

## SUPPLEMENTARY TABLES

Table S1. Sample of Emphysema Scoresheet

Study ID: XXXXXXXX

| Emphysema/low attenuation subtype  | Severity (0%-100%) |             |             |             |             |             |
|--|--------------------|-------------|-------------|-------------|-------------|-------------|
|  | Upper zone         |             | Mid zone    |             | Lower zone  |             |
|  | Right              | Left        | Right       | Left        | Right       | Left        |
| Centrilobular  | 8.0%               | 6.0%        | 3.0%        | 2.0%        | 1.0%        | 0.0%        |
| Panlobular   | 0.0%               | 0.0%        | 0.0%        | 0.0%        | 0.0%        | 0.0%        |
| Paraseptal   | 2.0%               | 2.0%        | 1.0%        | 0.0%        | 0.0%        | 1.0%        |
| Ambiguous*   | 0.0%               | 0.0%        | 0.0%        | 0.0%        | 0.0%        | 0.0%        |
| Total (auto sum column, maximum 100):  | <u>10.0%</u>       | <u>8.0%</u> | <u>4.0%</u> | <u>2.0%</u> | <u>1.0%</u> | <u>1.0%</u> |
| Other causes of low attenuation: (e.g., paracicatricial emphysema, cyst, non-paraseptal bullae, pneumatocele, cavity, honeycomb, bronchomalacia) | Free text          |             |             |             |             |             |

Zones: Upper zone is defined from apex to mid-aortic arch; mid zone from mid-aortic arch to mid-entry level of the most inferior pulmonary vein; and lower zone from mid-entry level of the most inferior pulmonary vein to the diaphragm. See methods for emphysema subtype and severity definitions.

\*Ambiguous subtype: Use this category if you are certain emphysema is present but uncertain of the subtype. Be as specific as possible (e.g., if you are confident that paraseptal emphysema is present but unsure if remainder of emphysema is centrilobular or panlobular, use the paraseptal and ambiguous categories).

Table S2. Characteristics of Participants Included in the Training and Validation Sets.

|  | Training Set | Validation Set |
|--|--------------|----------------|
| <b>Thoracic CT scans – no.</b>                                       | 40           | 127            |
| <b>Age – years</b>   | 68±5         | 68±7           |
| <b>Male – no. (%)</b>  | 18 (45)      | 69 (54)        |
| <b>Race-ethnicity – no. (%)*</b>                                     |              |                |
| <b>Caucasian</b>   | 30 (75)      | 91 (72)        |
| <b>African American</b>  | 3 (8)        | 27 (21)        |
| <b>Other</b>   | 7 (18)       | 9 (7)          |
| <b>Height – cm</b>   | 168±11       | 169±10         |
| <b>Weight – kg</b>   | 77±18        | 78±18          |
| <b>Body mass index</b>   | 27±5         | 27±6           |
| <b>Smoking status</b>  |              |                |
| <b>Current</b>   | 16 (40)      | 38 (30)        |
| <b>Former</b>  | 24 (60)      | 89 (70)        |
| <b>Pack-years – median (1<sup>st</sup>, 3<sup>rd</sup> quartile)</b> | 47 (25, 70)  | 39 (25, 55)    |
| <b>COPD – no. (%)†</b>   |              |                |
| <b>None</b>  | 14 (39)      | 41 (32)        |
| <b>Mild</b>  | 4 (11)       | 30 (24)        |
| <b>Moderate</b>  | 14 (39)      | 38 (30)        |
| <b>Severe / very severe</b>  | 3 (11)       | 18 (14)        |
| <b>Percent predicted FEV<sub>1</sub> – %†</b>                        | 77±22        | 81±25          |

Plus-minus values are mean ± standard deviation unless otherwise indicated. \*p<0.05 for pairwise comparison between training and validation set. †Spirometry was not available for 4 participants in the training set.

Abbreviations: CT denotes computed tomography, COPD chronic obstructive pulmonary disease and FEV<sub>1</sub> forced expired volume in the first second.

**Table S3. Reliability of Visually Detected Subtypes of Pulmonary Emphysema at CT in the Training Set.**

|  | <b>Presence of Emphysema</b>                           | <b>Extent of Emphysema</b>      |
|--|--|---------------------------------|
|  | <b>Unweighted Cohen's <math>\kappa</math> (95% CI)</b> | <b>ICC coefficient (95% CI)</b> |
| <b>Training set intra-reader reliability (n=10 participants x 4 readers)</b> |  |                                 |
| <b>Centrilobular emphysema</b>   | 0.84<br>(0.67 to 1.00)                                 | 0.82<br>(0.73 to 0.88)          |
| <b>Paraseptal emphysema</b>  | 0.89<br>(0.74 to 1.00)                                 | 0.81<br>(0.71 to 0.88)          |
| <b>Panlobular emphysema</b>  | 0.79<br>(0.58 to 1.00)                                 | 0.64<br>(0.48 to 0.76)          |
| <b>Any emphysema</b>   | 0.94<br>(0.82 to 1.00)                                 | 0.84<br>(0.76 to 0.90)          |
| <b>Training set inter-reader reliability (n=40 participants x 4 readers)</b> |  |                                 |
| <b>Centrilobular emphysema</b>   | 0.80<br>(0.62 to 0.99)                                 | 0.74<br>(0.56 to 0.85)          |
| <b>Paraseptal emphysema</b>  | 0.58<br>(0.34 to 0.83)                                 | 0.67<br>(0.46 to 0.81)          |
| <b>Panlobular emphysema</b>  | 0.11<br>(-0.18 to 0.40)                                | 0.59<br>(0.35 to 0.76)          |
| <b>Any emphysema</b>   | 0.78<br>(0.58 to 0.98)                                 | 0.76<br>(0.59 to 0.86)          |

Abbreviations: CT denotes computed tomography, ICC intra-class correlation, and CI confidence interval.

**Table S4. Reliability of Visually Detected Subtypes of Pulmonary Emphysema at CT in the Validation Set.**

|   | <b>Presence of Emphysema</b>                           | <b>Extent of Emphysema</b>      |
|---|--|---------------------------------|
|   | <b>Unweighted Cohen's <math>\kappa</math> (95% CI)</b> | <b>ICC coefficient (95% CI)</b> |
| <b>Validation set inter-reader reliability (n=127 participants x 3 readers)</b> |  |                                 |
| <b>Centrilobular emphysema</b>  | 0.78<br>(0.67 to 0.89)                                 | 0.72<br>(0.64 to 0.80)          |
| <b>Paraseptal emphysema</b>   | 0.54<br>(0.39 to 0.70)                                 | 0.93<br>(0.90 to 0.95)          |
| <b>Panlobular emphysema</b>   | 0.16<br>(0.00 to 0.36)                                 | 0.42<br>(0.31 to 0.55)          |
| <b>Any emphysema</b>  | 0.76<br>(0.65 to 0.87)                                 | 0.77<br>(0.69 to 0.83)          |

Abbreviations: CT denotes computed tomography, ICC intra-class correlation, and CI confidence interval.

**Table S5. Clinical Characteristics of MESA COPD Study Participants by Predominant Emphysema Subtype with Additional Adjustment for Percent Predicted FEV<sub>1</sub> and Percent Emphysema<sub><-950HU</sub>.**

| Clinical characteristic                                      | Predicted mean or proportion of clinical characteristic adjusted for age, gender, race-ethnicity, smoking status, percent predicted FEV <sub>1</sub> and percent emphysema <sub>&lt;-950HU</sub> <sup>†</sup> (95% CI) |  |  |  | Global P-value** |
|--|--|--|--|--|------------------|
|  | Adjusted P-value for multiple comparisons of subtypes to control group*  |  |  |  |                  |
|  | Absence of emphysema<br>N=205<br>(73%)   | Centrilobular predominant emphysema<br>N=65<br>(14%) | Paraseptal predominant emphysema<br>N=33<br>(9%) | Panlobular predominant emphysema<br>N=15<br>(4%) |                  |
| <b>Body mass index</b>                                       | 28<br>(27 to 29)<br>Reference  | 27<br>(25 to 28)<br>P=0.48                           | 28<br>(26 to 30)<br>P=0.98                       | 24<br>(21 to 27)<br>P=0.03                       | 0.008            |
| <b>Pack-years</b>  | 31<br>(28 to 35)<br>Reference  | 51<br>(45 to 57)<br>P<0.001                          | 35<br>(27 to 43)<br>P=0.81                       | 32<br>(20 to 43)<br>P=1.00                       | <0.001           |
| <b>Proportion with mMRC dyspnea scale ≥2 – %<sup>a</sup></b> | 5.5<br>(1.1 to 24)<br>Reference  | 9.0<br>(2.9 to 25)<br>P=0.29                         | 3.6<br>(0.6 to 19)<br>P=0.56                     | 7.0<br>(1.0 to 36)<br>P=0.76                     | 0.59             |
| <b>Percent predicted 6MWD<sup>a</sup></b>                    | 92<br>(88 to 96)<br>Reference  | 80<br>(74 to 87)<br>P=0.005                          | 90<br>(81 to 98)<br>P=0.93                       | 73<br>(58 to 87)<br>P=0.03                       | 0.002            |
| <b>White blood cell count – ·10<sup>9</sup>/L</b>            | 6.3<br>(6.0 to 6.6)<br>Reference   | 7.1<br>(6.6 to 7.7)<br>P=0.03                        | 7.0<br>(6.3 to 7.7)<br>P=0.20                    | 6.6<br>(5.6 to 7.7)<br>P=0.92                    | 0.02             |

<sup>†</sup>Predicted means and proportions are weighted to reflect distribution in the source population (see methods for details). \*P-values comparing emphysema subtypes to a control group (absence of emphysema) are adjusted for multiple comparisons using Dunnett's procedure. \*\*Global p-values are from likelihood ratio tests comparing models with and without emphysema subtype term. <sup>‡</sup>Plethysmography and diffusing capacity were measured on validation participants only. <sup>a</sup>6MWD was measured on 263 participants, and mMRC and resting SpO<sub>2</sub> measured on 297 participants.

Abbreviations: MESA denotes Multi-Ethnic Study of Atherosclerosis, COPD chronic obstructive pulmonary disease, CI confidence interval, mMRC modified Medical Research Council, FEV<sub>1</sub> forced expired volume in the first second, RV residual volume, FRC functional residual capacity, TLC total lung capacity, D<sub>lco</sub> diffusing capacity of the lung for carbon monoxide, 6MWD six minute walk distance, HU Hounsfield units, and SpO<sub>2</sub> pulse-oximeter estimated arterial oxygen-hemoglobin saturation.

**Table S6. Clinical Characteristics of MESA COPD Study Participants without COPD by Presence of Emphysema on CT.**

| Clinical characteristic           | Mean or proportion of clinical characteristic among MESA COPD Study participants without COPD<br>(95% CI) |                           | P-value* |
|-----------------------------------|---|---------------------------|----------|
|                                   | Emphysema absent<br>N=138   | Emphysema present<br>N=28 |          |
| Age – years                       | 68<br>(67 to 69)  | 67<br>(65 to 70)          | 0.84     |
| Proportion male – %               | 53<br>(44 to 61)  | 57<br>(38 to 77)          | 0.68     |
| Race/ethnicity – %                |   |                           |          |
| Caucasian                         | 46<br>(37 to 54)  | 36<br>(17 to 55)          | 0.33     |
| African American                  | 22<br>(15 to 30)  | 39<br>(20 to 59)          | 0.06     |
| Other                             | 16<br>(24 to 40)  | 25<br>(7.9 to 42)         | 0.47     |
| Proportion of current smokers – % | 16<br>(9.8 to 22)   | 50<br>(30 to 70)          | <0.001   |
| Height – cm                       | 167<br>(165 to 168)   | 168<br>(164 to 171)       | 0.51     |
| Weight – kg                       | 81  | 79                        | 0.58     |

|   |                        |                        |       |
|---|------------------------|------------------------|-------|
|   | (78 to 84)             | (72 to 85)             |       |
| <b>Body mass index</b>  | 29<br>(28 to 30)       | 28<br>(26 to 30)       | 0.24  |
| <b>Pack-years</b>   | 30<br>(27 to 34)       | 41<br>(33 to 48)       | 0.01  |
| <b>Proportion with<br/>mMRC dyspnea scale <math>\geq 2</math> - %<sup>a</sup></b> | 7.0<br>(2.9 to 11)     | 0<br>(0 to 9)          | 0.36  |
| <b>Percent predicted FEV<sub>1</sub></b>  | 100<br>(97 to 103)     | 100<br>(95 to 106)     | 0.91  |
| <b>Percent predicted FVC</b>  | 97<br>(94 to 99)       | 100<br>(94 to 105)     | 0.37  |
| <b>FEV<sub>1</sub>/FVC</b>  | 0.78<br>(0.78 to 0.79) | 0.77<br>(0.75 to 0.79) | 0.11  |
| <b>Percent predicted RV‡</b>  | 84<br>(75 to 93)       | 92<br>(76 to 108)      | 0.37  |
| <b>Percent predicted FRC‡</b>   | 94<br>(86 to 101)      | 106<br>(93 to 119)     | 0.11  |
| <b>Percent predicted TLC‡</b>   | 97<br>(91 to 102)      | 102<br>(92 to 112)     | 0.34  |
| <b>Percent predicted D<sub>LCO</sub>/VA‡</b>                                      | 80<br>(76 to 85)       | 76<br>(65 to 88)       | 0.44  |
| <b>Percent predicted 6MWD<sup>a</sup></b>   | 95<br>(91 to 98)       | 82<br>(74 to 90)       | 0.003 |
| <b>Percent emphysema<sub>&lt;-950HU</sub></b>                                     | 1.0<br>(0.7 to 1.4)    | 1.2<br>(1.0 to 1.4)    | 0.36  |
| <b>Proportion<br/>with SpO<sub>2</sub> <math>\leq</math> 95% - %</b>              | 13<br>(7.4 to 19)      | 19<br>(2.9 to 34)      | 0.54  |

|   |                     |                     |      |
|---|---------------------|---------------------|------|
| <b>White blood cell count – ·10<sup>9</sup>/L</b> | 6.1<br>(5.8 to 6.4) | 6.9<br>(6.2 to 7.5) | 0.03 |
|---|---------------------|---------------------|------|

\*P-values represent bi-variate comparison of mean or proportion using Chi-square, Fisher's exact or Student t-test where appropriate. †Plethysmography and diffusing capacity were measured on validation participants only. <sup>a</sup>6MWD and mMRC dyspnea scale were measured in a subset of participants (n=145 and n=156 participants, respectively).

Abbreviations: MESA denotes Multi-Ethnic Study of Atherosclerosis, COPD chronic obstructive pulmonary disease, CI confidence interval, mMRC modified Medical Research Council, FEV<sub>1</sub> forced expired volume in the first second, FVC forced vital capacity, RV residual volume, FRC functional residual capacity, TLC total lung capacity, D<sub>LCO/VA</sub> diffusing capacity of the lung for carbon monoxide divided by alveolar volume, 6MWD six minute walk distance, HU Hounsfield units, and SpO<sub>2</sub> pulse-oximeter estimated arterial oxygen-hemoglobin saturation.