



Update on QIBA CT Lung Density Profile and the Relationship Between Lung Density and Lung Cancer

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¹Imbio, LLC; ²University of Michigan; ³University of Wisconsin; ⁴National Jewish Health; ⁵Ryerson University; ⁶Siemens; ⁷Toshiba; ⁸NIST

RSNA QIBA: Quantitative Imaging Biomarker Alliance

- **QIBA mission**

- “QIBA seeks to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, sites, patients and time.”

- **Three steps of the QIBA process**

- Define the clinical question and proposed biomarker.
- Produce the protocol and profile.
- Profile validation, disseminate and maintenance.

- **Four modality-based Coordinating Committees:**

- Q-CT, Q-MR, Q-NM and Q-US.

- **Nineteen Biomarker Committees, 4 within CT:**

- CT: Angiography, volumetry and small lung nodules, **lung density**

Lung Density (aka densitometry)

- An “imaging biomarker of emphysema”



Chest

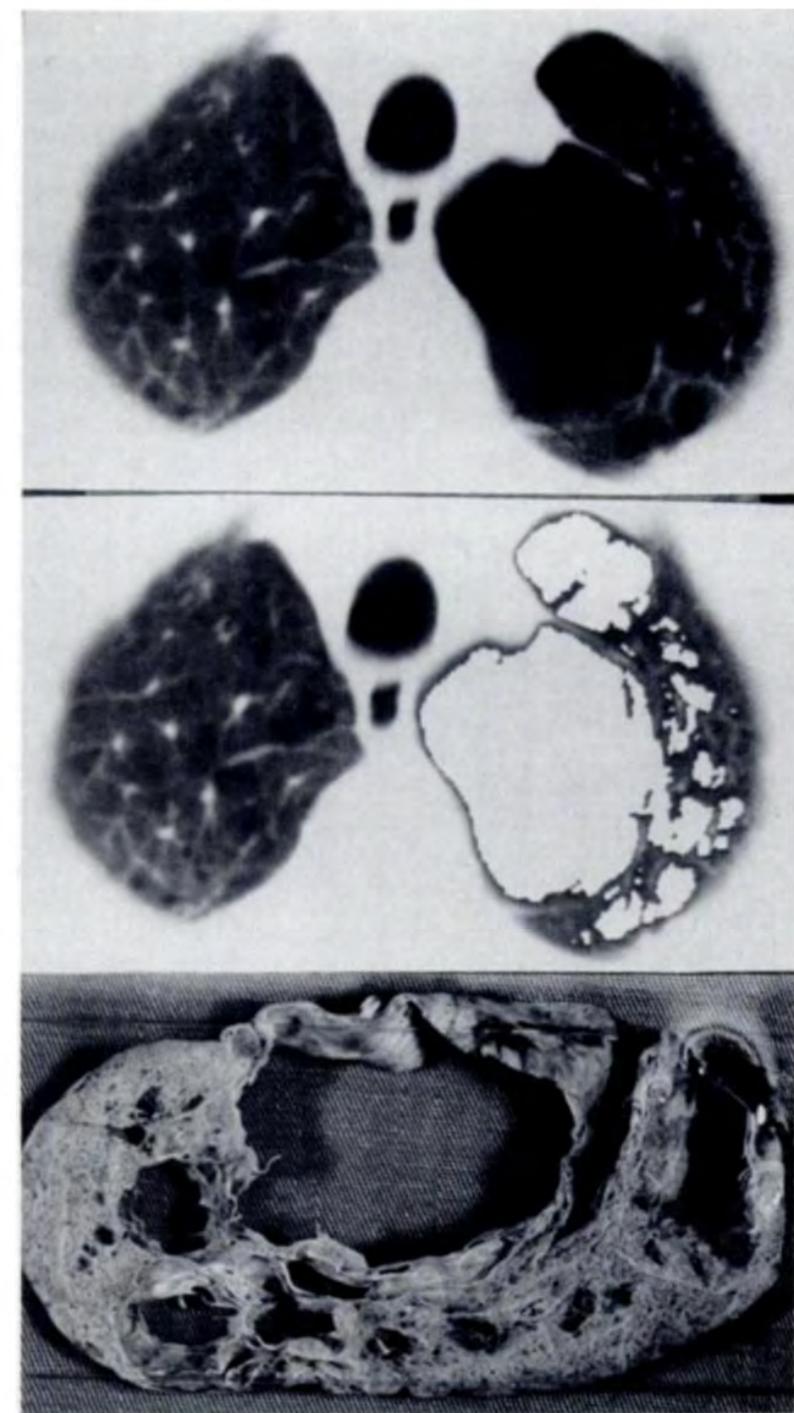
Volume 94, Issue 4, October 1988, Pages 782-787



“Density Mask”: An Objective Method to Quantitate Emphysema Using Computed Tomography

Nestor L. Müller M.D., Ph.D., F.C.C.P. ^{a, †}, Catherine A. Staples M.D. ^{a, †}, Roberta R. Miller M.D., F.C.C.P. [‡], Raja T. Abboud M.D., F.C.C.P. ^{a, §}

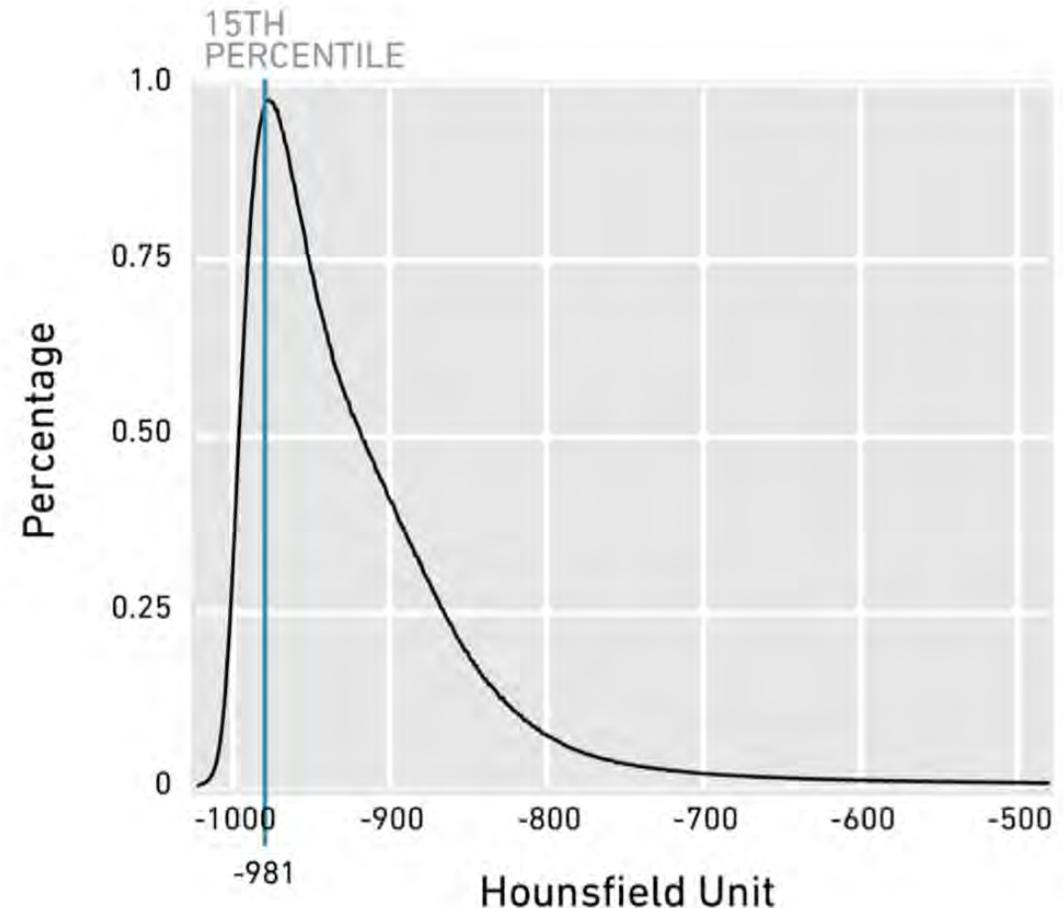
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Lung Density



- Low attenuation area (LAA or RA): % voxels in the lung less than a certain HU.
 - Easy to interpret/visualize.
 - Usually -950 HU
- Perc15. HU value corresponding to the 15th percentile.
 - Real number, typically normally distributed within groups.



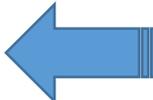
Lung Density: Non-biological sources of variability

- Tube current (dose)
- Reconstruction kernel
- Slice thickness
- Scanner make and model
- Analysis software
- **Breath-hold volumes:**
 - **Most important source of variability – difficult to control**
 - **Ventilation Adjustment techniques**

CT Lung Density Biomarker Committee

- Qualify and standardize emphysema biomarkers LAA-950 HU, and Perc15
- Identify **Claims** that estimate achievable bias and repeatability
- Author a Consensus **Profile** document that defines minimum best practices to achieve the stated claims.
- Identify and implement **Ground Work** projects to resolve open issues

Stage	Description
Biomarker Committee (BC) Drafting and Review	The Profile specifies requirements and guidance on best practices to achieve the performance stated in the claims.
Public Comment and Review	Stakeholders* in the public domain offer constructive comment that is formally address by the BC.
Field Testing and Technical Confirmation	Profile is made available for testing at more than one facility, systems, and persons and is understood and shown to meet the specifications.
Claim Confirmed	Overall performance was determined and claim was achieved.

 We are in the public review process now!

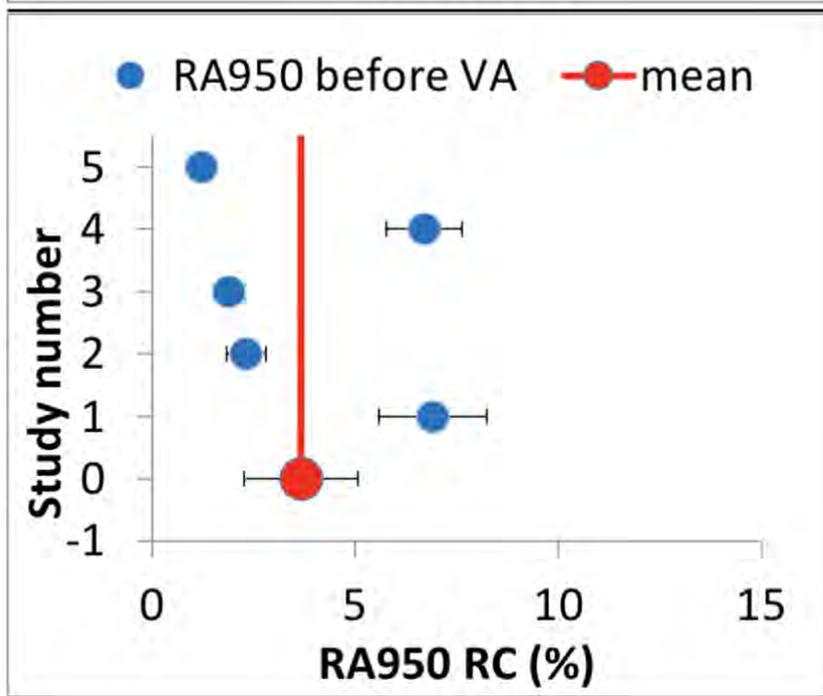
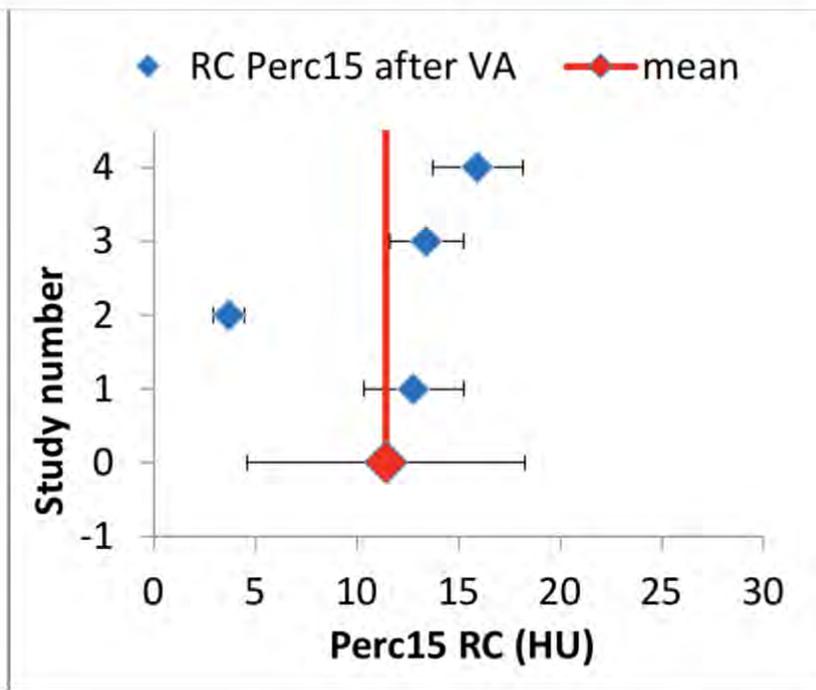
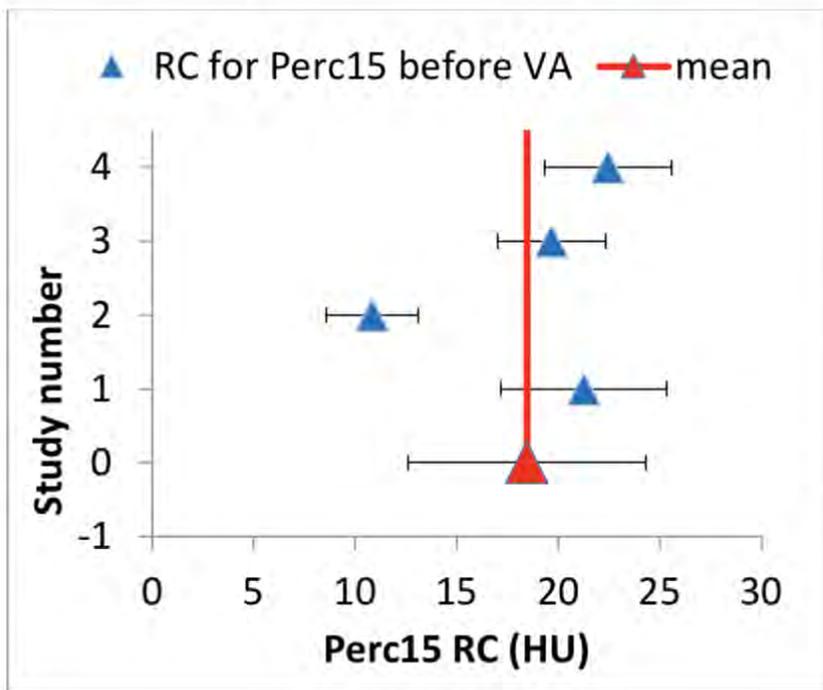
*Stakeholders include academic, government, commercial partners: identify potential strategies for error mitigation and collaborate on hardware, software and image acquisition solutions

Claims: Formal Statement

- Claim 1: **Without volume adjustment**, an increase in LAA-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.

Claims established via Meta-Analysis

- 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.
- For Perc15, the minimum threshold for real change is 11 HU **with** volume adjustment.
- Negligible bias ($< 0.5\%$, < 1.2 HU) for both measures.



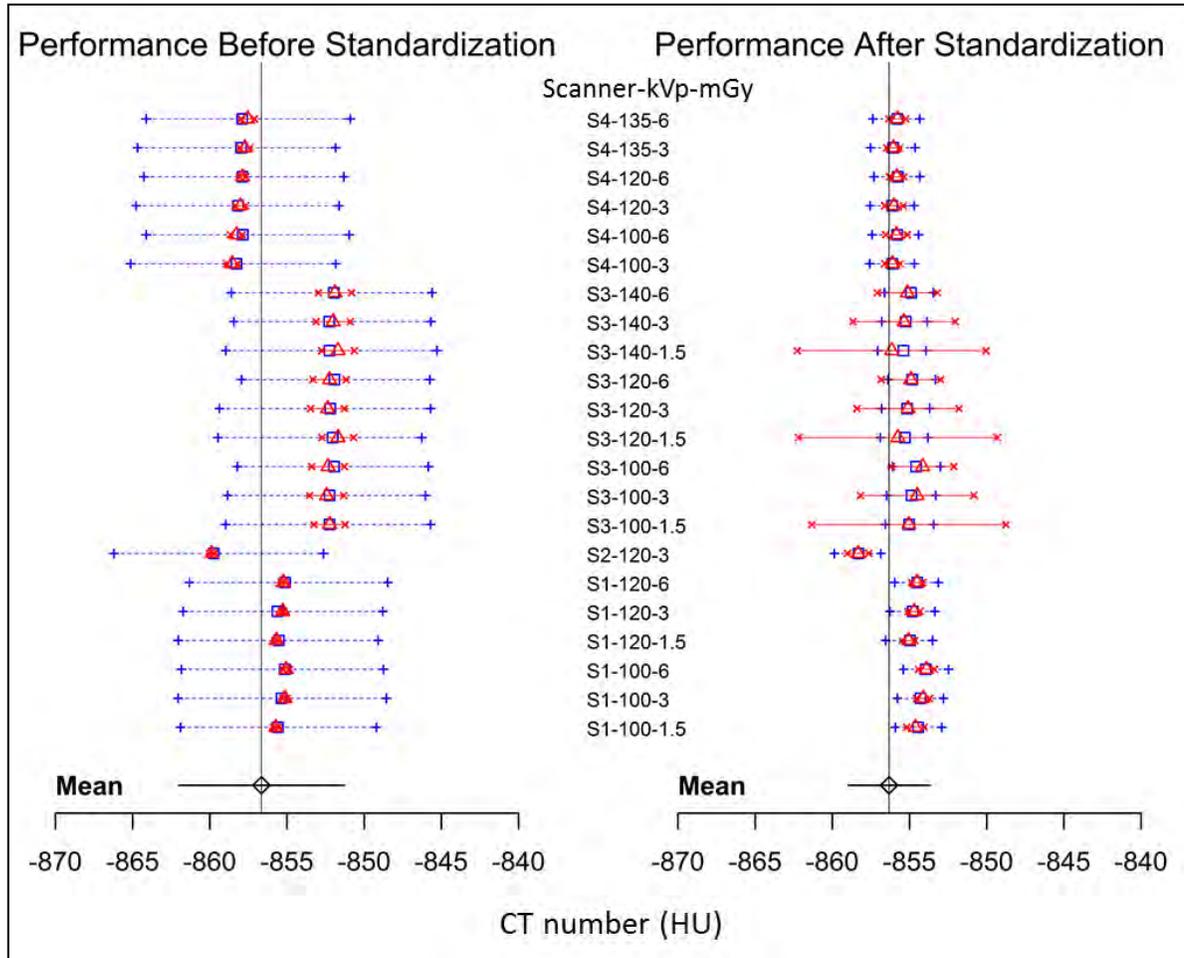
Refining Claims

- Need more repeatability studies with and without volume adjustment to support the LAA-950 HU measure.
- Severe asthma research program (SARP) repeatability data set: N = 30 scans performed at UW-Madison
- SPIROMICS has 92 scans of COPD patients with a 30-day interval between scans. Results will be added once published.

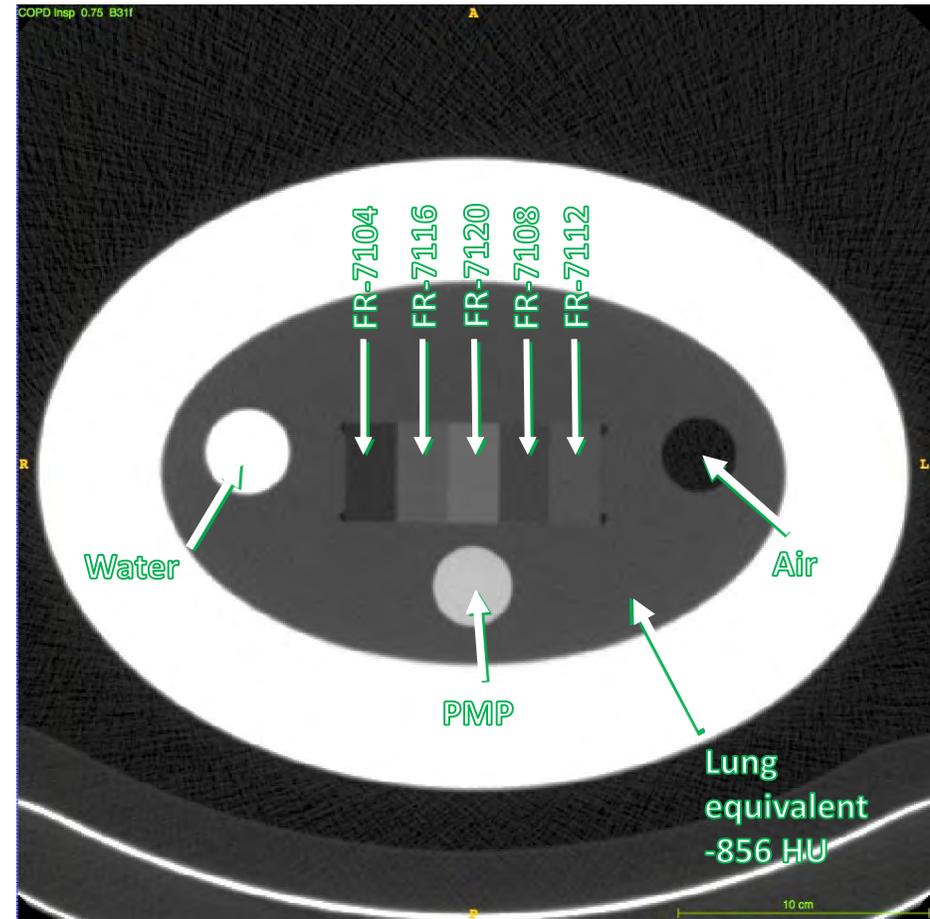
Ground work projects

- Harmonization of CT Hounsfield unit values across scanner makes and models.
- Inter-software reproducibility.
- Low-dose vs full-dose.

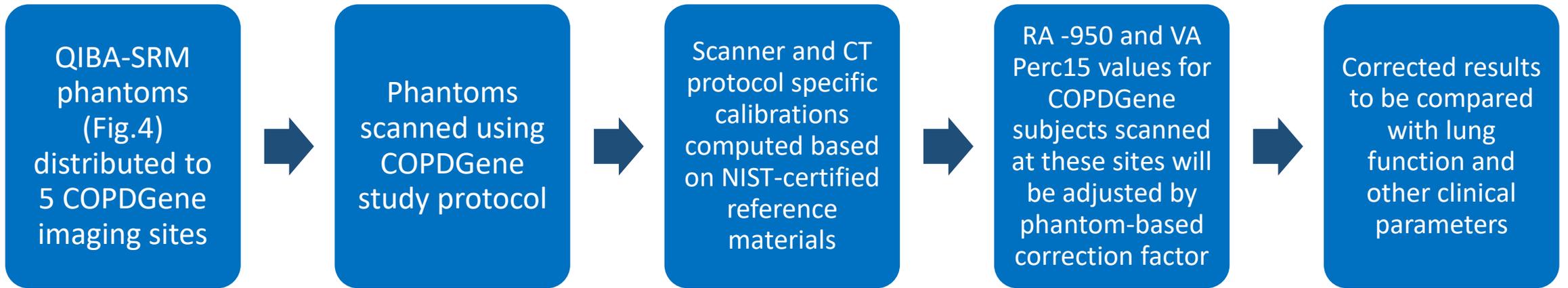
QIBA-SRM Phantom Development and Testing



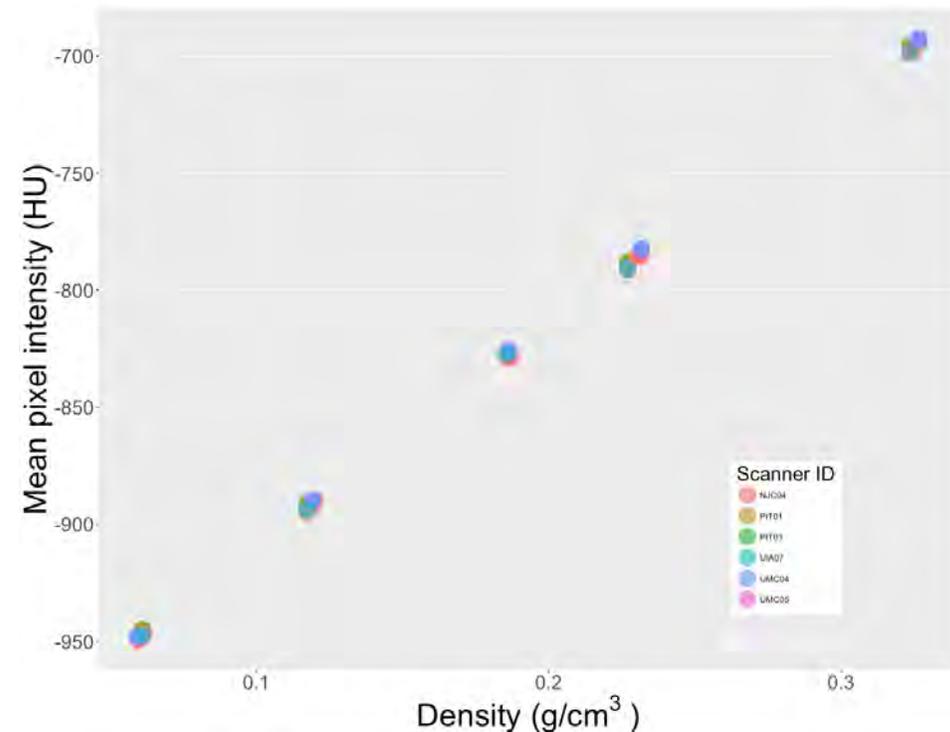
Chen-Mayer, HH, et al. "Standardizing CT lung density measure across scanner manufacturers." Medical physics 44.3 (2017): 974-985.



General Plastics, FR-7104, 7108, 7112, 7116 and 7120 – last two digits represent nominal density in lb/ft³

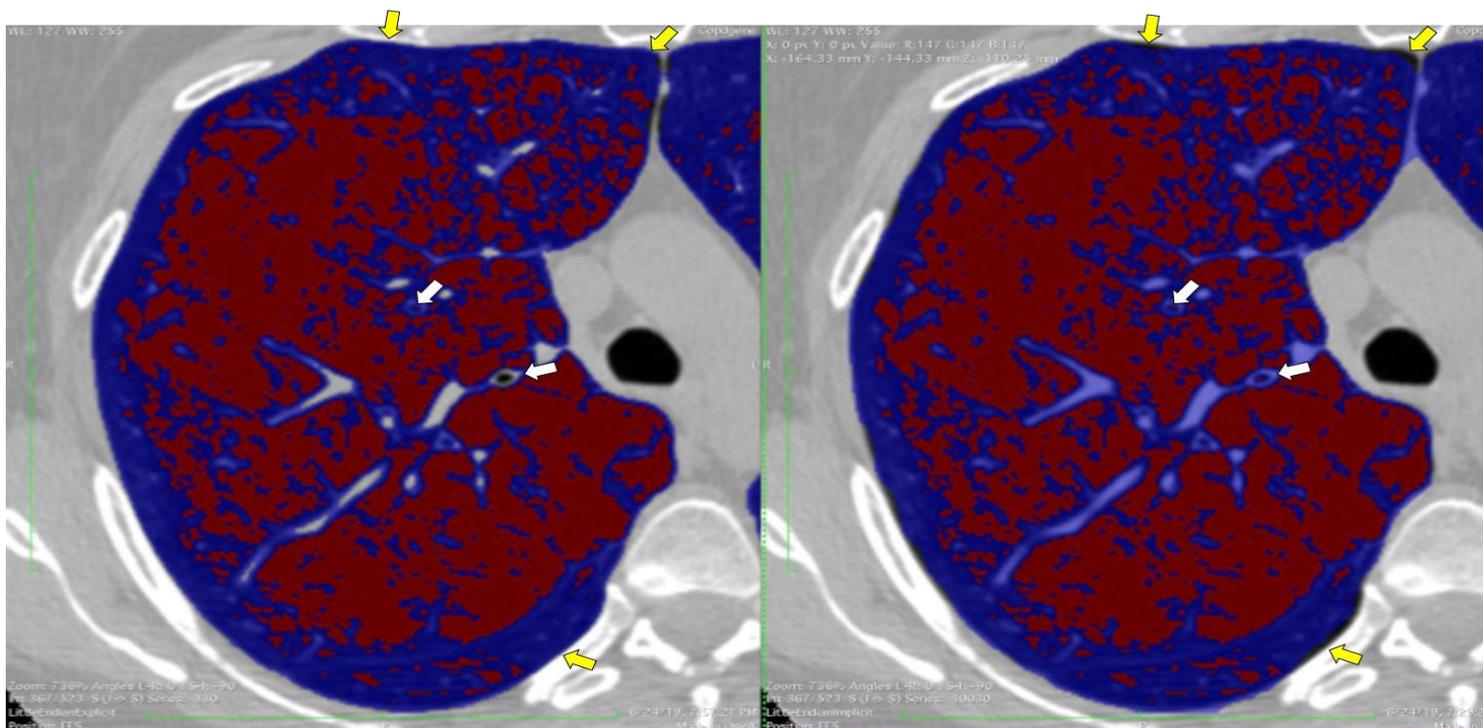


Scatterplot of known physical densities versus mean HU value in scans obtained at several COPD Gene imaging sites. Mean pixel intensities within NIST-certified foam materials in QIBA-SRM phantoms provide data for calculation of scanner-specific correction factors.



Inter-software reproducibility study

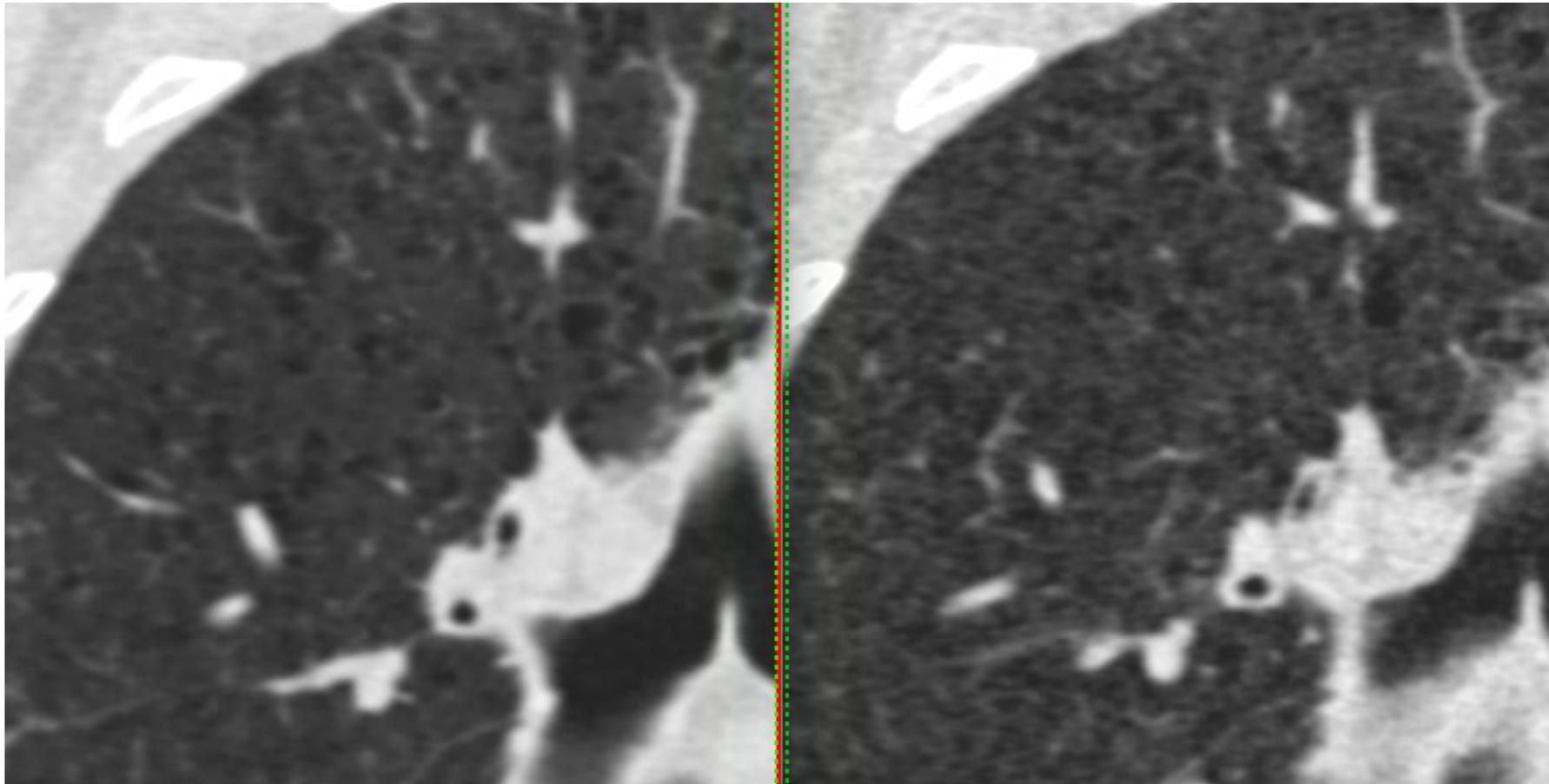
- 4 academic groups and 4 commercial software vendors.
- 50 subjects from COPDGene, 10 from each GOLD status.
- 100 total scans, 50 full-dose and 50 low-dose.

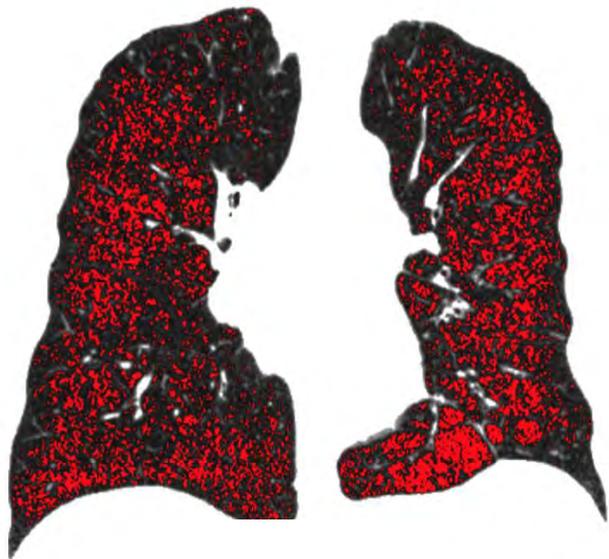


Inter-software reproducibility study

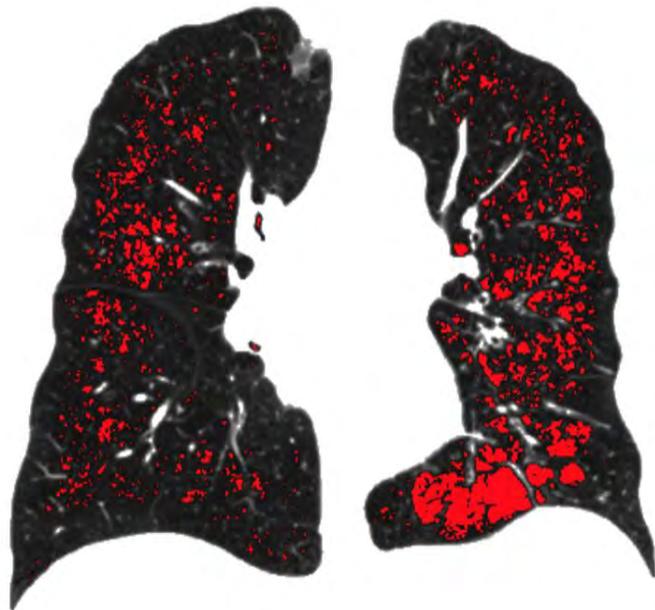
- Inter-software reproducibility coefficient (RDC) was:
 - 0.35L lung volume.
 - 1.2% for LAA.
 - 1.8 HU for Perc15.
 - About 1 order of magnitude lower than repeatability RDC
- All software investigated had an intra-software RDC of 0.

Full-dose -> low-dose

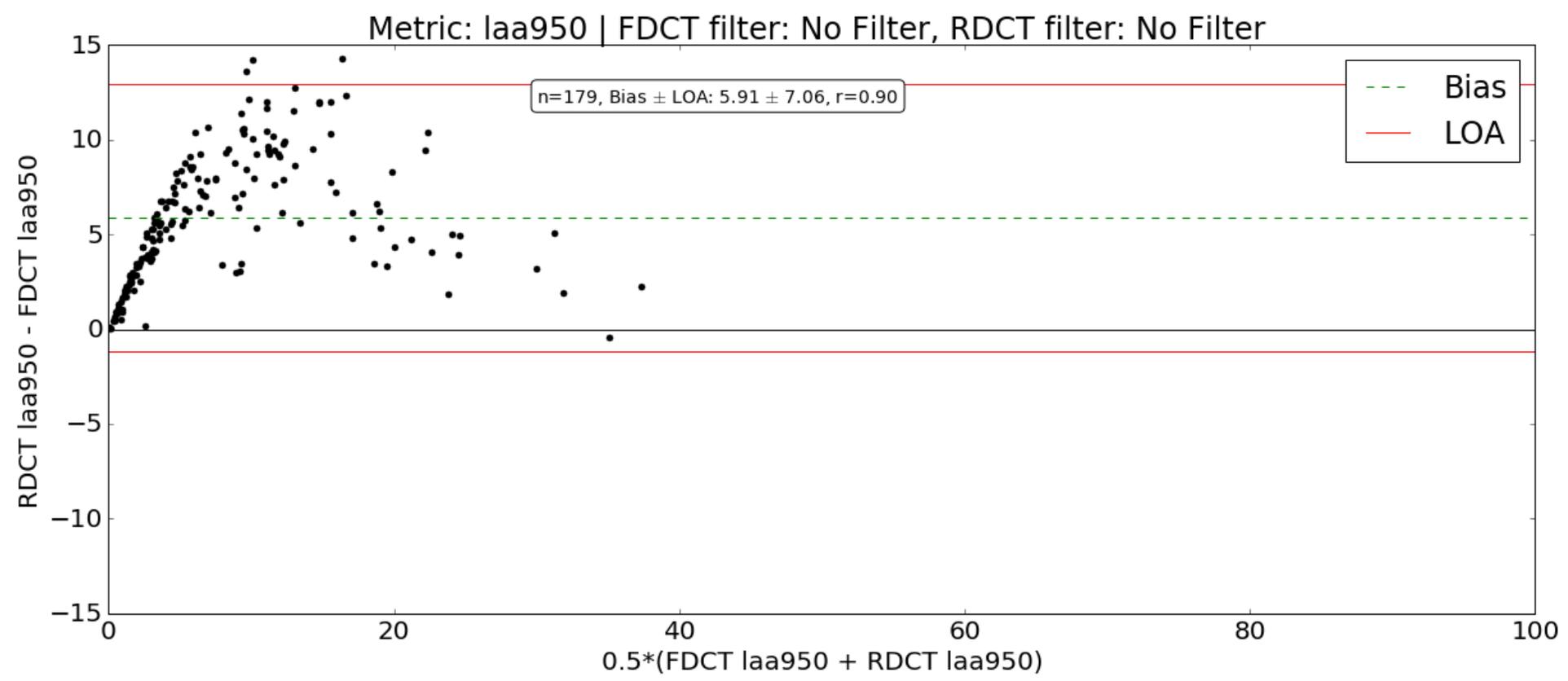




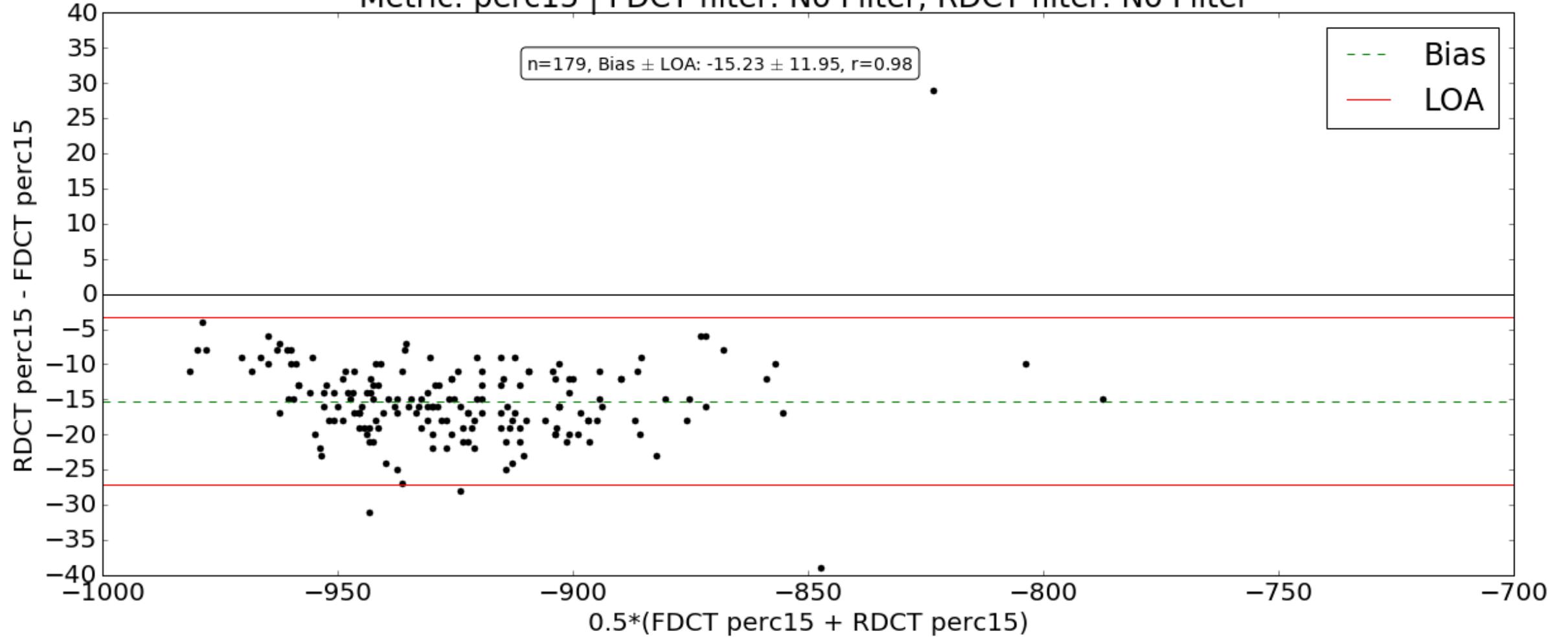
RDCT:17%

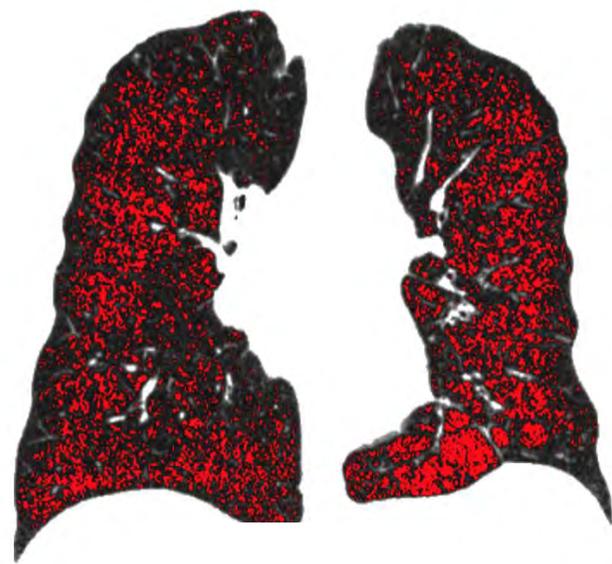


FDCT: 7%

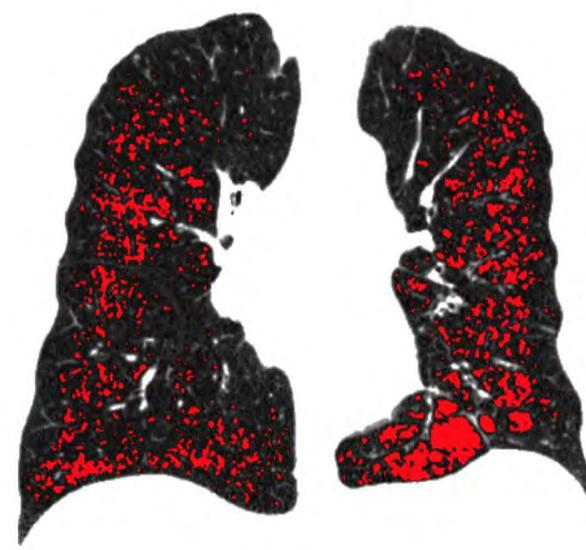
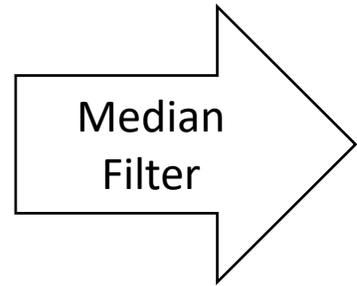


Metric: perc15 | FDCT filter: No Filter, RDCT filter: No Filter

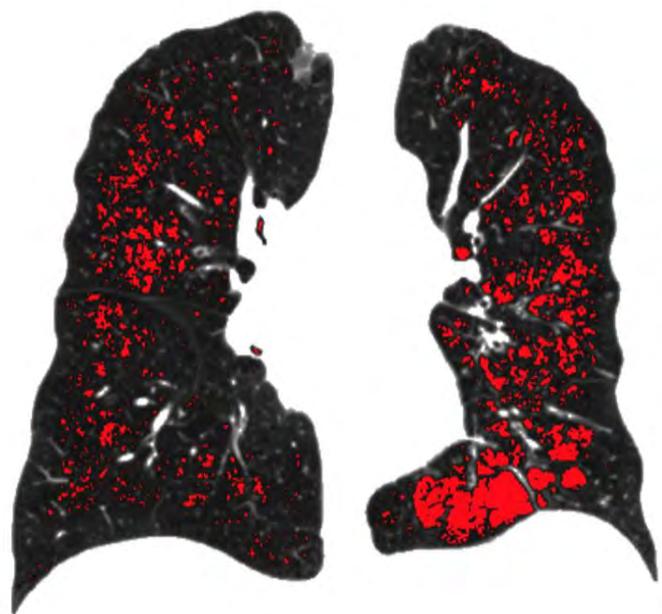




RDCT:17%

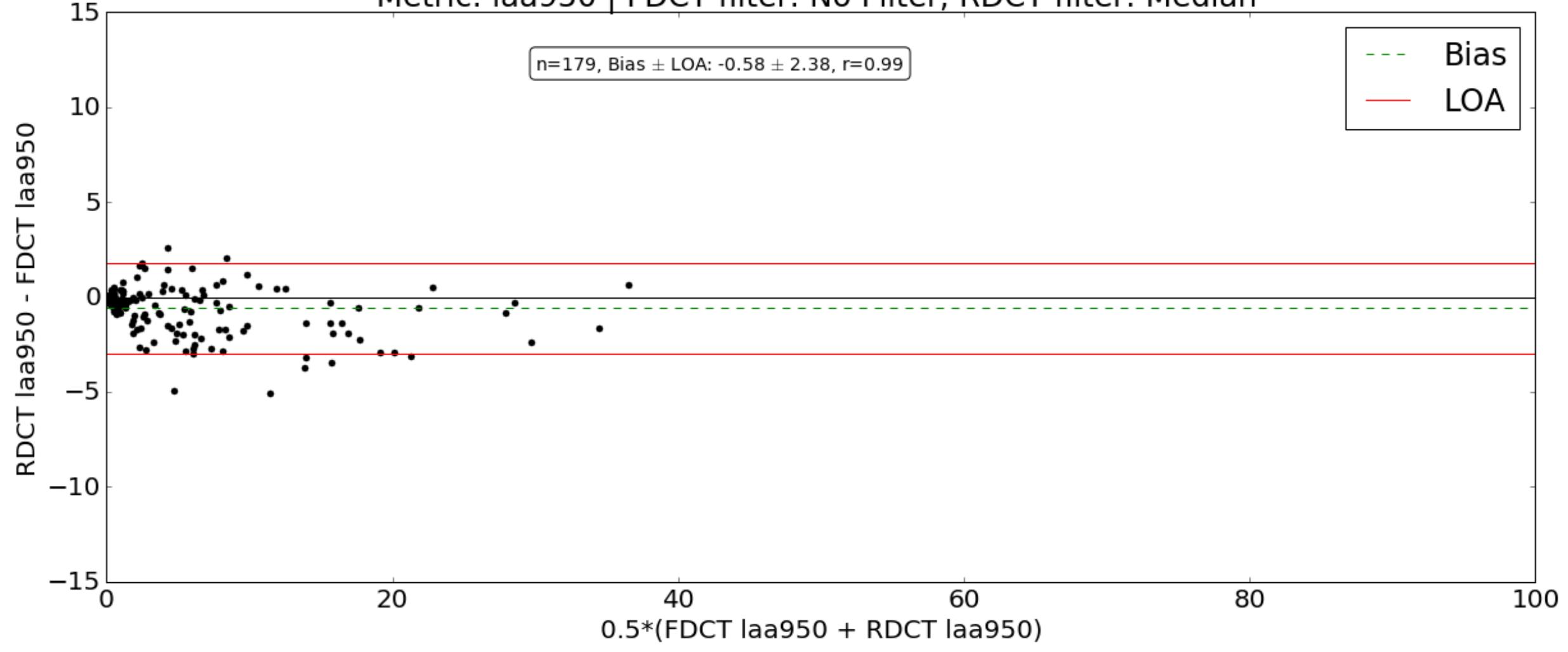


RDCT, Median Filter:9%

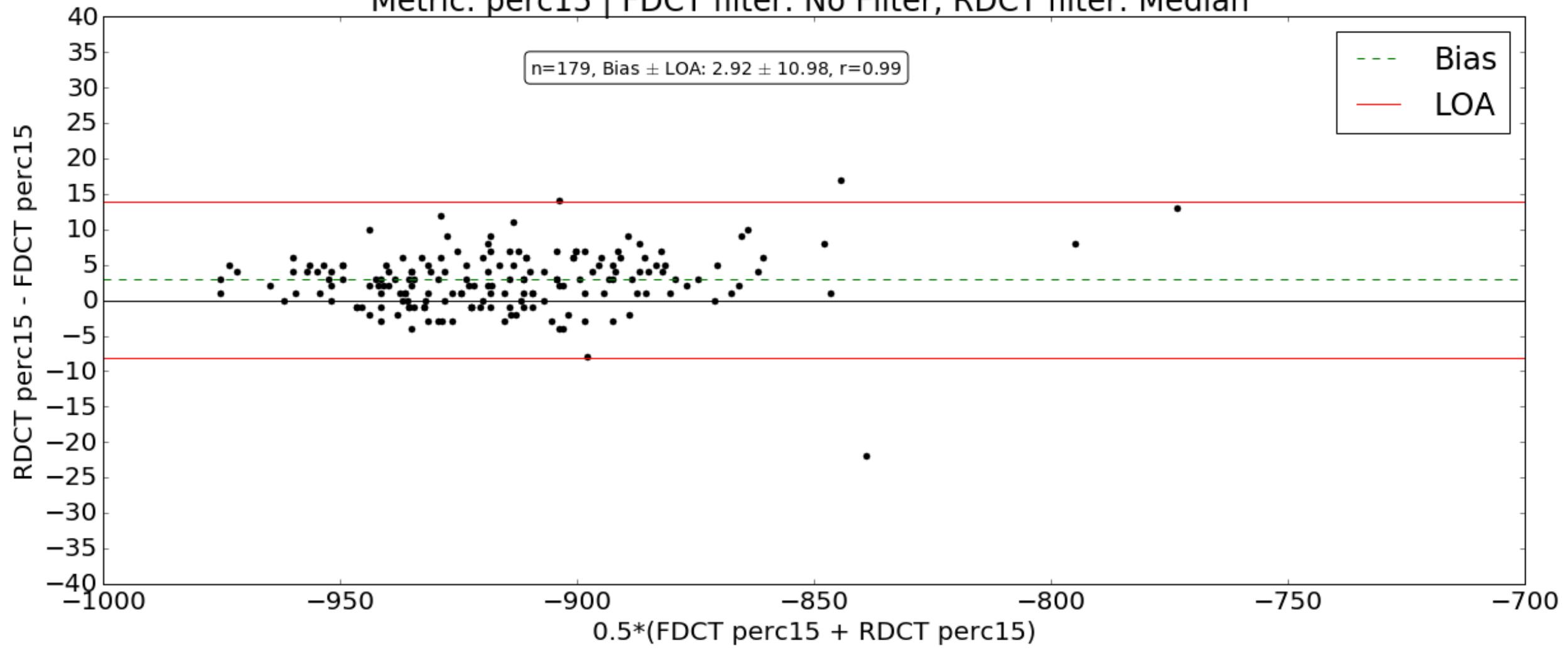


FDCT: 7%

Metric: laa950 | FDCT filter: No Filter, RDCT filter: Median



Metric: perc15 | FDCT filter: No Filter, RDCT filter: Median



Ongoing, or on the Horizon

- Next biomarkers for qualification?
 - COPD
 - Airway analysis
 - Fissure completeness
 - Gas-trapping
 - Deep learning?
 - Other
 - Fibrosis
 - CAC
 - BMD
 - Body composition
- Refining claims as repeatability studies become available...
 - We need more repeatability data.
 - Retrospective data from LCS programs in US?
- CBQC

CBQC

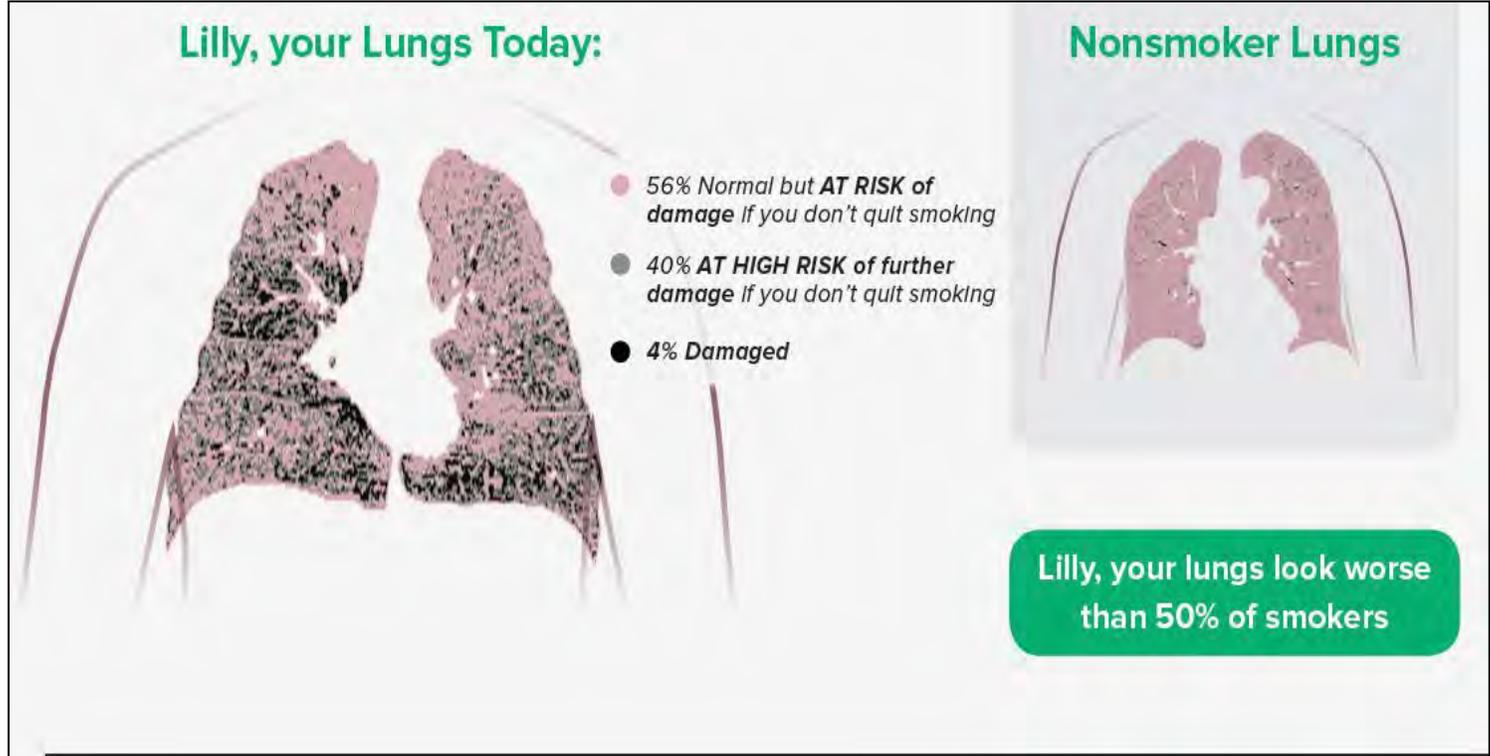


- FDA: CDER Biomarker Qualification Program.
 - Support outreach to stakeholders for the identification and development of new biomarkers
 - Provide a framework for the review of biomarkers for use in regulatory decision-making
 - Qualify biomarkers for specific contexts of use that address specified drug development needs
- COPD Biomarkers Qualification Consortium.
- Currently working on a letter of intent.
- “The rate of decrease in lung density (rate of loss or remodeling of lung tissue) on serial assessment will be used as an outcome to objectively measure disease progression and in clinical trials, the effect of therapy on that progression. “
- Validating using Perc15 progression as a predictor of mortality.

Lung Density for Smoking Cessation

 **Lilly's CT Lung Health Report**
CT Scan Performed on 6/30/2017

Name: Lilly Doe
Sex: Female
Patient ID: 11269
Age: 60



Lilly, you have an excellent opportunity to quit smoking now before things get worse:
Because of your lung health and smoking status you are up to...

- 12%** MORE LIKELY TO DIE in the next six years than a nonsmoker.
- 4X** MORE LIKELY TO HAVE A HEART ATTACK.
- 9%** MORE LIKELY OF BEING DIAGNOSED WITH LUNG CANCER in 5 years.
- 2X** MORE LIKELY TO HAVE A STROKE.

Lilly, you have an excellent opportunity to quit smoking now before things get worse:
Because of your lung health and smoking status you are up to...

- 12%** MORE LIKELY TO DIE in the next six years than a nonsmoker.
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- 9%** MORE LIKELY OF BEING DIAGNOSED WITH LUNG CANCER in 5 years.
- 2X** MORE LIKELY TO HAVE A STROKE.

Lilly, your body starts healing the minute you quit smoking.



Emphysema detected on computed tomography and risk of lung cancer: A systematic review and meta-analysis

Benjamin M. Smith ^a  , Lancelot Pinto ^a , Nicole Ezer ^a , Nicola Sverzellati ^b , Shigeo Muro ^c , Kevin Schwartzman ^a 

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<https://doi.org/10.1016/j.lungcan.2012.02.019>

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Of 187 citations, 7 were included in the qualitative synthesis and 5 in the meta-analysis. Three studies assessing emphysema visually observed an association with lung cancer, independent of smoking history and airflow obstruction. Three studies using [densitometry](#) to detect emphysema found no association with lung cancer.

Conclusion

Systematic literature review shows emphysema detected visually on CT to be independently associated with increased odds of lung cancer. This association did not hold with automated emphysema detection.

Why no relationship found?

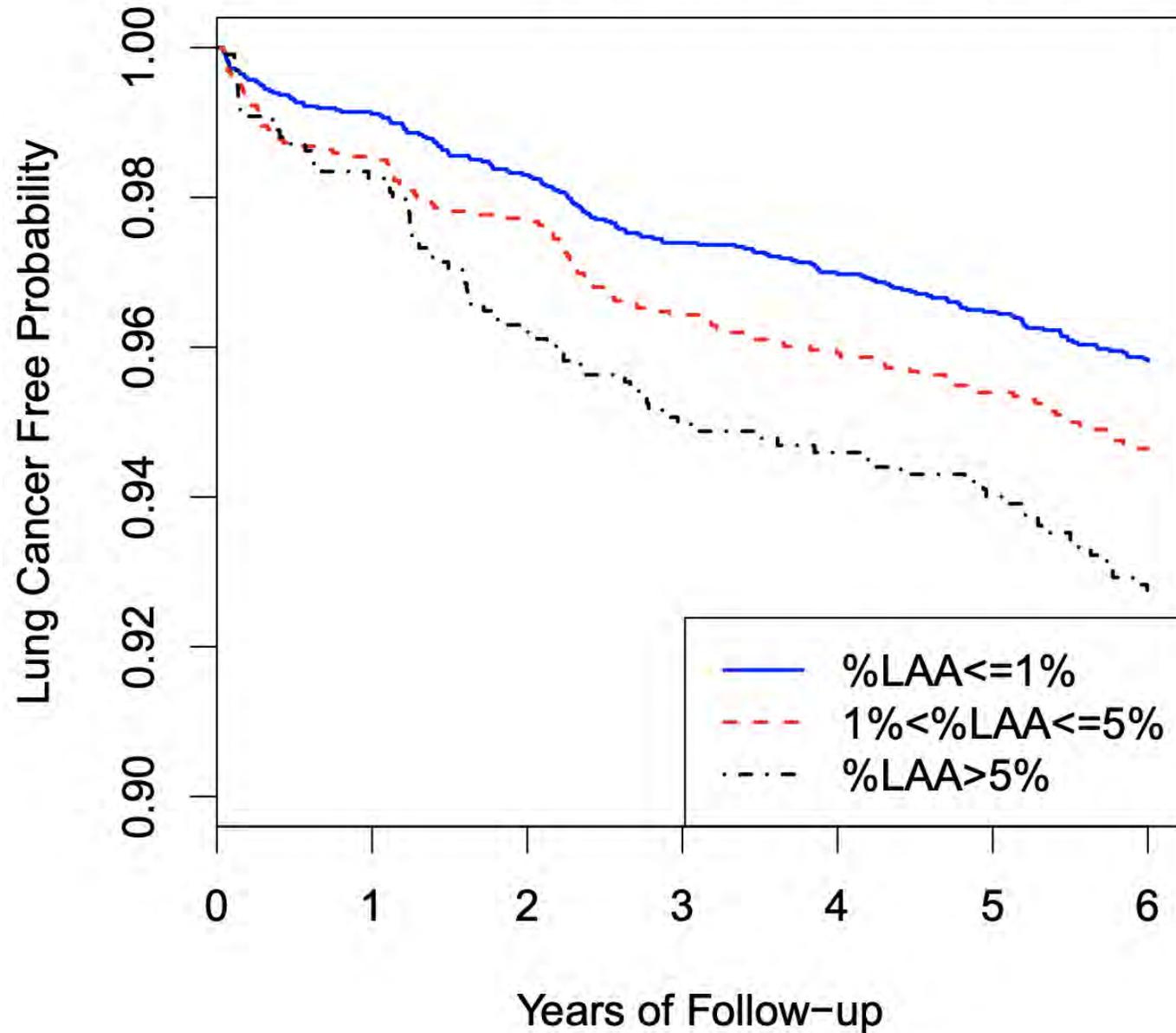
- No standardized protocol:
 - Multiple thresholds used (-900, -910)
 - Sharp kernels
 - Various slice thickness
 - Older machines
 - Low tube current

Incremental Quantitative Emphysema on Low-Dose Screening Chest CT Is Associated with Lung Cancer Incidence and Mortality: An Analysis of the National Lung Screening Trial

W.W. Labaki⁴, W. Wang², S. Murray², C.R. Hatt¹, L.A. Keith¹, C.J. Galban³, B.D. Ross³, F.J. Martinez⁵, D.A. Arenberg⁴, E.A. Kazerooni³, M.K. Han⁴, [Show All...](#)

- 7,519 NLST participants
 - mean age 61.5 years,
 - 41.6% women
 - 5.1% with self-reported COPD
- 352 (4.7%) developed lung cancer over 6 years of follow-up.
- 111 participants died of lung cancer (31.5% of those diagnosed with lung cancer and 24.4% of all deaths).
- Mean baseline %LAA was 2.6% and 13.3% of participants had emphysema greater than 5%.
- An increase of 1% in %LAA was associated with
 - A lung cancer development hazard ratio of 1.02 (95% CI 1.00-1.04; p=0.02)
 - A lung cancer death hazard ratio of 1.04 (95% CI 1.01-1.07; p=0.008).

Cox Inverse-weighted Time-to-event Probabilities for Lung Cancer Incidence



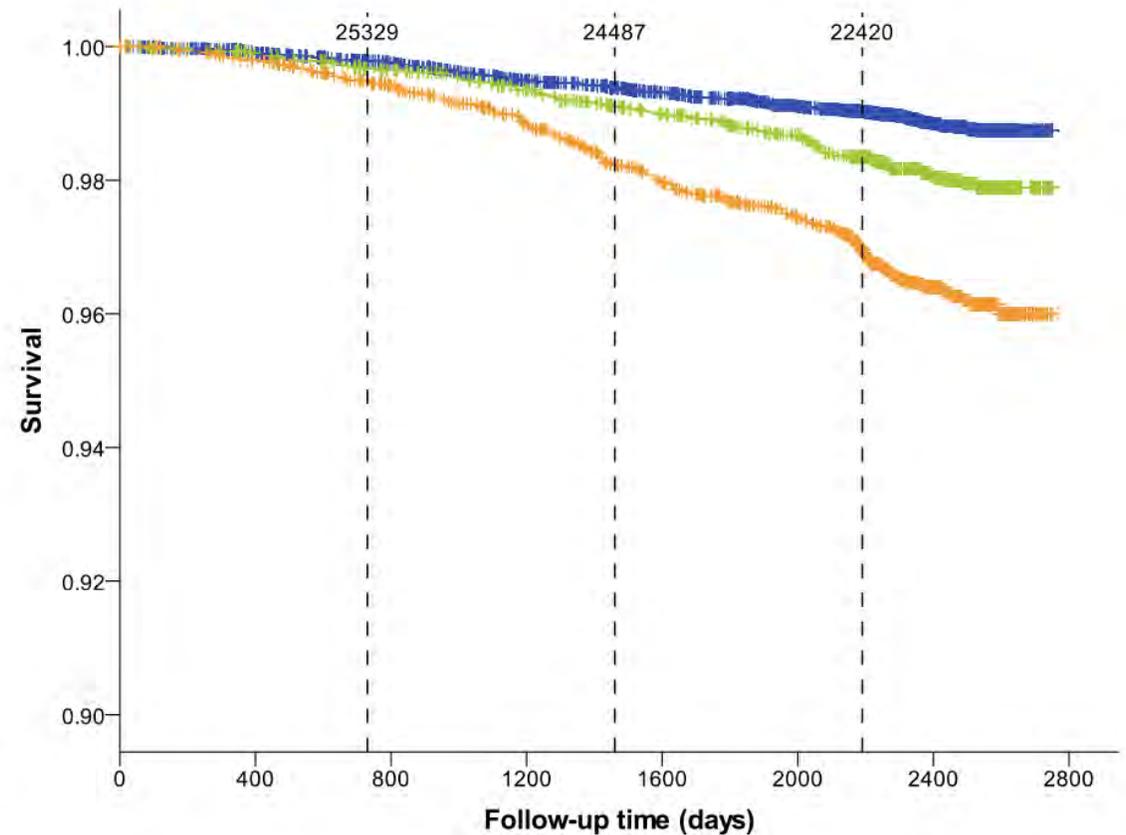
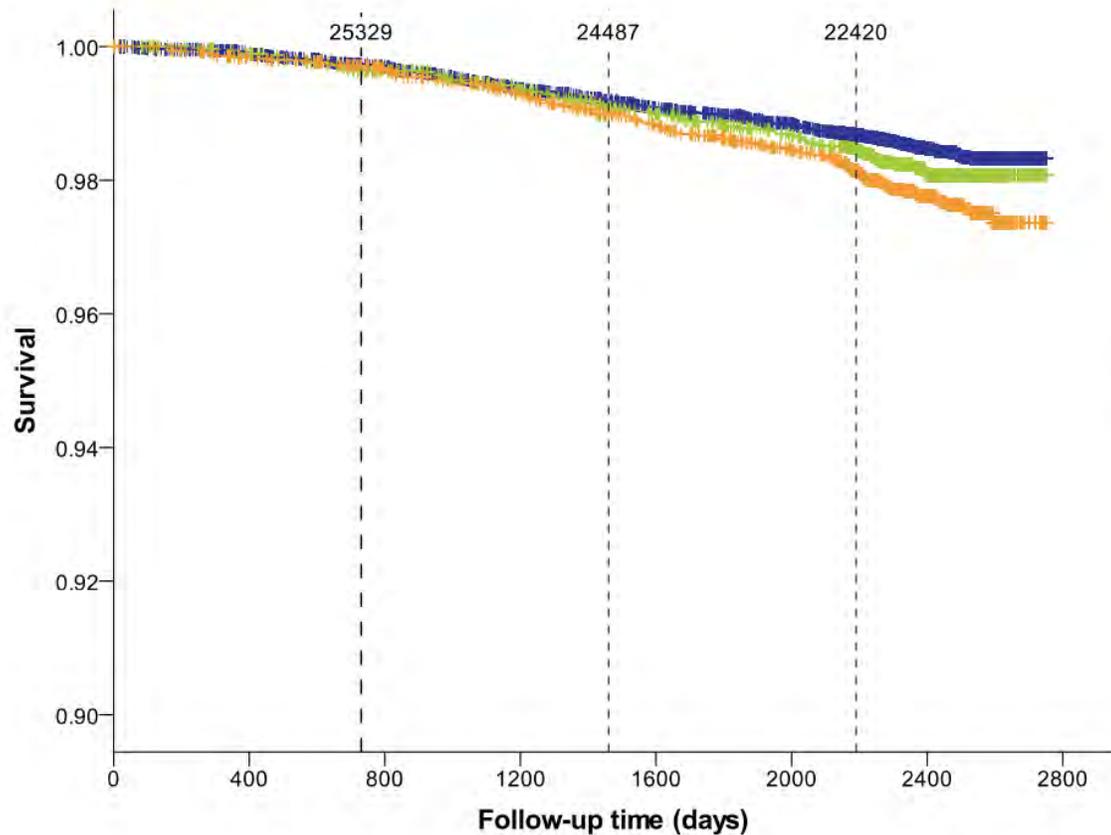
OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

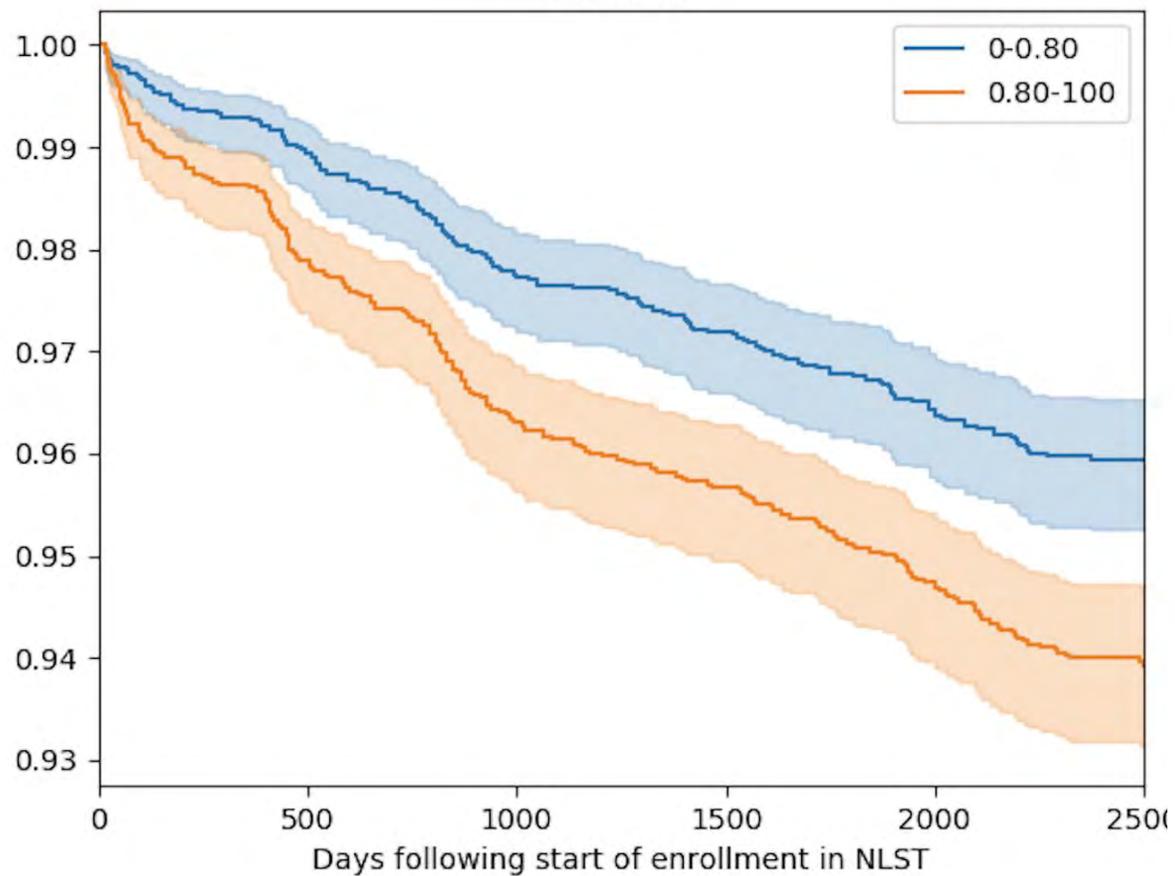
Normalized emphysema scores on low dose CT: Validation as an imaging biomarker for mortality

Leticia Gallardo-Estrella , Esther Pompe, Pim A. de Jong, Colin Jacobs, Eva M. van Rikxoort, Mathias Prokop, Clara I. Sánchez, Bram van Ginneken

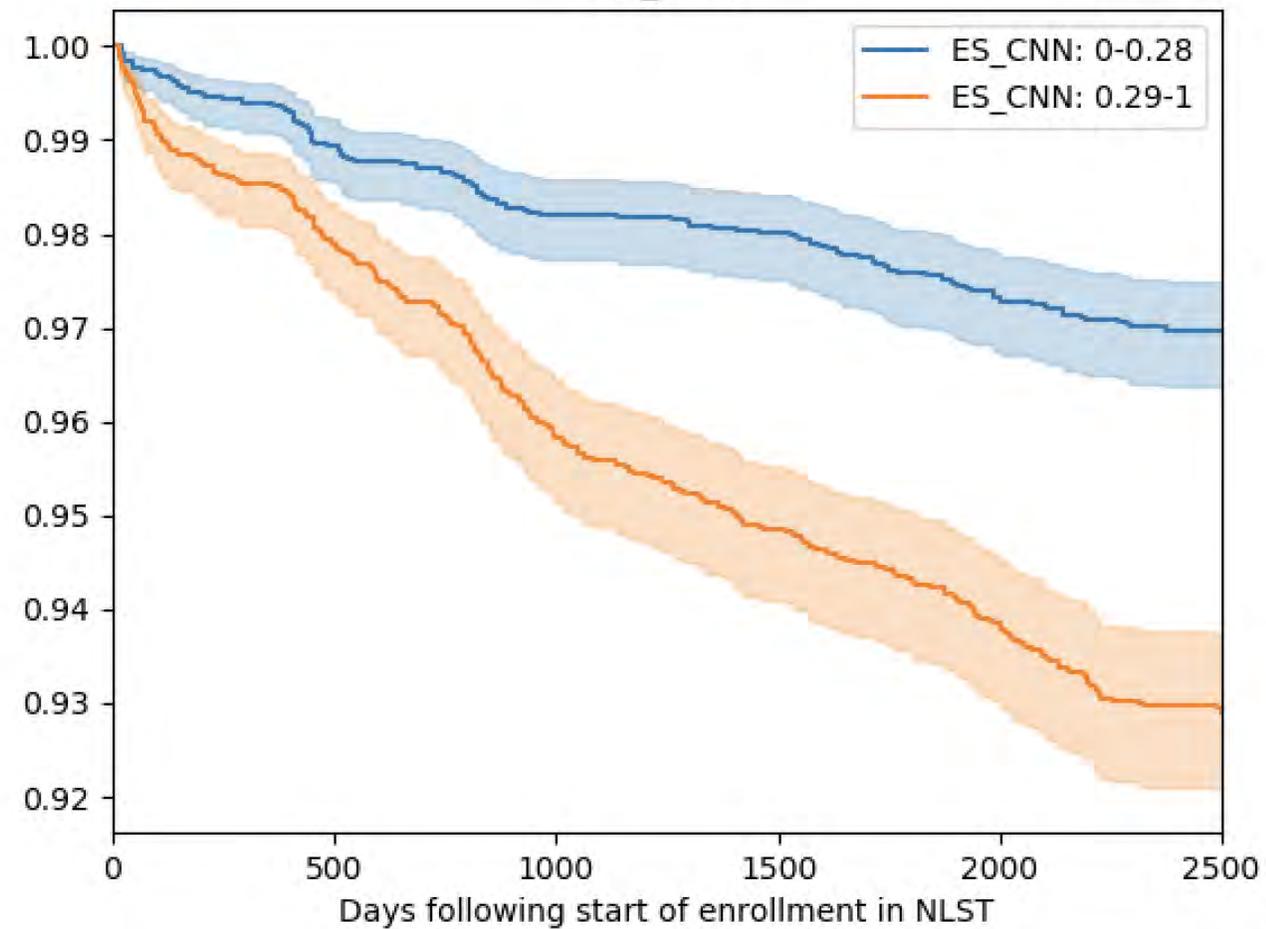
Published: December 11, 2017 • <https://doi.org/10.1371/journal.pone.0188902>



LAA950



ES_CNN



American Journal of Respiratory and Critical Care Medicine 2019;199:A1123

The Association Between Emphysema Detected by Lung Density Analysis and Healthcare Utilization in Patients Undergoing Lung Cancer Screening

S. Vehar³, P. Kirupaharan³, R. Yadav², P.J. Mazzone⁴, H. Choi¹,
https://doi.org/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A1123

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PDF

A24 COPD: THERAPY, IMAGING, AND MOLECULAR MARKERS / Poster Discussion Session / Sunday, May 19/9:15 AM-11:15 AM / Room C141/C143/C149 (Level 1), KBHCCD

The Association Between Emphysema Detected by Lung Density Analysis and Healthcare Utilization in Patients Undergoing Lung Cancer Screening

S. Vehar¹, P. Kirupaharan¹, R. Yadav², P. J. Mazzone³, H. Choi⁴; ¹Internal Medicine Residency Program, Cleveland Clinic Foundation, Cleveland, OH, United States, ²Diagnostic Radiology, Cleveland Clinic Foundation, Cleveland, OH, United States, ³Cleveland Clinic, Respiratory Inst, Cleveland, OH, United States, ⁴Respiratory Inst, Cleveland Clinic, Cleveland, OH, United States.

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Rational: Emphysema is a common incidental finding on low-dose computed tomography (LDCT) among patients participating in lung cancer screening (LCS). Automated software is available to quantify the presence of emphysematous changes using lung density analysis (LDA). There is no clear guideline to help providers select which patients should be further

- LAA > 0% (101/321 patients) was associated with
 - High rate of pulmonary outpatient visits (43% vs 27%).
 - More frequently prescribed treatment for COPD (47.2% vs 25.4%)

Acknowledgements

- Lung Density Biomarker Committee members for their commitment
 - All volunteers
- Clinical study authors and vendor representatives for thoughtful discussion
- QIBA/RSNA Concept Awards (NIBIB-PB-EB-1010-159-JKS)
 - National Institute of Biomedical Imaging and Bioengineering (NIBIB)
 - National Institutes of Health (NIH), Department of Health and Human Service, under Contracts Nos. HHSN268201000050C, HHSN268201300071C and HHSN268201500021C

Questions?