Quantitative Assessment of Emphysema Progression

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Disclosures

• Research funding
  • Pulmonary fibrosis foundation
  • NIH-NHLBI

• Other
  • Quantitative Imaging Solutions - scientific advisor/owner
Background
Roles for objective thoracic medical image analysis*

*an incomplete list

• *In vivo* understanding of structure/function and disease pathogenesis

• Disease diagnosis
  • Primary disease
  • Secondary diseases

• **Measurement of disease severity**
  • Cross sectional
  • **Longitudinal**
    • Response to therapy

• **Association with and prediction of outcomes**
  • Likelihood of response to intervention
Exposure → Disease → Mortality

Susceptibility → Disease → Morbidity
Baseline

Exposure

Susceptibility

Disease 1

Disease 2

Disease 3

Morbidity

Mortality

Measure

INTERVENTION

Follow-up

Disease 1

Disease 2

Disease 3

Morbidity

Mortality

Measure

Disease Specific Measure
What is the clinical significance of this change?
Figure 1. Kaplan-Meier survival estimates by low-attenuation area (%LAA) tertiles, n = 947 subjects from the GenKOLS study 2003–2005. (A–E) Respiratory mortality (A), cardiovascular mortality (B), cancer mortality (C), lung cancer mortality (D), and all-cause mortality (E) from baseline through June 2011. Blue line, low %LAA (<3); red line, medium %LAA (3–10); green line, high %LAA (>10).
Barriers to Use of Quantitative Thoracic Imaging as Biomarker

Technical
• Image acquisition parameters
• Variation in manufacturers
• Variable reconstruction algorithms
• Device calibration
• Image quality assurance
• Patient/scanner interaction

Clinical
• Association of change with clinically relevant outcome
• Clinical reproducibility/patient level confounders
Barriers to Use of Quantitative Thoracic Imaging as Biomarker

**Technical**

**Clinical**
- Association of change with clinically relevant outcome
- Clinical reproducibility/patient level confounders

QIBA Profile:
Computed Tomography: Lung Densitometry
TABLE 1. LUNG PARENCHYMAL PARAMETERS COMMONLY EMPLOYED TO ESTIMATE EXTENT OF EMPHYSEMA USING QUANTITATIVE COMPUTED TOMOGRAPHY

<table>
<thead>
<tr>
<th>Measured Parameters</th>
<th>Confounding Factors</th>
<th>Derived Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Sum of voxels</td>
<td>Mass = Volume × CT density</td>
</tr>
<tr>
<td>Total lung</td>
<td>Both lungs or right/left</td>
<td>Tissue volume = Mass/tissue density</td>
</tr>
<tr>
<td>Lobar</td>
<td>Sum of voxels on specific lobes</td>
<td>Air volume = Total volume – tissue volume</td>
</tr>
<tr>
<td>X-ray attenuation</td>
<td>Hounsfield units (HU)</td>
<td>CT density</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specific lung inflation</td>
</tr>
<tr>
<td>Low attenuation area</td>
<td>% voxels &lt; predefined threshold (i.e., −950 HU)</td>
<td>Low attenuation cluster analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slope of regression line of cumulative number of low attenuation clusters vs. size of low attenuation cluster</td>
</tr>
<tr>
<td>Percentile</td>
<td>HU at predefined percentile value of frequency distribution of X-ray attenuation values (e.g., lowest 15th percentile)</td>
<td>Image noise; depth of inspiration</td>
</tr>
</tbody>
</table>
Lung Density Perc15

FIGURE 1. Density distribution in the lung. Histogram of densities from a subject with normal lungs (solid line) and a patient with emphysema (dashed line). The 15th percentile point is the density value on the x-axis that covers 15% of all densities of the histogram. †: 15th percentile point.
Barriers to Use of Quantitative Thoracic Imaging as Biomarker

Technical

- Quantitative Imaging Biomarkers Alliance (QIBA)
- QIBA Profile: Computed Tomography: Lung Densitometry

Clinical

- PIVOT (Patient-Inspired Validation of Outcome Tools)
Study Design

• **Objective:**
  • Determine if emphysema progression over 3-5 years is associated with subsequent:
    • Mortality
    • Respiratory specific mortality

• **Cohorts:**
  • COPDGene Study
  • Evaluation of COPD Longitudinallly to Identify Predictive Surrogate End-points (ECLIPSE)

• **Groups:**
  • Ever smokers *with emphysema* (primary analyses)
  • All ever smokers (secondary analyses)
  • *Never smokers for development of MCID*
Methods

• Predictor:
  • Lung Density Perc15 adjusted for lung volume based on the sponge model
    • Annualized rate of change (continuous)
    • Progressor vs. non-progressor (dichotomous)

• Definitions:
  • Emphysema at baseline: those with low attenuation area (LAA) > the upper limit of normal defined by the MESA study

• Progression:
  • Absolute Lung Density Perc15 decline of more than the mean repeatability coefficient from QIBA (11 g/L)
  • Rate of Lung Density Perc15 decline ½ SD more than the mean rate in ‘never-smoking normals’

Dirksen 2008
Hoffman 2014
## Mortality by Progression Rate

<table>
<thead>
<tr>
<th>All Cause Mortality</th>
<th>Hazard Ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPDGene</td>
<td>1.08</td>
<td>1.01</td>
<td>1.16</td>
<td>0.03</td>
</tr>
<tr>
<td>ECLIPSE</td>
<td>1.06</td>
<td>1.00</td>
<td>1.13</td>
<td>0.045</td>
</tr>
</tbody>
</table>

### Respiratory Specific Mortality

| COPDGene             | 1.22         | 1.13   | 1.31   | < 0.001|

1. Effects expressed as change in the risk of all-cause mortality per 1 g/L/year faster rate of change in density.
2. Mortality assessed as time since follow-up visit.
3. All cause mortality models adjusted for: a) Race and gender; b) Baseline age, smoking status, pack years, forced expiratory volume in one second, six minute walk distance and volume adjusted lung density measured at the 15th percentile of the CT lung density histogram (Lung Density Perc15); c) Change in smoking status, rate of change in forced expiratory volume in one second and rate of change in six minute walk distance.
4. Respiratory specific mortality models adjusted for race, gender and age, and performed using the Fine and Gray method of accounting for competing risk.

### Notes

- Results shown are in those with emphysema at baseline.
- Ash *In press*
Mortality by Progression Category

Adjusted Survival Curve for Change in Lung Density
Perc15 Relative to the Repeatability Coefficient
COPDGene - Those with emphysema at baseline

Hazard Ratio = 1.65
p = 0.01

Adjusted Survival Curve for Change in Lung Density
Perc15 Relative to the Repeatability Coefficient
ECLIPSE - Those with emphysema at baseline

Hazard Ratio = 1.39
p = 0.10
Mortality by Progression Category

Adjusted Survival Curve for Rate of Change in Lung Density Perc15 Relative to Minimum Clinically Important Difference COPDGene - Those with emphysema at baseline

Hazard Ratio = 1.75
p = 0.001

Adjusted Survival Curve for Rate of Change in Lung Density Perc15 Relative to Minimum Clinically Important Difference ECLIPSE - Those with emphysema at baseline

Hazard Ratio = 1.63
p = 0.003
## Comparison of Model Performance - COPDGene

<table>
<thead>
<tr>
<th>Comparison</th>
<th>NRI</th>
<th>First Model vs. Second Model (non-nested only)</th>
<th>Second Model vs. First Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline vs. Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Spirometry vs. Baseline Imaging</td>
<td>-0.12</td>
<td>0.08</td>
<td>0.92</td>
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<tr>
<td>Baseline Spirometry vs. Baseline Spirometry + Baseline Imaging</td>
<td>0.07</td>
<td>N/A</td>
<td>0.02</td>
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<tr>
<td>Baseline Imaging vs. Baseline Spirometry + Baseline Imaging</td>
<td>0.19</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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<tr>
<td><strong>Longitudinal vs. Longitudinal</strong></td>
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<tr>
<td>Longitudinal Spirometry vs. Longitudinal Imaging</td>
<td>-0.04</td>
<td>0.20</td>
<td>0.80</td>
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<tr>
<td>Longitudinal Spirometry vs. Longitudinal Spirometry + Longitudinal Imaging</td>
<td>0.13</td>
<td>N/A</td>
<td>0.01</td>
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<tr>
<td>Longitudinal Imaging vs. Longitudinal Spirometry + Longitudinal Imaging</td>
<td>0.15</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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<tr>
<td><strong>Baseline vs. Longitudinal</strong></td>
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<tr>
<td>Baseline Spirometry vs. Longitudinal Spirometry</td>
<td>0.18</td>
<td>N/A</td>
<td>0.002</td>
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<tr>
<td>Baseline Imaging vs. Longitudinal Imaging</td>
<td>0.23</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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<tr>
<td>Baseline Spirometry + Baseline Imaging vs. Longitudinal Spirometry + Longitudinal Imaging</td>
<td>0.25</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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</tbody>
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## Comparison of Model Performance - ECLIPSE

<table>
<thead>
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<th>Second Model vs. First Model</th>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Spirometry vs. Baseline Imaging</td>
<td>-0.09</td>
<td>0.17</td>
<td>0.83</td>
</tr>
<tr>
<td>Baseline Spirometry vs. Baseline Spirometry + Baseline Imaging</td>
<td>0.15</td>
<td>N/A</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline Imaging vs. Baseline Imaging</td>
<td>0.21</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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<tr>
<td>Baseline Spirometry + Baseline Imaging</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Longitudinal vs. Longitudinal</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Longitudinal Spirometry vs. Longitudinal Imaging</td>
<td>-0.08</td>
<td>0.15</td>
<td>0.85</td>
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<tr>
<td>Longitudinal Spirometry vs. Longitudinal Spirometry + Longitudinal Imaging</td>
<td>0.12</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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<tr>
<td>Longitudinal Imaging vs. Longitudinal Imaging</td>
<td>0.24</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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<tr>
<td>Longitudinal Spirometry + Longitudinal Imaging</td>
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<td></td>
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<tr>
<td><strong>Baseline vs. Longitudinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Spirometry vs. Longitudinal Imaging</td>
<td>0.21</td>
<td>N/A</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline Imaging vs. Longitudinal Imaging</td>
<td>0.17</td>
<td>N/A</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline Spirometry + Baseline Imaging vs. Longitudinal Spirometry + Longitudinal Imaging</td>
<td>0.18</td>
<td>N/A</td>
<td>&lt; 0.001</td>
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Emphysema Current Status

• Letter of intent for qualification of volume adjusted lung density Perc15 resubmitted to the FDA after initial favorable comments
• CBQC transitioned to PIVOT
• White paper consensus document in progress
Summary

• Densitometric emphysema progression is associated with all cause and respiratory specific mortality in ever smokers with emphysema

• In combination with extensive prior work on densitometry, this suggests that volume adjusted Lung Density can be used as an imaging biomarker

• Additional work is needed in clinical cohorts and to determine what interventions might change the course of emphysema progression
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