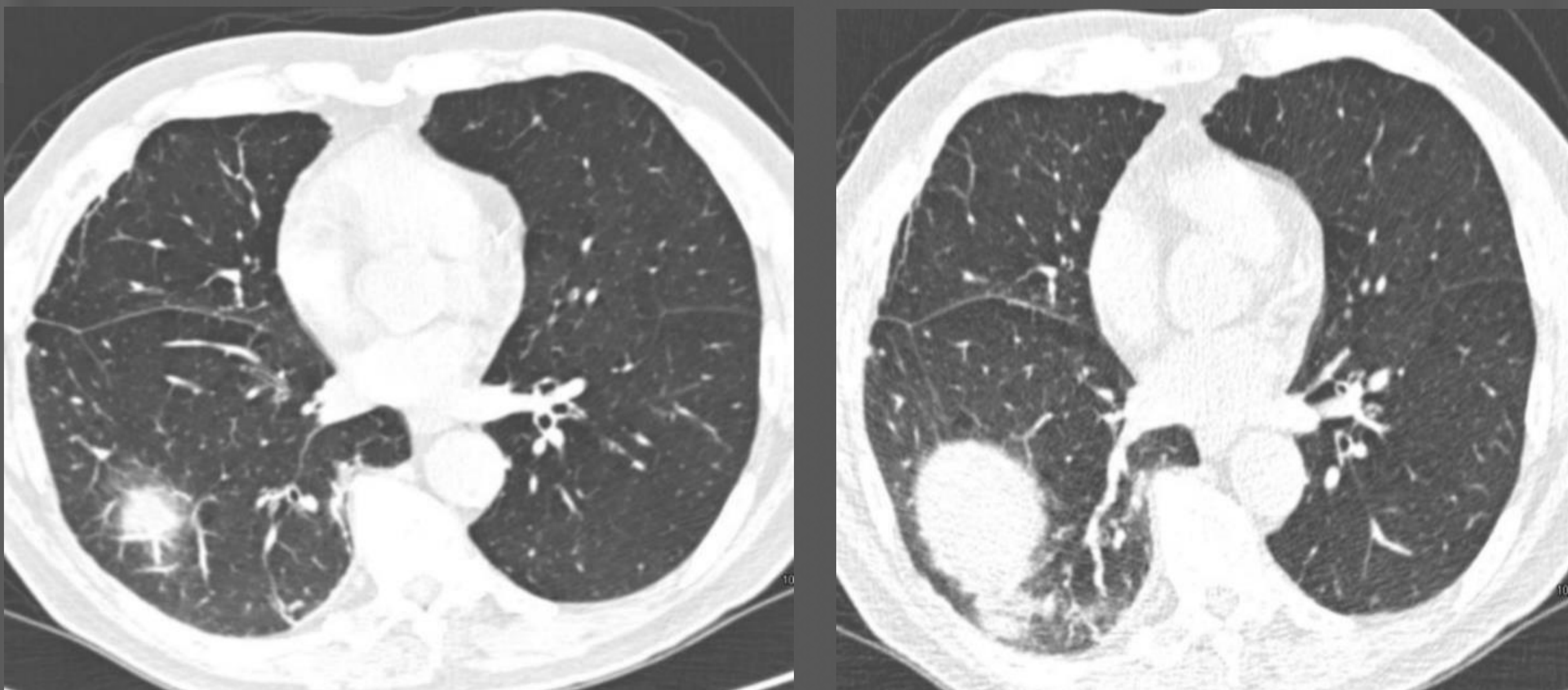
Quantitative phenotyping: emphysema



% LAA < -950	25%
15^{th} percentile	-962 HU
Lung density at 15^{th} percentile	38 g/L
Total volume (TLC)	5.8 L
Predicted TLC	5.9 L
TLC correction	0.97
Volume adjusted lung density	37 g/L

Obstructive small airways disease in COPD

Inspiration **Expiration**

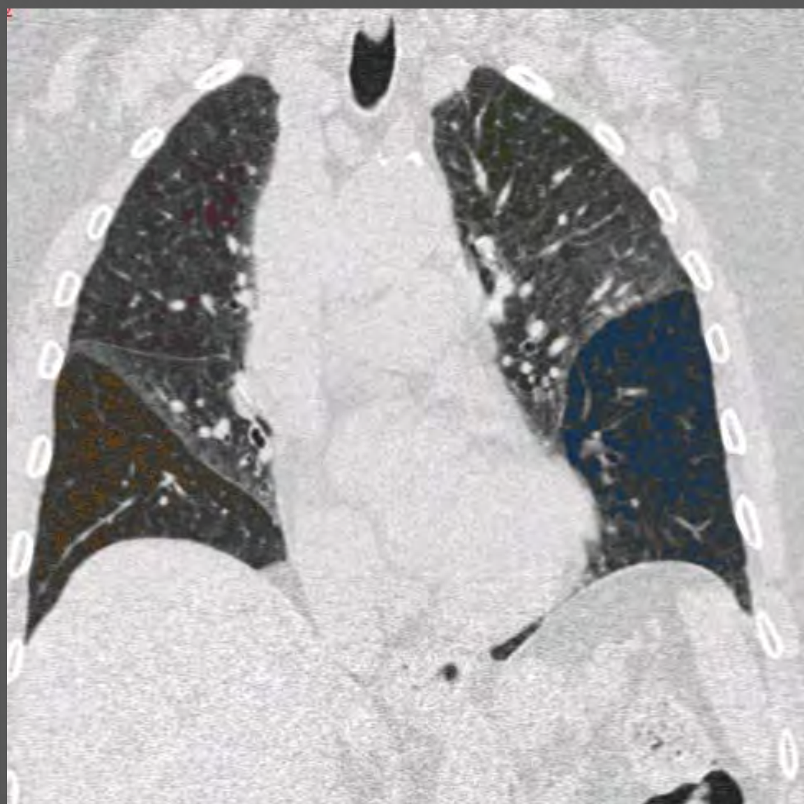


Expiratory air trapping

- End-Tidal expiration (Functional Residual Capacity)
- End maximal expiration (Residual Volume)

- % lung < -856 HU
- Expiratory/inspiratory mean lung density ratio
- Expiratory/inspiratory mean lung volume ratio
- Parametric response mapping

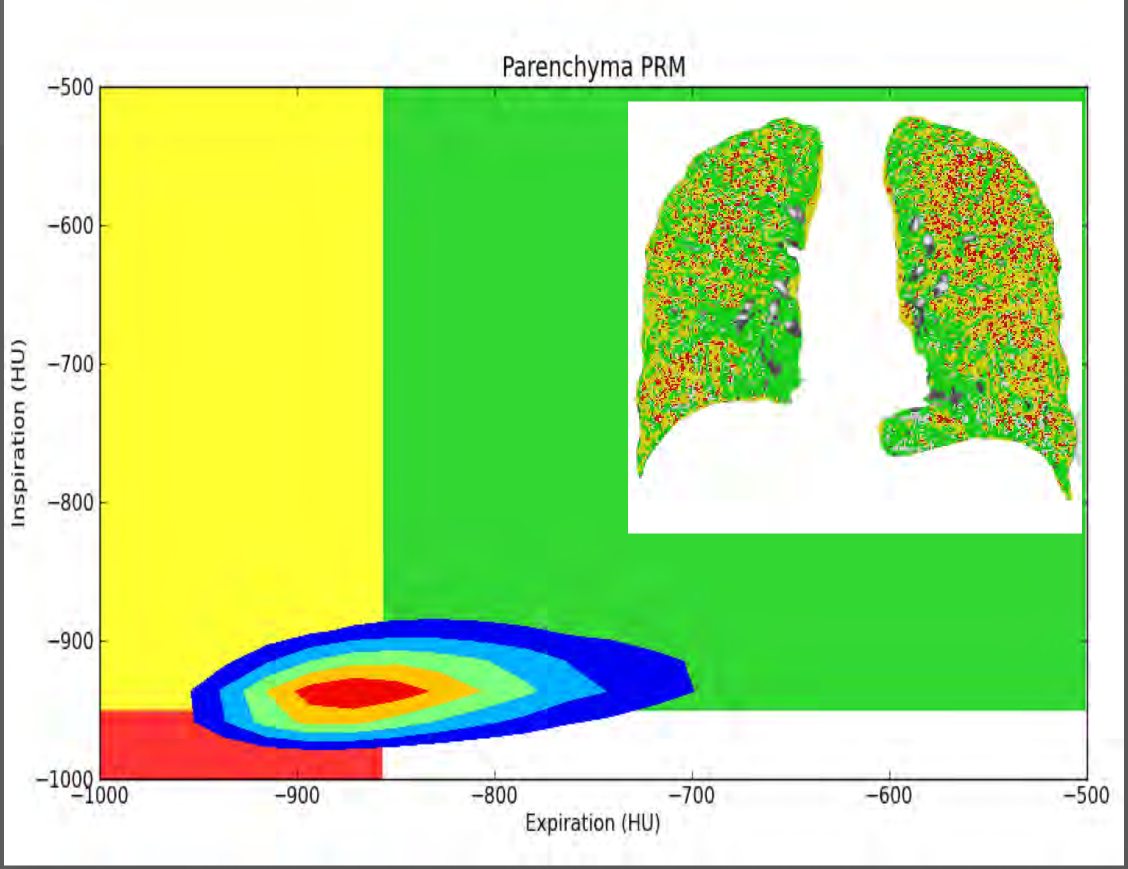
Quantitative phenotyping: air trapping



Total volume (FRC)	3.1 L
% below -856	27%
FRC/TLC ratio	0.53
FRC/TLC density ratio	0.54

COPDGene® COPD Genetic Epidemiology

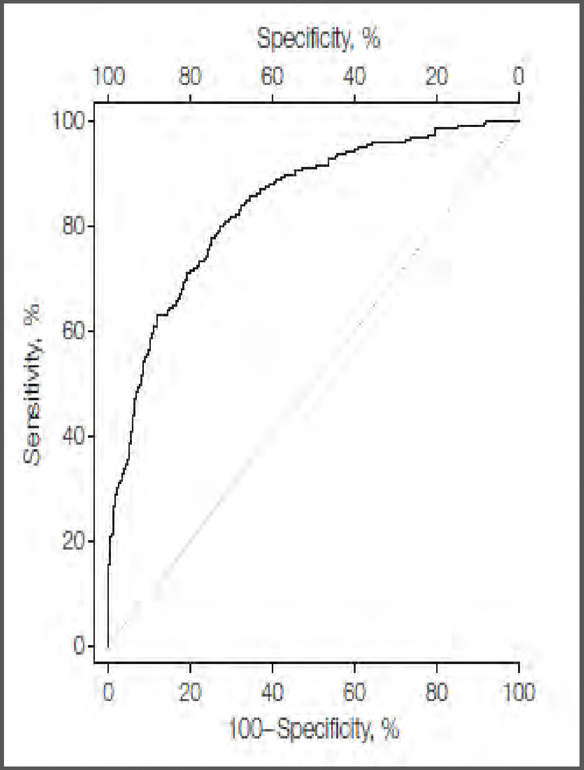
Parametric response mapping



PRM emphysema	10.2%
PRM functional small airways disease (fSAD)	20.1%
PRM normal	65.9%
PRM other	3.8%

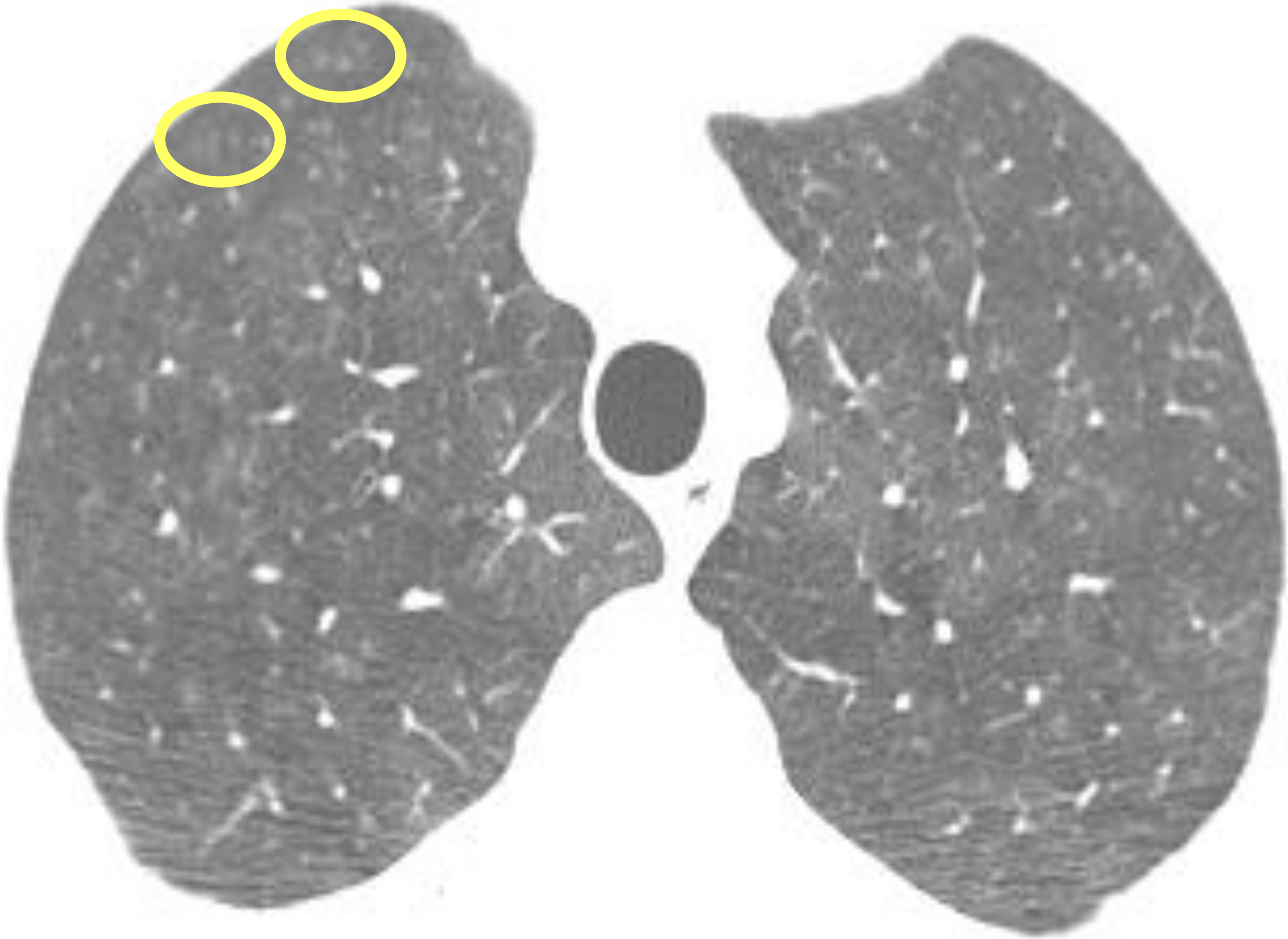
QCT identification of COPD in lung cancer screening scans

- A diagnostic model with CT emphysema, CT air trapping, body mass index, pack-years, and smoking status yielded an area under the receiver operating characteristic curve of 0.83 (95% CI, 0.81-0.86), for diagnosis of COPD.

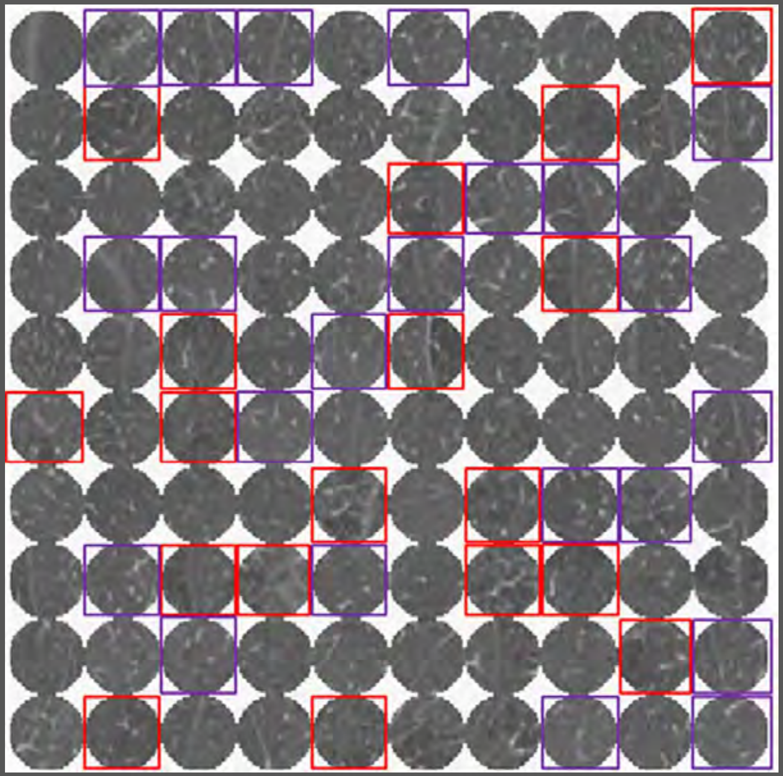


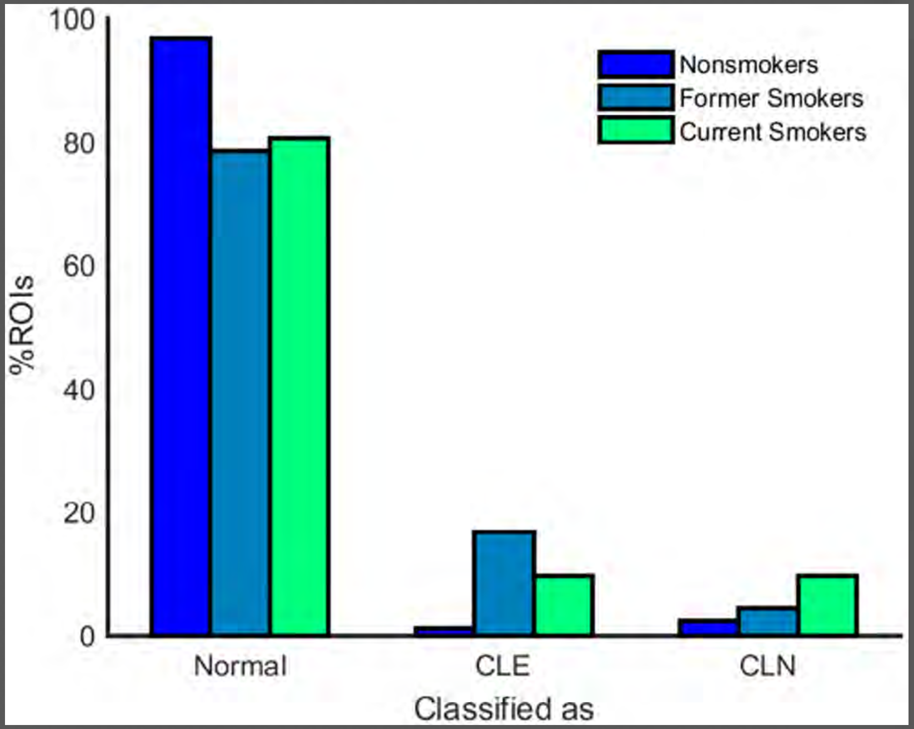
Mets et al. JAMA. 2011;306(16):1775-1781

Inflammatory small airways disease in COPD: Respiratory bronchiolitis



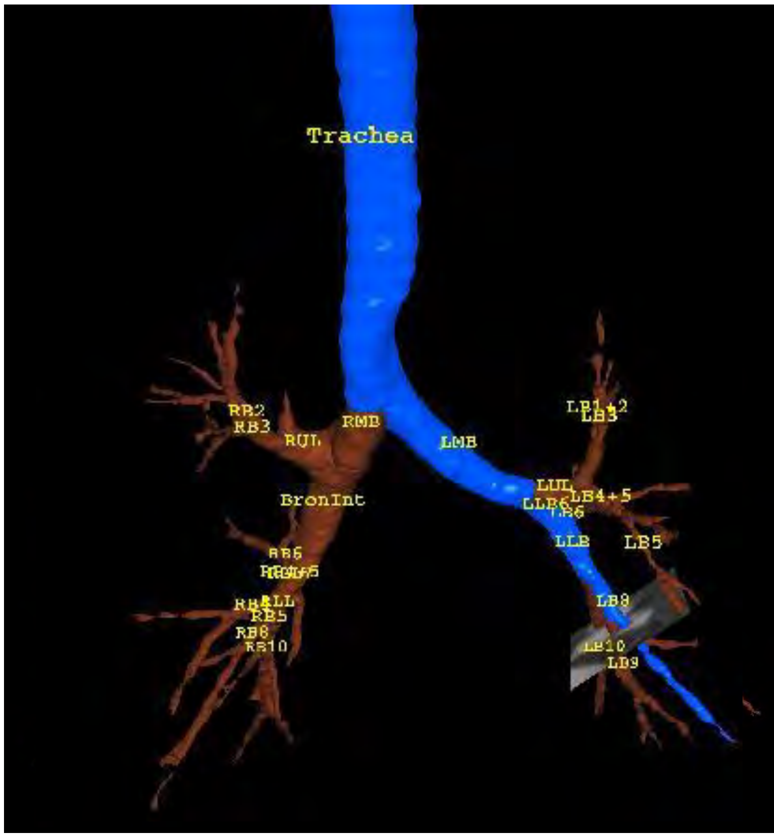
Texture-based detection of centrilobular nodules

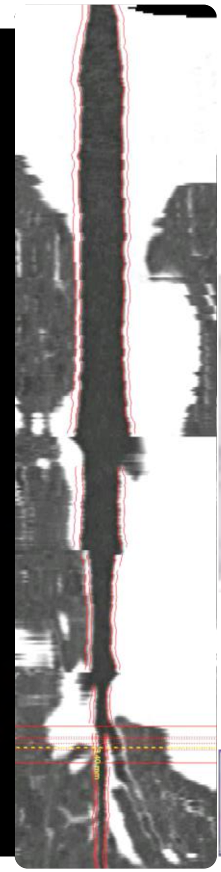


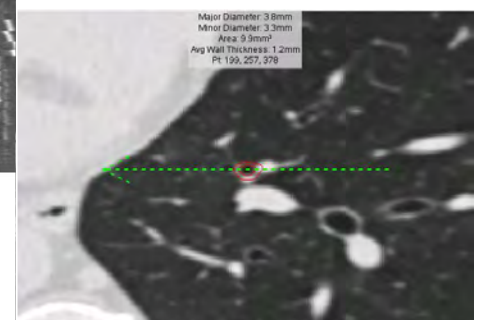


Ginsburg et al. Acad Radiol 2016; 23:1349–1358

Quantitative phenotyping: Larger airways (bronchi)





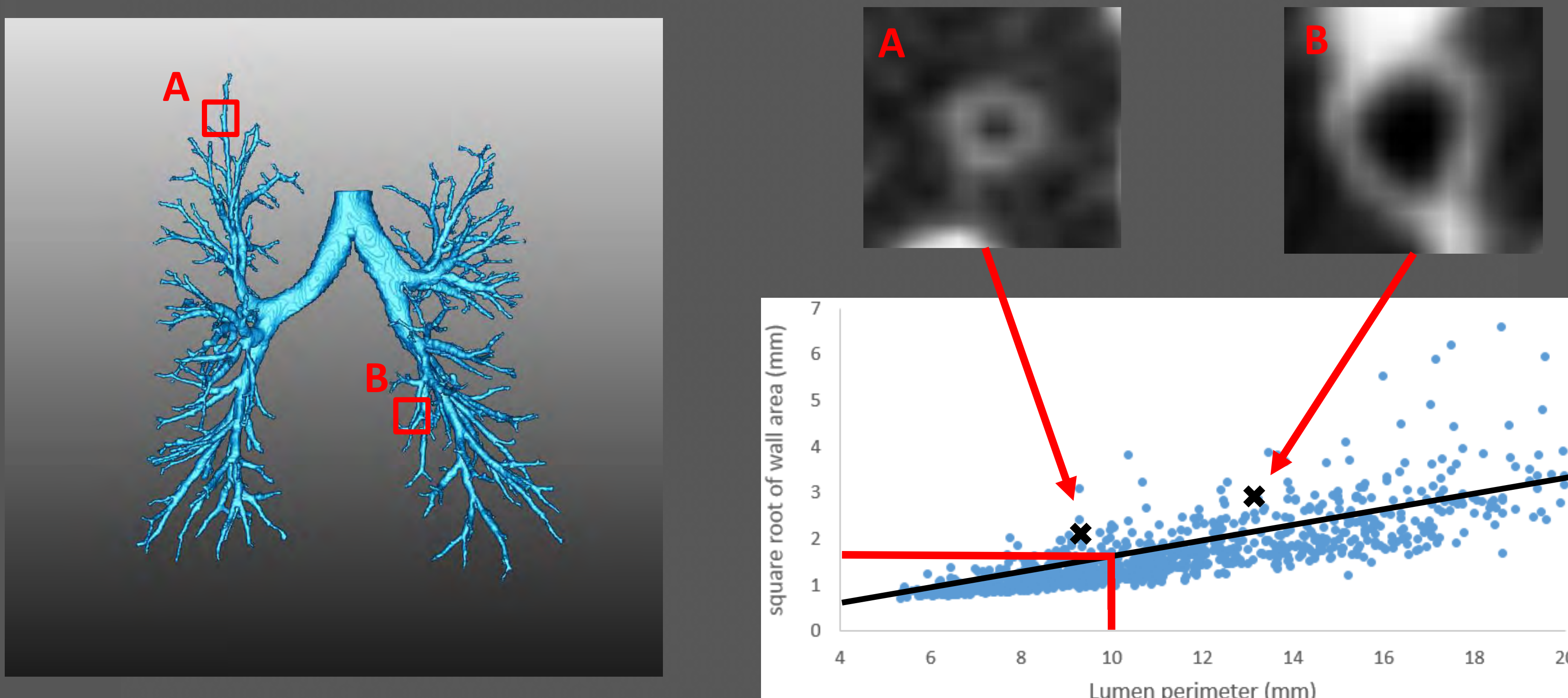


COPDGene®
COPD Genetic Epidemiology

Airway parameters

- Internal bronchial diameter, area
- Bronchial wall thickness, area
- Bronchial wall area %
- Pi10 = Square root of wall area of a bronchus of internal perimeter 10 mm
- Segmental, subsegmental, subsubsegmental
- Total airway count

Pi10



A
B
A
B
square root of wall area (mm)
Lumen perimeter (mm)
0
1
2
3
4
5
6
7
4
6
8
10
12
14
16
18
20

Prediction of COPD: ROC analysis

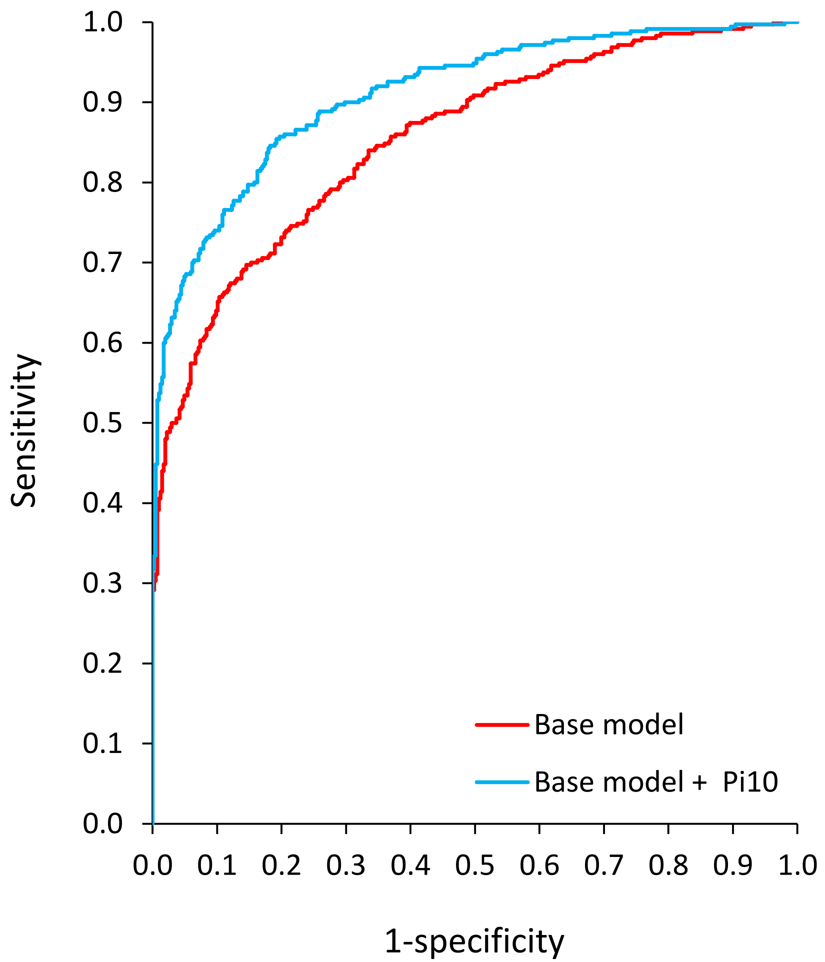
ROC analysis for prediction of COPD

Base model includes

- Age
- Gender
- BMI
- pack years
- smoking status
- TLC
- LAA%-950

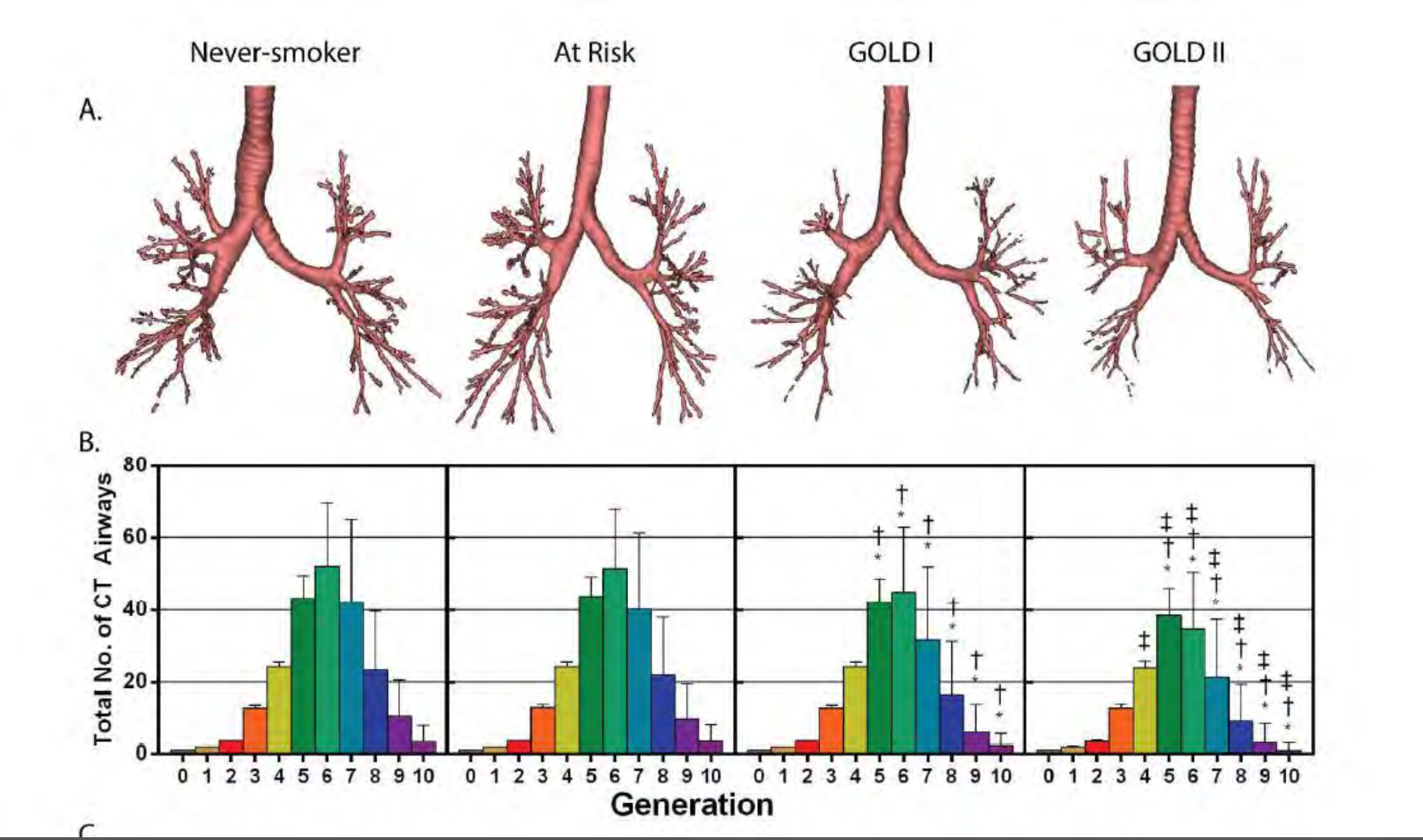
Base model AUC= 0.85

Model with Pi10 AUC= 0.91



J-P Charbonnier: manuscript in progress

CANCold study: Decreasing total airway count with increasing severity of COPD



Kirby et al. AJRCCM 10.1164/rccm.201704-0692OC

CANCold study: Multivariable Regression Model for FEV1/FVC

Parameter	Standardized Estimate	p
LAA_{856}	-0.12	<0.0001
LAA_{950}	-0.20	<0.0001
Total airway count	0.40	<0.0001
Pi10	-0.02	0.48
Inner Area	0.08	0.009

Total airway count is an independent predictor of longitudinal decline in FEV1 ($p=0.02$) and FEV1/FVC ($p=0.01$) over 6 years

Kirby et al. AJRCCM 10.1164/rccm.201704-0692OC

CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society[1]

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Massimo Pistolesi, MD
Edwin K. Silverman, MD, PhD
James D. Crapo, MD

The purpose of this statement is to describe and define the phenotypic abnormalities that can be identified on visual and quantitative evaluation of computed tomographic (CT) images in subjects with chronic obstructive pulmonary disease (COPD), with the goal of contributing to a personalized approach to the treatment of patients with COPD. Quantitative CT is useful for identifying and sequentially evaluating the extent of emphysematous lung destruction, changes in airway walls, and expiratory air trapping. However, visual assessment of CT scans remains important to describe patterns of altered lung structure in COPD. The classification system proposed and illustrated in this article provides a structured approach to visual and quantitative assessment of COPD. Emphysema is classified as centrilobular (subclassified as trace, mild, moderate, confluent, and advanced destructive emphysema), panlobular, and paraseptal (subclassified as mild or substantial). Additional important visual features include airway wall thickening, inflammatory small airways disease, tracheal abnormalities, interstitial lung abnormalities, pulmonary arterial enlargement, and bronchiectasis.

Radiology 2015; 277: 192-205

Visual scoring of emphysema

- Centrilobular emphysema
  - Absent
  - Trace
  - Mild
  - Moderate
  - Confluent
  - Advanced destructive
- Paraseptal emphysema
  - Absent
  - Mild
  - Substantial
- Bronchial wall thickening
  - Absent
  - Possible
  - Definite

Distribution of visual emphysema grades in COPDGene (n=3156)

	N Total (%)
No emphysema	1080 (34%)
Trace CLE	541 (17%)
Mild CLE	580 (18%)
Moderate CLE	478 (15%)
Confluent CLE	337 (11%)
Advanced destructive CLE	140 (4%)

Emphysema grade vs death rate

	N Total (%)	N Deaths
No emphysema	1080 (34%)	70 (6%)
Trace CLE	541 (17%)	52 (10%)
Mild CLE	580 (18%)	79 (14%)
Moderate CLE	478 (15%)	99 (21%)
Confluent CLE	337 (11%)	143 (42%)
Advanced destructive CLE	140 (4%)	51 (36%)

Emphysema grade vs survival: base model*

	N Total (%)	N Deaths	Hazard Ratio	95% Confidence Interval		P Value
No emphysema	1080 (34%)	70 (6%)	Reference			
Trace CLE	541 (17%)	52 (10%)	1.40	0.97	2.03	0.0733
Mild CLE	580 (18%)	79 (14%)	1.78	1.36	2.35	<.0001
Moderate CLE	478 (15%)	99 (21%)	2.58	1.75	3.81	<.0001
Confluent CLE	337 (11%)	143 (42%)	5.52	4.07	7.49	<.0001
Advanced destructive CLE	140 (4%)	51 (36%)	4.36	2.56	7.44	<.0001

* Adjusted for race, sex, age, weight, height, smoking pack-years, current smoking status, and educational level

Emphysema grade vs survival: model with LAA-950*

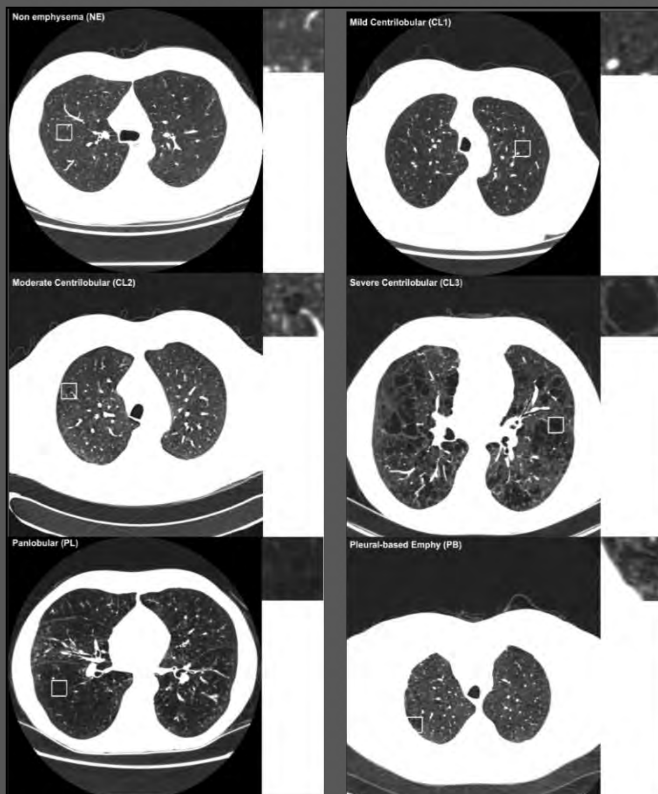
	N Total (%)	N Deaths	Hazard Ratio	95% Confidence Interval		P Value
No emphysema	1080 (34%)	70 (6%)	Reference			
Trace CLE	541 (17%)	52 (10%)	1.38	0.95	2.01	0.09
Mild CLE	580 (18%)	79 (14%)	1.69	1.27	2.24	0.0003
Moderate CLE	478 (15%)	99 (21%)	2.10	1.39	3.15	0.0004
Confluent CLE	337 (11%)	143 (42%)	3.23	2.20	4.75	<.0001
Advanced destructive CLE	140 (4%)	51 (36%)	1.96	1.07	3.58	0.03
%LAA-950			1.03	1.02	1.04	<.0001

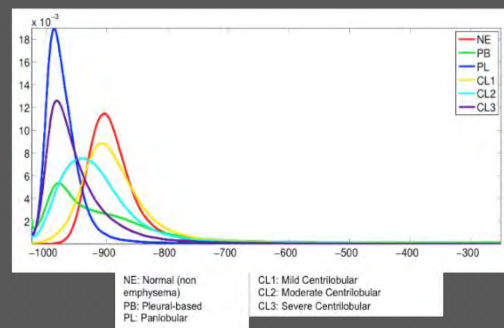
* Adjusted for race, sex, age, weight, height, smoking pack-years, current smoking status, and educational level

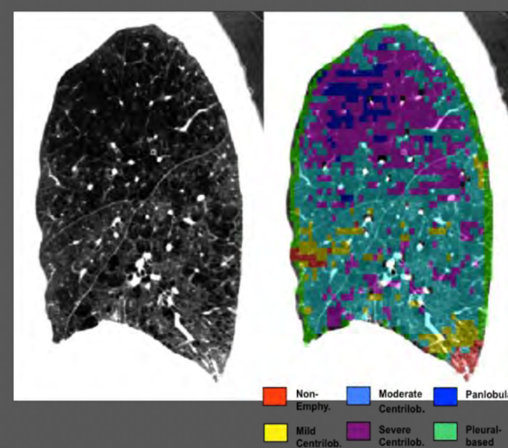
Emphysema grade vs survival:
model with LAA-950 and FEV1

	N Total (%)	N Deaths	Hazard Ratio	95% Confidence Interval		P Value
No emphysema	1080 (34%)	70 (6%)	Reference			
Trace CLE	541 (17%)	52 (10%)	1.22	0.85	1.75	0.28
Mild CLE	580 (18%)	79 (14%)	1.38	1.04	1.82	0.02
Moderate CLE	478 (15%)	99 (21%)	1.46	0.97	2.19	0.07
Confluent CLE	337 (11%)	143 (42%)	2.25	1.54	3.27	<.0001
Advanced destructive CLE	140 (4%)	51 (36%)	1.50	0.81	2.77	0.20
%LAA-950			1.01	1	1.02	0.045
FEV1			0.45	0.38	0.55	<.0001

Emphysema Subtypes by Local Histogram Analysis



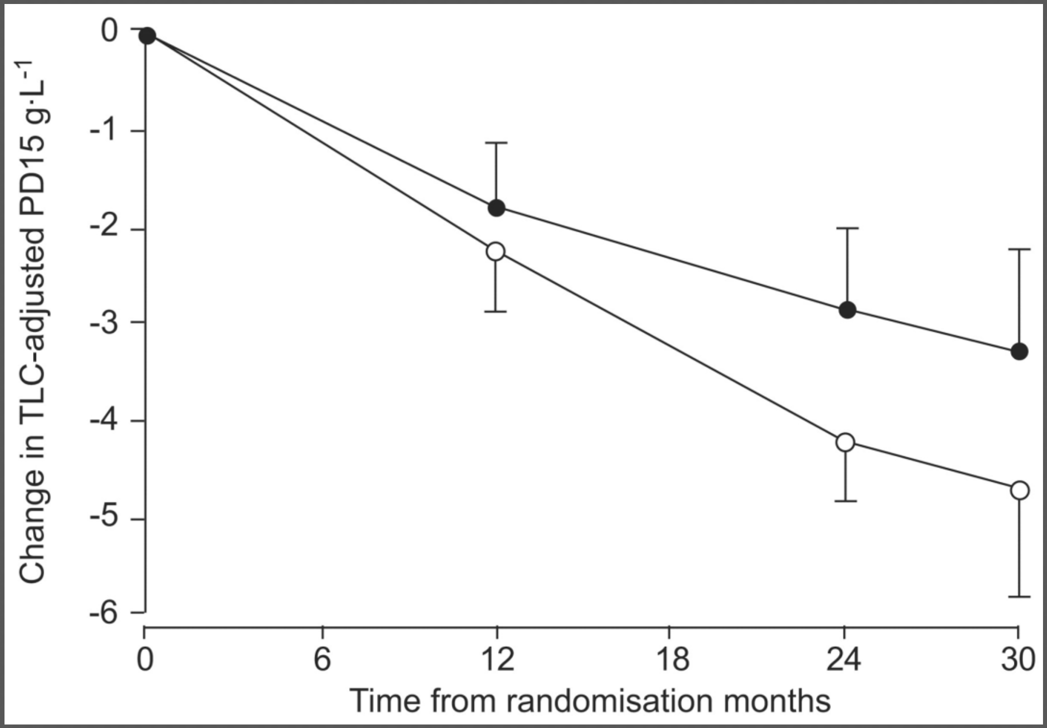




Castaldi et al. AJRCCM 2013:188; 1083-1090

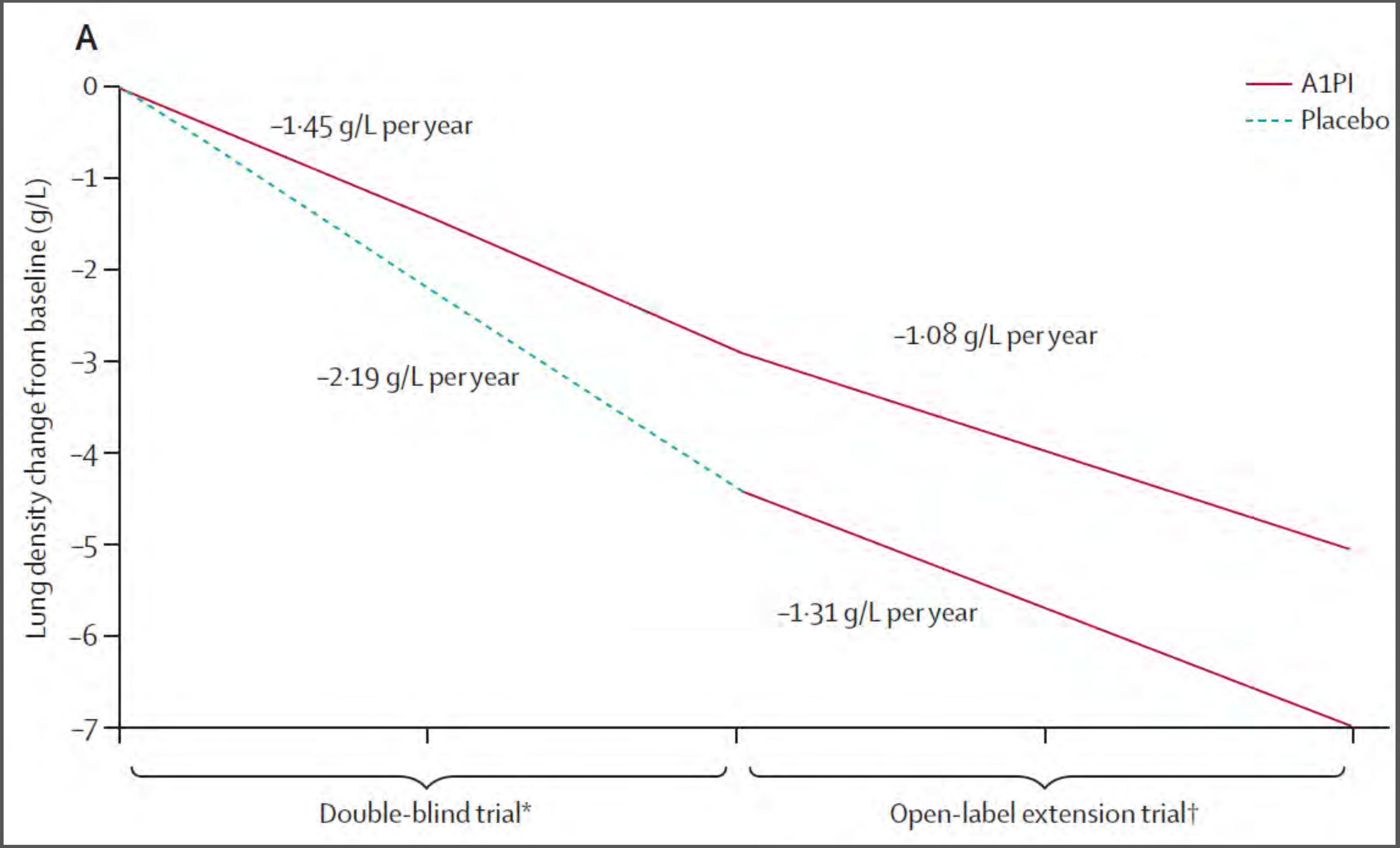
Longitudinal change

Longitudinal change in lung density: EXACTLE study of Alpha-1 antitrypsin deficiency



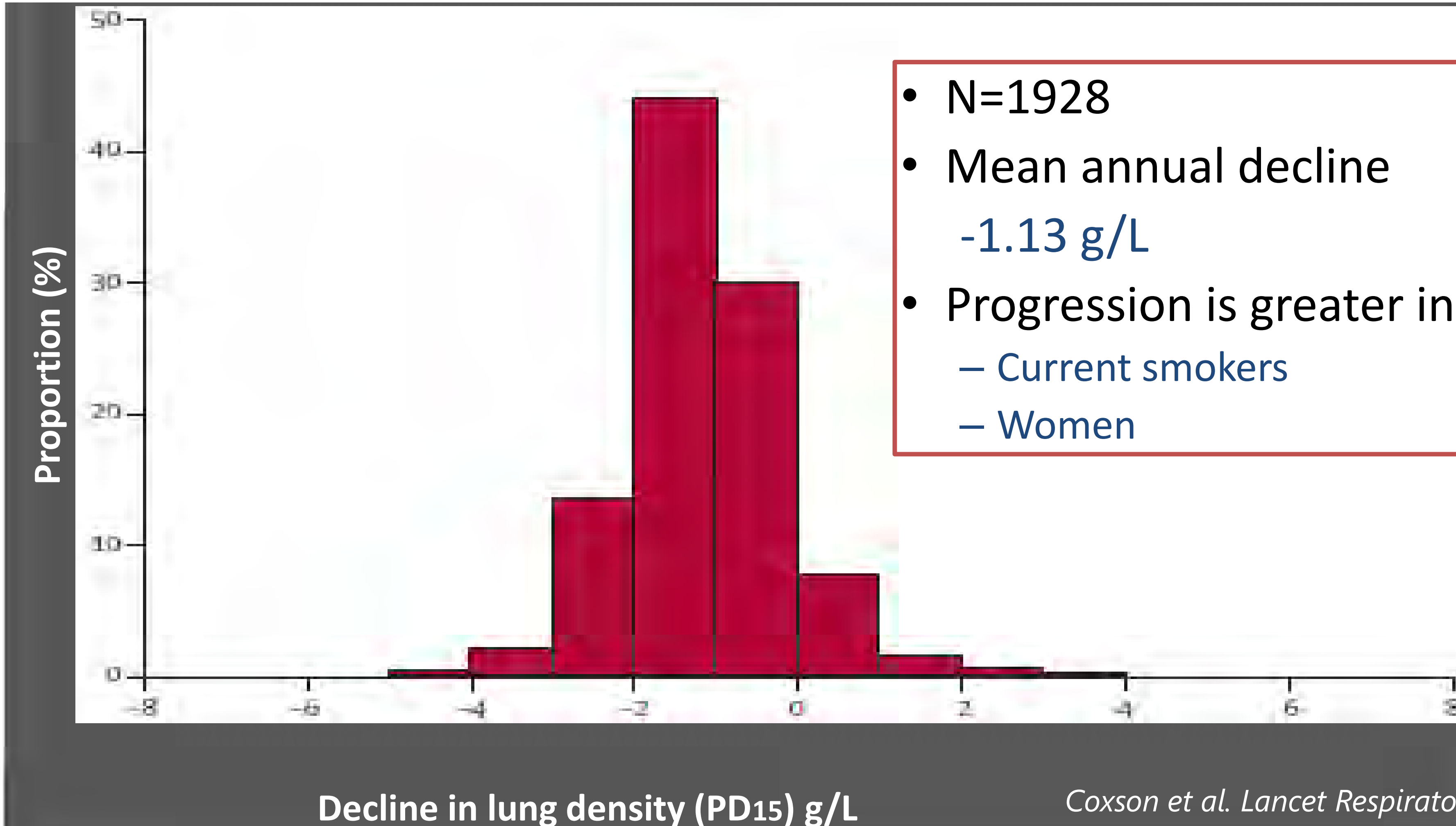
Dirksen et al. Eur Respir J. 2009;33(6):1345-53.

Longitudinal change in lung density: RAPID study of Alpha-1 antitrypsin deficiency



Chapman et al. Lancet 2015; 386: 360–68

Longitudinal change: ECLIPSE study



- N=1928
- Mean annual decline
  -1.13 g/L
- Progression is greater in:
  – Current smokers
  – Women

Coxson et al. Lancet Respiratory Medicine. 2013;1(2):129-36.

COPDGene:
Longitudinal change in emphysema parameters

	COPD	
Measurement	Value	95% CI
Lung Vol (L)	0.05	-0.02, 0.11
Log(LAA-950%)	0.13**	0.05, 0.22
MLD (HU)	-1.81	-3.98, 0.36
Perc15 (HU)	-3.41**	-5.04, -1.78
Volume-adjusted density (g/L)	-3.97**	-5.20, -2.73

Van Rikxoort et al. Manuscript in preparation

COPDGene:
Longitudinal change in emphysema parameters

	COPD		No COPD	
Measurement	Value	95% CI	Value	95% CI
Lung Vol (L)	0.05	-0.02, 0.11	0.07*	0.02, 0.13
Log(LAA-950%)	0.13**	0.05, 0.22	No fit	
MLD (HU)	-1.81	-3.98, 0.36	-3.73**	-5.93, -1.54
Perc15 (HU)	-3.41**	-5.04, -1.78	-2.38*	-3.88, -0.87
Volume-adjusted density (g/L)	-3.97**	-5.20, -2.73	-1.49**	-2.36, -0.62

Van Rikxoort et al. Manuscript in preparation

Longitudinal change in adjusted lung density

	Without FEV1 in model		
GOLD stage	Value	95% CI	p
PRISM	-2.96	-5.03, -0.90	0.005
0	-1.06	-2.02, -0.10	0.03
1	-3.16	-5.64, -0.69	0.01
2	-3.31	-4.97, -1.65	<.0001
3	-3.64	-6.05, -1.24	0.003
4	-7.58	-11.81, -3.34	0.0006

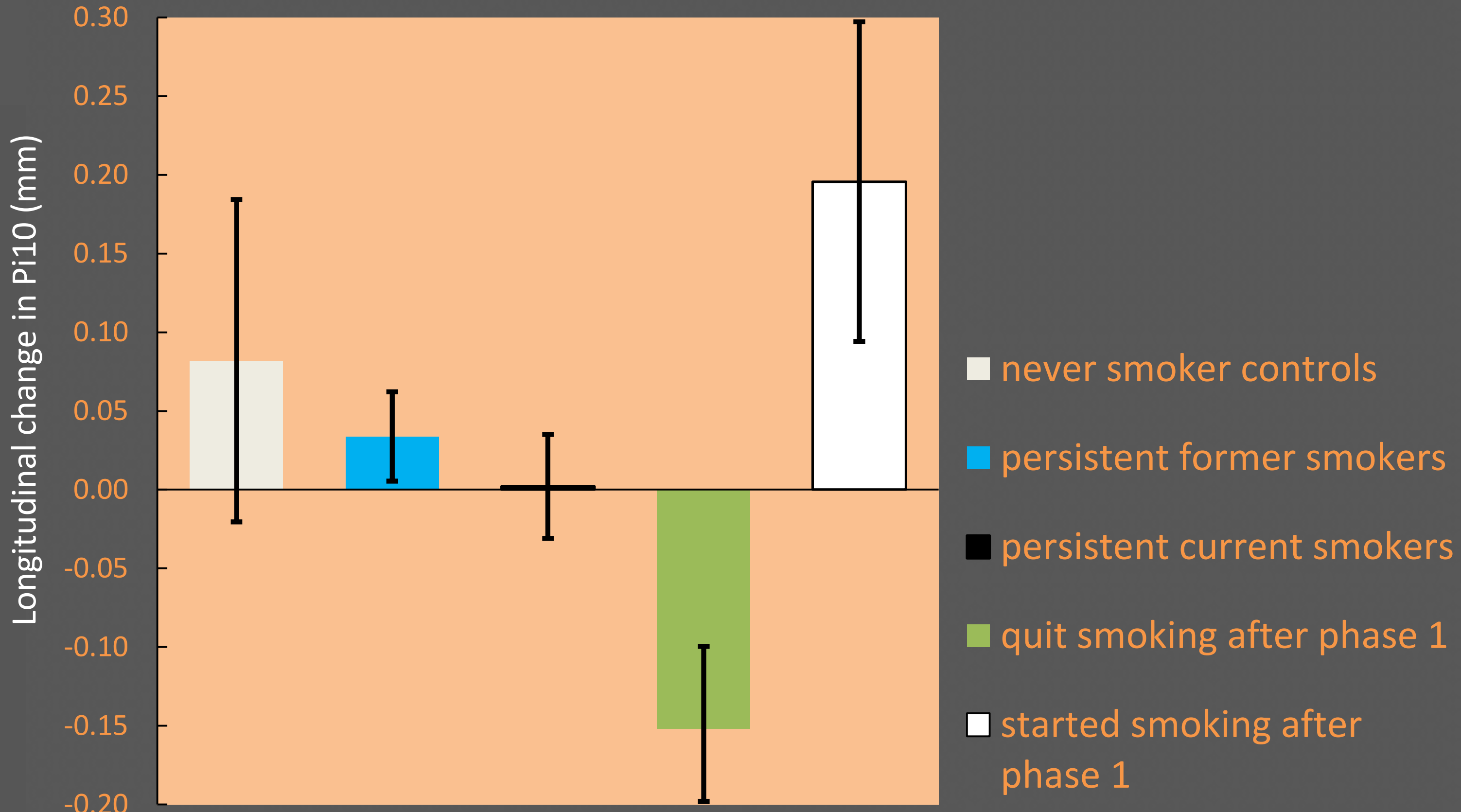
Van Rikxoort et al. Manuscript in preparation

Longitudinal change in adjusted lung density

	Without FEV1 in model			With FEV1 in model		
GOLD stage	Value	95% CI	p	Value	95% CI	p
PRISM	-2.96	-5.03, -0.90	0.005	-2.94	-5.02, -0.87	0.006
0	-1.06	-2.02, -0.10	0.03	-1.02	-1.98, -0.06	0.03
1	-3.16	-5.64, -0.69	0.01	-2.82	-5.36, -0.28	0.03
2	-3.31	-4.97, -1.65	<.0001	-2.58	-4.24, -0.92	0.002
3	-3.64	-6.05, -1.24	0.003	-3.21	-5.59, -0.82	0.009
4	-7.58	-11.81, -3.34	0.0006	-7.46	-11.70, -3.22	0.0008

Van Rikxoort et al. Manuscript in preparation

Change in Pi10 according to smoking status



J-P Charbonnier: manuscript in progress

Limitations of quantitative imaging

- Sources of variation
  - Inspired lung volume
  - Field of view
  - Scanner make and model
  - CT dose
  - Iterative reconstruction and other reconstruction techniques
- Software/workflow issues
- Need more understanding of normal subjects

Quantitative Imaging Biomarkers Alliance:
Standardizing measurement of emphysema progression

1. Calibration/ Periodic QA

- Standardized phantom
- Harmonization of technique

2. Acquisition

- Subject handling
  - Positioning
  - Breath-hold coaching
- Parameter settings
  - Coverage
  - Spatial resolution
  - Breath-hold time
  - CT dose

3. Reconstruction

- Kernel
- Slice thickness
- Interval
- Display field of view

4. Measurement

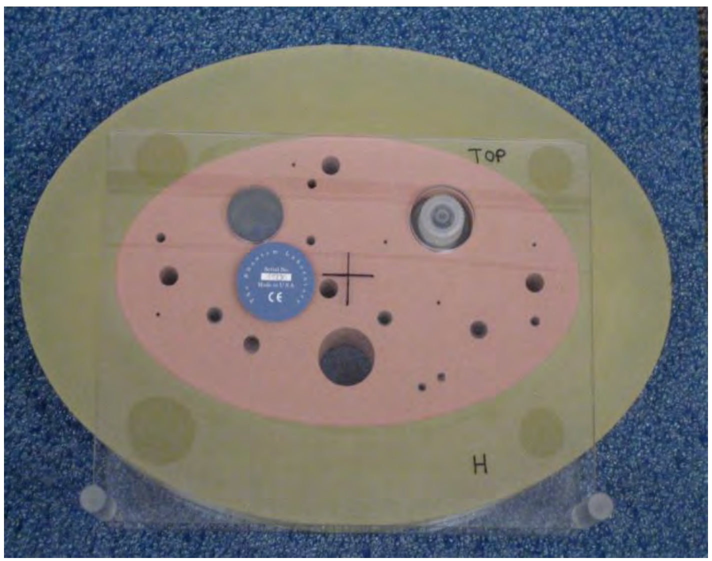
- Thoracic cavity segmentation
- Airway and blood vessel removal
- Image histogram
- Calculation of RA-950, Perc 15

5. Interpretation

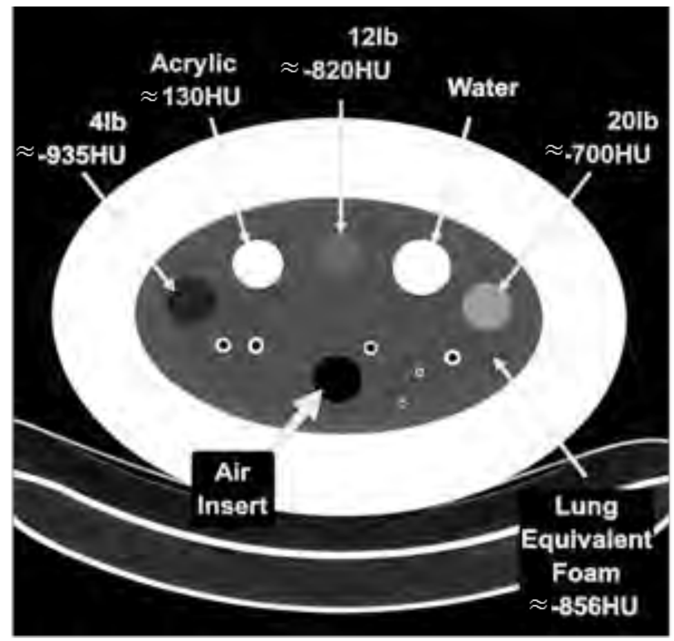
- Meaningful change?
- Clinical action?

Standardized Phantom: COPDGene

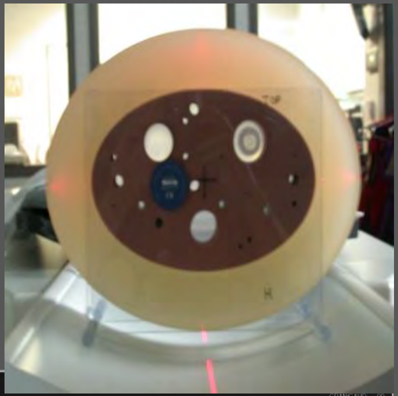
Original COPDGene phantom

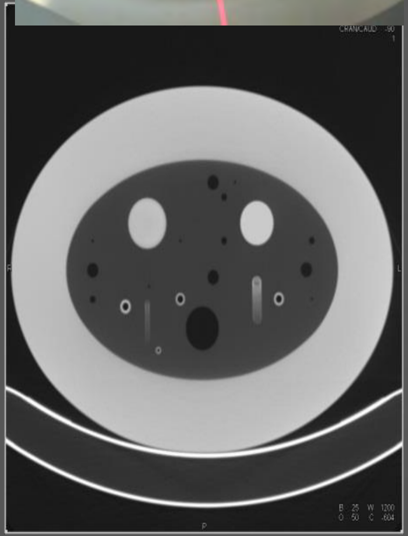


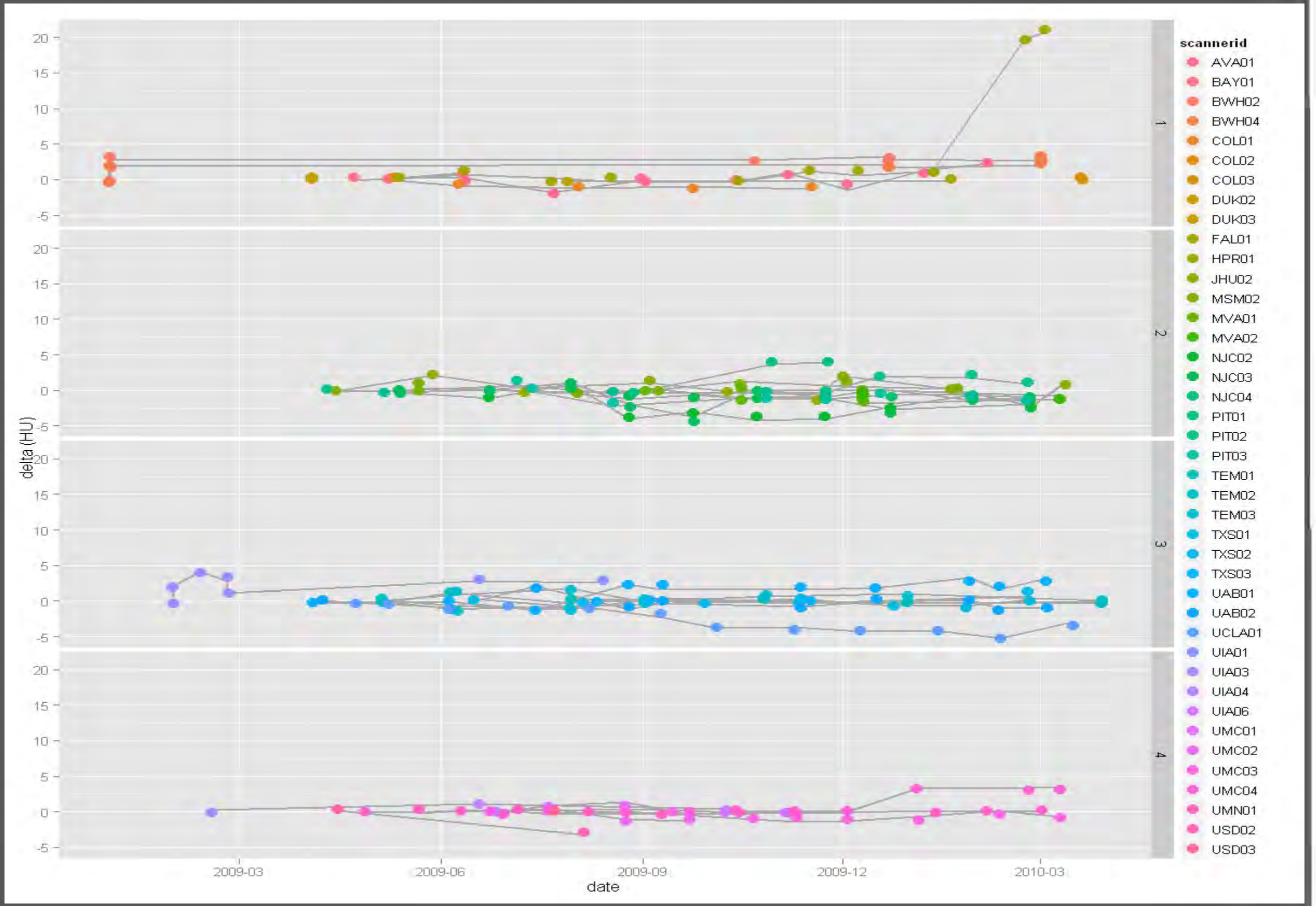
COPDGene Phantom with NIST-Calibrated foams



Standardized Phantom: COPDGene



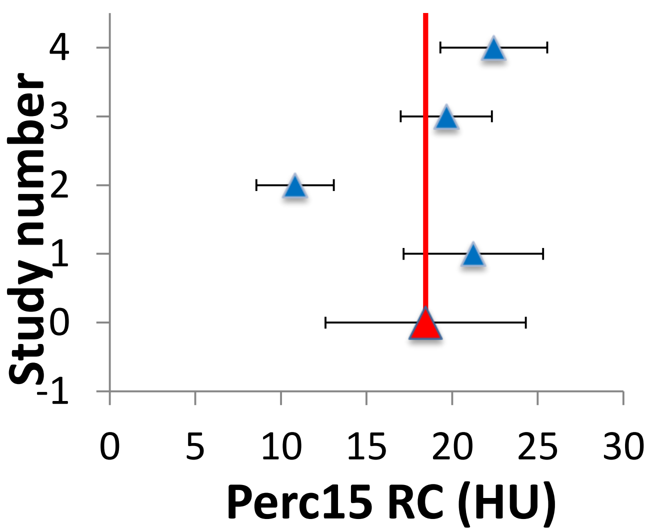




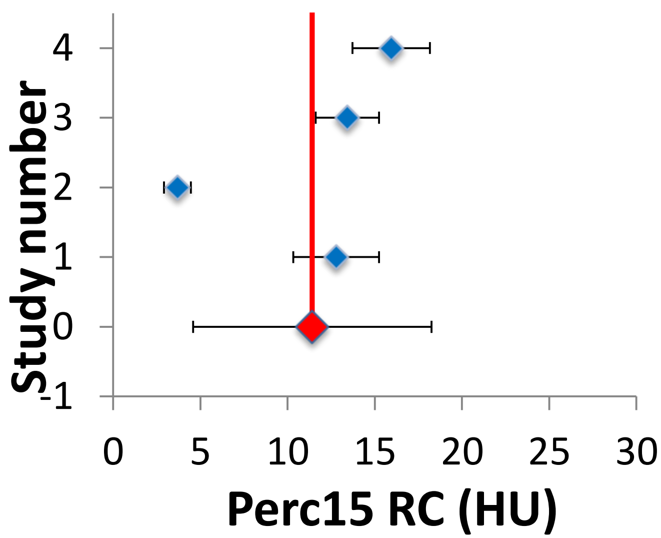
Sieren et al RSNA 2010

Perc 15: Meta-analysis of Reproducibility Studies
Forest plots of repeatability coefficient

Before Volume Adjustment

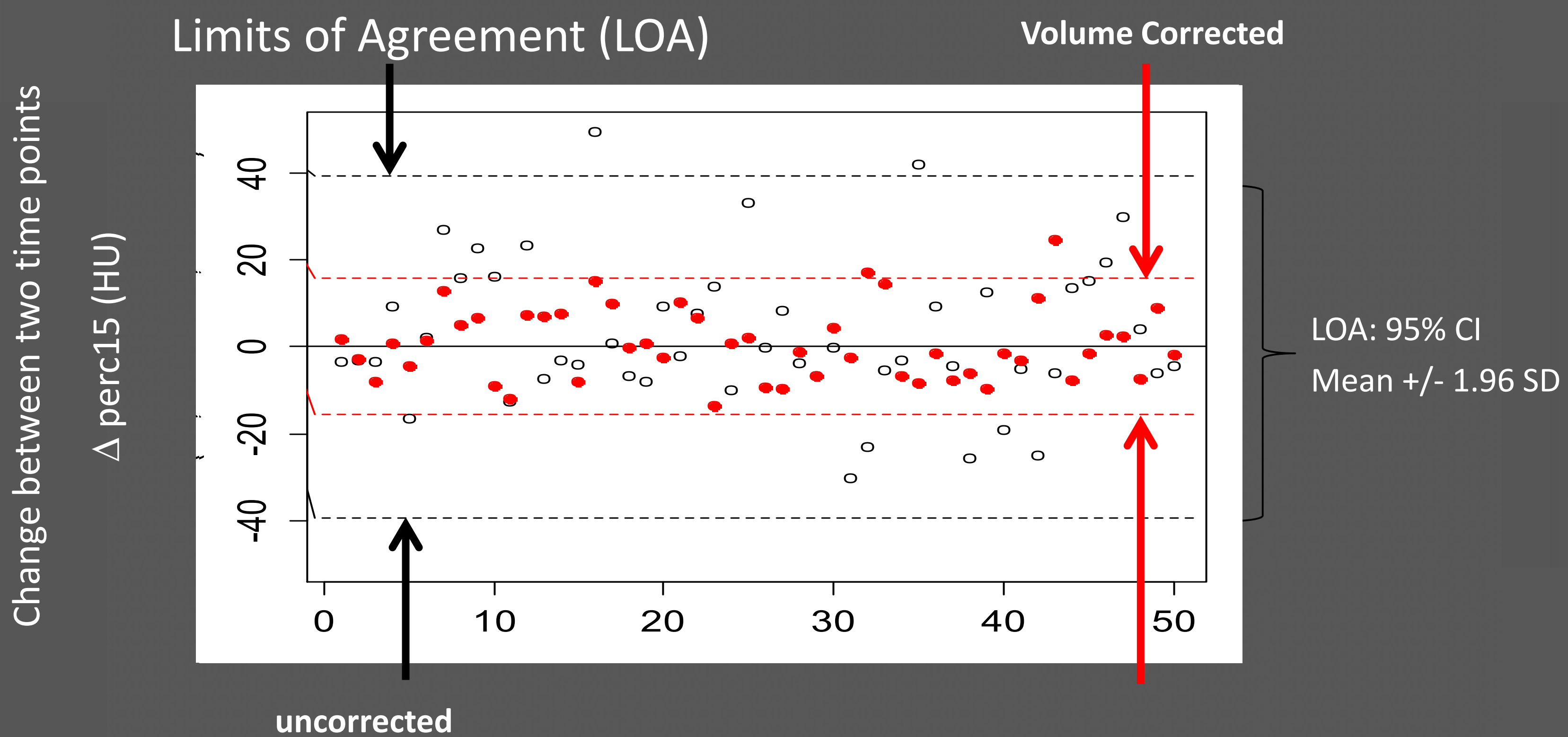


After Volume Adjustment



Courtesy: Sean Fain, PhD, Heather Chen-Meyer, PhD

Bland-Altman: Typical Result



Courtesy: Sean Fain, PhD, Heather Chen-Meyer, PhD

Conclusions of Meta-Analysis

- Negligible bias (< 0.5%, < 1.2 HU) for both measures.
- For RA-950 HU, the minimum threshold for real change is 3.7% **without** volume adjustment.
  - Insufficient studies at present to support a meta-analysis of RA-950 HU with VA.
- Volume adjustment should be considered to improve repeatability for longitudinal studies.
- For Perc15, the minimum threshold for real change is 11 HU **with** volume adjustment.

Courtesy: Sean Fain, PhD, Heather Chen-Meyer, PhD

Claims: Formal Statement

- Claim 1: **Without volume adjustment**, an increase in RA-950 HU of at least 3.7%, or a decrease in Perc15 of at least 18 HU, is required for detection of an increase in the extent of emphysema, with 95% confidence.

- Claim 2: **With volume adjustment**, a decrease in Perc15 of at least 11 HU is required for detection of an increase in the extent of emphysema, with 95% probability.

Courtesy: Sean Fain, PhD

These claims hold when:

- The thoracic cavity is fully represented in the field of view and readily segmented from the chest wall.
- Contrast agent is not present. Contrast agents shall not be used in the CT assessment of parenchymal lung density.
- The difference in lung inflation is smaller than 10% of baseline lung inflation.
- The lung parenchyma is sufficiently clear and uncorrupted by motion due to loss of breath-hold (cardiac motion is acceptable and unavoidable).
- Voxel noise, spatial resolution, and CT dose meet the specifications described in Section 3.4.2.

Summary

- Emphysema densitometry
  - Volume adjusted lung density is most robust in patients with COPD; assessment of patients without COPD is more complex
  - Longitudinal progression may be largely independent of FEV1 change, and is more severe in subjects with more advanced GOLD stages
- Visual scoring of emphysema, a novel biomarker, correlates with mortality
- Respiratory bronchiolitis may be detectable by textural analysis
- Air trapping is an important index of airway obstruction
- Total airway count is a potentially important marker of COPD, and predictor of lung function decline
- QIBA profile is almost ready for circulation
  - Much work remains to improve reproducibility and reduce inter-scanner variability

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