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

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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”
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 15\textsuperscript{th} 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
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tr>
<td>Biomarker Committee (BC) Drafting and Review</td>
<td>The Profile specifies requirements and guidance on best practices to achieve the performance stated in the claims.</td>
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<tr>
<td>Public Comment and Review</td>
<td>Stakeholders* in the public domain offer constructive comment that is formally address by the BC.</td>
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<tr>
<td>Field Testing and Technical Confirmation</td>
<td>Profile is made available for testing at more than one facility, systems, and persons and is understood and shown to meet the specifications.</td>
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<tr>
<td>Claim Confirmed</td>
<td>Overall performance was determined and claim was achieved.</td>
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*Stakeholders include academic, government, commercial partners: identify potential strategies for error mitigation and collaborate on hardware, software and image acquisition solutions*

We are in the public review process now!
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


General Plastics, FR-7104, 7108, 7112, 7116 and 7120 – last two digits represent nominal density in lb/ft³
QIBA-SRM phantoms (Fig. 4) distributed to 5 COPDGene imaging sites

Phantoms scanned using COPDGene study protocol

Scanner and CT protocol specific calibrations computed based on NIST-certified reference materials

RA-950 and VA Perc15 values for COPDGene subjects scanned at these sites will be adjusted by phantom-based correction factor

Corrected results to be compared with lung function and other clinical parameters

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

n=179, Bias ± LOA: -15.23 ± 11.95, r=0.98

- 0.5*(FDCT perc15 + RDCT perc15)

- Bias
- LOA
RDCT: 17%

FDCT: 7%

Median Filter

RDCT, Median Filter: 9%
Metric: laa950 | FDCT filter: No Filter, RDCT filter: Median

n=179, Bias ± LOA: -0.58 ± 2.38, r=0.99
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, your Lungs Today:
- 56% Normal but AT RISK of damage if you don’t quit smoking
- 40% AT HIGH RISK of further damage if you don’t quit smoking
- 4% Damaged

Lilly, your lungs look worse than 50% of smokers

Nonsmoker Lungs
- 12% MORE LIKELY TO DIE in the next six years than a nonsmoker.
- 9% MORE LIKELY OF BEING DIAGNOSED WITH LUNG CANCER in 5 years.
- 4x MORE LIKELY TO HAVE A HEART ATTACK.
- 2x MORE LIKELY TO HAVE A STROKE.
Emphysema detected on computed tomography and risk of lung cancer: A systematic review and meta-analysis

Benjamin M. Smith, Lancelot Pinto, Nicole Ezer, Nicola Sverzellati, Shigeo Muro, Kevin Schwartzman.

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

Lucía Gallardo-Estrella, Esther Pompe, Pin 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
The graphs show the survival rates for two different groups, LAA950 and ES_CNN, over time. The x-axis represents the days following the start of enrollment in NLST, and the y-axis represents the survival rate.

- **LAA950**
  - Blue line: 0-0.80
  - Orange line: 0.80-100

- **ES_CNN**
  - Blue line: ES_CNN: 0-0.28
  - Orange line: ES_CNN: 0.29-1
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%)
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Questions?