Imaging Advances in Smoking-related Injury: From COPD to Interstitial Lung Disease

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Brigham and Women’s Hospital

Quantitative Imaging Workshop, XV
Smoking Related Lung Disease

Emphysema/COPD ↔ Overlap ↔ Pulmonary Fibrosis
What are the *imaging endophenotypes* that are linked to the clinical manifestation and the prognostication of smoking related injury and *poor lung development*?
Emphysema Subtyping via Local Histogram

Mean Local Histogram for Emphysema Patterns

- **NT**: Normal (non-emphysema)
- **PS**: Paraseptal
- **PL**: Panlobular
- **CL1**: Mild Centrilobular
- **CL2**: Moderate Centrilobular
- **CL3**: Severe Centrilobular

Local Histogram Subtypes have novel GWAS

- Novel associations within genes associated with cell migration (*MYO1D*) and cell signaling (*VWA8*).

- GWAS observed at previously established COPD-associated loci
  - 14q31 (nearby gene *HHIP*), 15q25(*CHRNA3/5/IREB2*), 11q22 (*MMP12*), and 19q13 (*CYP2D6*).

Castaldi et al, AJRCCM, 2013
Emphysema Subtypes and Lung Cancer

Proportion of Total Lung

Kinsey CM, ATS; 2016
## Lung Cancer Risk by Emphysema Subtype

<table>
<thead>
<tr>
<th>Lung Parenchymal Feature</th>
<th>OR</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%LAA -950 (density threshold alone)</td>
<td>1.01</td>
<td>[0.99, 1.02]</td>
<td>0.146</td>
</tr>
<tr>
<td>Mild centriflobular (CL1)</td>
<td>0.26</td>
<td>[0.17, 1.61]</td>
<td>0.263</td>
</tr>
<tr>
<td><strong>Moderate centriflobular (CL2)</strong></td>
<td><strong>2.41</strong></td>
<td><strong>[1.09, 5.32]</strong></td>
<td><strong>0.029</strong></td>
</tr>
<tr>
<td>Severe centriflobular (CL3)</td>
<td>6.12</td>
<td>[0.97, 38.6]</td>
<td>0.054</td>
</tr>
<tr>
<td>Panlobular (PL)</td>
<td>4.99</td>
<td>[0.23, 108.8]</td>
<td>0.306</td>
</tr>
<tr>
<td>Pleural-based (PB)</td>
<td>13.4</td>
<td>[0.00, 1137]</td>
<td>0.713</td>
</tr>
</tbody>
</table>

*Each model includes one of the above lung parenchymal features and is adjusted for age, gender, pack years, and airflow obstruction.*

*With the exception of %LAA-950, all morphologies were measured by the LH method at the level of the secondary pulmonary lobule.*
Interstitial Lung Abnormalities

MUC5B Promoter Polymorphism and Interstitial Lung Abnormalities

Gary M. Hunninghake, M.D., M.P.H., Hiroto Hatabu, M.D., Ph.D., Yuka Okajima, M.D., Wei Gao, M.S., Josée Dupuis, Ph.D., Jeanne C. Latourelle, D.Sc., Mizuki Nishino, M.D., Yuka Okajima, M.D., Tsuneo Yamashino, M.D., James C. Ross, M.S., Raúl San José Estépar, Ph.D., David A. Lynch, M.D., John M. Brehm, M.D., M.P.H., Katherine P. Andriole, Ph.D., Alejandro A. Diaz, M.D., Ramin Khorasani, Ph.D., Katherine D’Aco, M.S., Frank C. Scirica, M.D., Edwin K. Silverman, M.D., Ph.D., Hiroto Hatabu, M.D., Ph.D., and Ivan O. Rosas, M.D., for the COPDgene Investigators.

Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities


This article was published on May 21, 2013, at NEJM.org.

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Local Histogram with Interstitial Patterns

Ash SY, Harmouche R, Academic Radiology 2017;24
Detection of ILA matches visual diagnosis

AUC 0.82 for the detection of visually defined interstitial lung abnormalities

AUC 0.89 for the detection of visually defined fibrotic parenchymal abnormalities

Ash SY, Harmouche R, Academic Radiology 2017;24
## Susceptibility without visual ILA

<table>
<thead>
<tr>
<th>All Participants</th>
<th>Change per 5% Increase in Interstitial Features</th>
<th>Adjusted</th>
<th>Cl</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1%</td>
<td>-2.65</td>
<td>-3.15, -2.14</td>
<td>&lt;0·001</td>
<td></td>
</tr>
<tr>
<td>FVC%</td>
<td>-2.47</td>
<td>-2.88, -2.06</td>
<td>&lt;0·001</td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>-0.004</td>
<td>-0.007, -0.001</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>SGRQ</td>
<td>1.36</td>
<td>0.92, 1.81</td>
<td>&lt;0·001</td>
<td></td>
</tr>
</tbody>
</table>

### No ILA (0 only)

<table>
<thead>
<tr>
<th>Without Visual ILA</th>
<th>Adjusted</th>
<th>Cl</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1%</td>
<td>-4.83</td>
<td>-5.78, -3.89</td>
<td>&lt;0·001</td>
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<tr>
<td>FVC%</td>
<td>-4.09</td>
<td>-4.85, -3.32</td>
<td>&lt;0·001</td>
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<tr>
<td>FEV1/FVC</td>
<td>-0.010</td>
<td>-0.016, -0.005</td>
<td>&lt;0·001</td>
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<tr>
<td>SGRQ</td>
<td>0.806</td>
<td>-0.027, 1.639</td>
<td>0.058</td>
</tr>
</tbody>
</table>

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Ash, *Chest* 2017
# Mortality and Interstitial Features

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio* (5% Absolute increase of ILA Features)</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>1.29</td>
<td>1.21, 1.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subgroup A – Those without ILA</td>
<td>1.27</td>
<td>1.16, 1.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subgroup B – Those without ILA and without indeterminate findings</td>
<td>1.20</td>
<td>1.02, 1.42</td>
<td>0.031</td>
</tr>
<tr>
<td>Subgroup C – Those with normal spirometry</td>
<td>1.25</td>
<td>1.07, 1.46</td>
<td>0.004</td>
</tr>
<tr>
<td>Subgroup D – Those without chronic dyspnea or bronchitis</td>
<td>1.26</td>
<td>1.11, 1.44</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Ash, *Chest* 2017
Parenchymal Subtyping Predicts Mortality

Mortality Predicted by Combined Emphysema/ILD Status

with average age, BMI, pack years and FEV1 and assuming male sex, nonblack race, current nonsmoker and enrolled at National Jewish Hospital

Proportion Alive

- Emphysema-/Interstitial-
- Emphysema-/Interstitial+
- Emphysema+/Interstitial-
- Emphysema+/Interstitial+

days

Ash, Radiology 2018
The AI Revolution: A new paradigm?

Low level features

Medium level features

High level features
Direct Regression of Outcomes

Endotype
Histopathology / Structural Changes

Hypotheses

Imaging Phenotype

Endophenotype

Neutral Network

Neural Phenotyping

Diagnosis Prediction Monitoring
ILA subtyping with Deep Learning
## Ensemble of Convolutional Neural Networks

<table>
<thead>
<tr>
<th>BCNN²D</th>
<th>MSTAGE-CNN²D</th>
<th>MCONTEXT-CNN²D</th>
<th>BCNN².5D</th>
<th>MSTAGE-CNN².5D</th>
<th>BCNN³D</th>
<th>MSTAGE-CNN³D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Input:</strong> 48x48</td>
<td><strong>Input:</strong> 48x48</td>
<td><strong>Input:</strong> 48x48</td>
<td><strong>Input:</strong> 3x48x48</td>
<td><strong>Input:</strong> 48x48x7</td>
<td><strong>Input:</strong> 48x48x7</td>
<td><strong>Input:</strong> 48x48x7</td>
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<tr>
<td>Conv: 48@3x3</td>
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<td>MaxPool: 2x2</td>
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<td>BatchNorm</td>
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<td>FC: 64</td>
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<tr>
<td>MaxPool: 6x6</td>
<td>BatchNorm</td>
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<td>MaxPool: 6x6</td>
<td>BatchNorm</td>
<td>FC: 64</td>
<td>MaxPool: 6x6</td>
</tr>
<tr>
<td>Conv: 48@3x3</td>
<td>Conv: 48@3x3</td>
<td>Conv: 48@3x3</td>
<td>BatchNorm</td>
<td>FC: 64</td>
<td>MaxPool: 6x6</td>
<td>BatchNorm</td>
</tr>
<tr>
<td>MaxPool: 2x2</td>
<td>MaxPool: 2x2</td>
<td>BatchNorm</td>
<td>BatchNorm</td>
<td>FC: 64</td>
<td>MaxPool: 6x6</td>
<td>BatchNorm</td>
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<tr>
<td>BatchNorm</td>
<td>BatchNorm</td>
<td>MaxPool: 2x2</td>
<td>BatchNorm</td>
<td>FC: 64</td>
<td>MaxPool: 6x6</td>
<td>BatchNorm</td>
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<td>Softmax: 8</td>
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<td>Softmax: 8</td>
<td>Softmax: 8</td>
<td>Softmax: 8</td>
</tr>
</tbody>
</table>

Bermejo, Scientific Reports, 2018, under review
Ensemble stabilize performance

- Training in 37,424 locations
- Testing in 36,336 locations

**Sensitivity**

- A: BCNN$^{2D}$
- B: MSTAGE – CNN$^{2D}$
- C: MCONTEXT – CNN$^{2D}$
- D: BCNN$^{3D}$
- E: MSTAGE – CNN$^{3D}$
- F: BCNN$^{2.5D}$
- G: MSTAGE – CNN$^{2.5D}$
- H: Ensemble

**Specificity**

- A: BCNN$^{2D}$
- B: MSTAGE – CNN$^{2D}$
- C: MCONTEXT – CNN$^{2D}$
- D: BCNN$^{3D}$
- E: MSTAGE – CNN$^{3D}$
- F: BCNN$^{2.5D}$
- G: MSTAGE – CNN$^{2.5D}$
- H: Ensemble
Comparison with other architectures

- ECNN (AUC = 0.98)
- VGG-P (AUC = 0.95)
- VGG (AUC = 0.80)
- ILD CNN (AUC = 0.84)
- GoogleNet-P (AUC = 0.89)
- GoogleNet (AUC = 0.79)
- LH (AUC = 0.71)
Reconstruction Stability

SN: Train: B50 / Test: B50, 85.0; Train: B50 / Test: B35, 75.2
SN: Train: B35 / Test: B35, 82.5

SP: Train: B50 / Test: B50, 96.5; Train: B50 / Test: B35, 78.0
SP: Train: B35 / Test: B35, 94.5

GM: Train: B50 / Test: B50, 90.6; Train: B35 / Test: B35, 84.3
GM: Train: B35 / Test: B50, 89.6
GM: Train: B35 / Test: B35, 87.0

BA: Train: B50 / Test: B50, 90.7; Train: B35 / Test: B35, 84.8
BA: Train: B35 / Test: B50, 89.9
BA: Train: B35 / Test: B50, 87.5
Direct Biomarker Regression

Bone Mineral Density

Emphysema Score

González G et al, SPIE 2018
Emphysema Scoring From X-Ray

Iturrioz, ISBI 2018
Emphysema Scoring From X-Ray

Max error: 43.2697
Min error: 0.000489235
Mean error: 3.96156
STD: 4.59705
Median: 2.38871
Mode: 0.51

90% data has error ≤ 9.629729
76% data has error ≤ 4.933455
Input: 512x512x1

\[ X_i \]

\[ \text{C1: 128x128x16} \]

\[ \text{C2: 32x32x32} \]

\[ \text{C3: 8x8x64} \]

\[ \text{FC1: 1024} \]

\[ \{w_n\}_{L_1} \]

\[ \{w_n\}_{L_2} \]

\[ \{w_n\}_{L_3} \]

\[ \{w_n\}_{L_4} \]

\[ Y_i \]

\text{Clinical Phenotype}
## Deep Learning Performance for COPD Assessment

<table>
<thead>
<tr>
<th>COPDGene Reconstruction Kernel</th>
<th>Replication ECLIPSE (n=1,547)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV1</strong> (r coef.)</td>
<td></td>
</tr>
<tr>
<td>STD (n=1,000)</td>
<td>SHARP (n=1,000)</td>
</tr>
<tr>
<td>0.735</td>
<td>0.735</td>
</tr>
<tr>
<td>[0.705 - 0.762]</td>
<td>[0.705 – 0.762]</td>
</tr>
<tr>
<td><strong>GOLD Stage (Accuracy)</strong></td>
<td></td>
</tr>
<tr>
<td>51.2% / 74.7%</td>
<td>52.0% / 73.8%</td>
</tr>
<tr>
<td><strong>ARD</strong> AUC</td>
<td></td>
</tr>
<tr>
<td>0.633</td>
<td>0.627</td>
</tr>
<tr>
<td>[0.602 - 0.663]</td>
<td>[0.597 – 0.658]</td>
</tr>
<tr>
<td><strong>Mortality AUC</strong></td>
<td></td>
</tr>
<tr>
<td>0.72</td>
<td>0.709</td>
</tr>
<tr>
<td>[0.6 - 0.78]</td>
<td>[0.58 – 0.737]</td>
</tr>
</tbody>
</table>

Conclusions

• Parenchymal Injury is a crucial marker of the host inflammatory response to tobacco injury.

• Quantitative assessment of parenchymal injury (emphysema and ILD) is clinically relevant even in asymptomatic.

• Artificial Intelligence may offer a new paradigm for image-based biomarker computation
  • Quality and through testing are a key factor for translation
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- German Gonzalez Serrano
- George Washko

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  - R01HL116473
  - COPDGene Study

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