Supplemental Figures Legends

Supplementary Figure 1: Kaplan–Meier curve of recurrence according to age in the NYU cohort. Patients were stratified into young (≤70 years) and old (>70 years) groups. No significant differences in recurrence-free survival were observed between groups (log rank test, $p = 0.58$). Numbers at risk and censored subjects are shown below the plot.

Supplementary Figure 2: Kaplan–Meier curve of recurrence according to age in external cohorts. (A) No significant differences in recurrence-free survival were observed between patients young (≤70 years) and old (>70 years) in TCGA cohort (log rank test, $p = 0.69$). (B) TRACERx cohort results showing significantly higher recurrence rate among older patients ($p = 0.014$). Numbers at risk and censored subjects are shown below the plot.

Supplementary Figure 3: Transcriptomic signatures associated with age in tumors and adjacent non-tumor lung (NAT) samples from the NYU cohort. (A) Principal coordinate analysis (PCoA) showing overall transcriptomic differences between young (≤70 years) and old (>70 years) patients in tumor tissue (PERMANOVA, p=ns). (B) Volcano plots of differentially expressed genes between young and old groups in tumor tissue. Genes upregulated in older patients are shown in blue, and those in younger patients in green. (C) PCoA showing overall transcriptomic differences between young (≤70 years) and old (>70 years) patients in NAT (PERMANOVA, p=ns). (D) Volcano plots of differentially expressed genes between young and old groups in NAT. Genes upregulated in older patients are shown in blue, and those in younger patients in green.

Supplementary Figure 4: Canonical pathway analysis by Ingenuity Pathways Analysis (IPA) of age-associated differential expression in the NYU cohort. A heatmap of canonical pathway analysis based on IPA comparing old (>70 years) versus young (≤70 years) patients in both tumor and normal adjacent tissue. Yellow shows upregulation of pathway, and blue shows downregulation.

Supplementary Figure 5: Transcriptomic signatures associated with age in tumors and adjacent non-tumor lung (NAT) samples in the TCGA cohort. (A) Principal coordinate analysis (PCoA) showing overall transcriptomic differences between young (≤70 years) and old (>70 years) patients in tumor tissue (PERMANOVA, p=ns). (B) Volcano plots of differentially expressed genes between young and old groups in tumor tissue. Genes upregulated in older patients are shown in blue, and those in younger patients in green. (C) PCoA showing overall transcriptomic differences between young (≤70 years) and old (>70 years) patients in NAT (PERMANOVA, p=ns). (D) Volcano plots of differentially expressed genes between the young and old groups in NAT. Genes upregulated in older patients are shown in blue, and those in younger patients are shown in green. (E) A heatmap of canonical pathway analysis based on IPA comparing old (>70 years) versus young (≤70 years) patients in both tumor and normal adjacent tissue. Yellow shows upregulation of pathways, and blue shows downregulation.

Supplementary Figure 6: Age-associated transcriptomic differences in tumors from the TRACERx cohort. (A) Principal coordinate analysis (PCoA) showing overall transcriptomic differences between young (≤70 years) and old (>70 years) patients (PERMANOVA, p=0.01). (B) Volcano plot of differentially expressed genes by age group; Genes upregulated in older patients are shown in blue, and those in younger patients in green. (C) A barplot based on IPA showing z-score values of pathways upregulated in old vs. young.

Supplementary Figure 7: Transcriptomic signatures associated with age in tumors and adjacent non-tumor lung (NAT) samples from the NYU and TCGA cohorts following adjusting for clinical covariates. (A) Volcano plots of differentially expressed genes between young and old groups in tumor tissue. Genes upregulated in older patients are shown in blue, and those in younger patients in green. (B) Volcano plots of differentially expressed genes between young and old groups in NAT. Genes upregulated in older patients are shown in blue, and those in younger patients in green. (C) Canonical pathway analysis by Ingenuity Pathways Analysis (IPA) of age-associated differential expression in the NYU cohort. A heatmap of canonical pathway analysis based on IPA comparing old (>70 years) versus young (≤70 years) patients in both tumor and normal adjacent tissue. Yellow shows upregulation of pathway, and blue shows downregulation.

(D) Differentially expressed genes between young and old groups in tumor tissue, TCGA cohort.

(E) Differentially expressed genes between young and old groups in NAT tissue, TCGA cohort.

(F) Canonical pathway analysis of age associated differentially expressed genes in the TCGA cohort. A heatmap of canonical pathway analysis based on IPA comparing old (>70 years) versus young (≤70 years) patients in both tumor and normal adjacent tissue

Supplementary Figure 8: Age-associated transcriptomic differences in tumors from the TRACERx cohort after adjusting for clinical covariates (A) Volcano plot of differentially expressed genes by age group; Genes upregulated in older patients are shown in blue, and those in younger patients in green. (B) A barplot based on IPA showing z-score values of pathways upregulated in old vs. young.

Supplementary Figure 9: Shared genes between the NYU, TCGA and TRACERx cohorts' gene datasets associated with recurrence among A) old and B) young patients. Asterisks resemble statistically significant GSEA analysis (FDR <0.05) showing a significant overlap between two groups.

Supplementary Figure 10: Transcriptomic signatures associated with recurrence in tumor tissue following adjusting for clinical covariates. (A, B) volcano plots of differentially expressed genes (FDR <0.2) between subjects with recurrence and without recurrence in old and young patients in the NYU cohort, respectively. (C) heatmap of canonical pathway analysis based on Ingenuity Pathway Analysis (IPA) comparing recurrence vs. no recurrence groups in old and young patients within the NYU cohort. Yellow shows upregulation of pathways, and blue shows downregulation. Similar analysis pattern in (D-F) TCGA cohort, and (H-J) TRACERx cohort.

Supplementary Figure 11: MEGENA-based co-expression network analysis of tumor samples in the NYU cohort. Sunburst plots show genes co-expression modules identified by MEGENA analysis that are associated with recurrence in (A) old and (B) young patients. Red shows upregulation of module, and blue downregulation of module. Major modules are highlighted: (A)

Modules associated with recurrence in older patients include ECM remodeling (M155), cell cycle (M169), and GPCR/matrisome signaling (M163). (B) Modules associated with recurrence in younger patients include organelle biogenesis (M159), surfactant metabolism (M104), and AP1/ATF2/IL-cytokine signaling (M651).

Supplementary Figure 12: Recurrence associated transcriptomic in normal adjacent tissue samples (NAT) stratified by age. (A, B) Principal Coordinate analysis (PCoA) comparing patients with recurrence vs. no recurrence in NYU cohort NAT samples from old (>70 years) and young (≤70 years) patients. (C, D) PCoA comparing patients with recurrence vs. no recurrence in TCGA cohort NAT samples from old (>70 years) and young (≤70 years) patients. No significant global separation by recurrence was observed in either cohort (PERMANOVA, p=ns).

Supplementary Figure 13: Shared genes between the NYU and TCGA cohorts associated with recurrence among A) old and B) young patients. Asterisks resemble statistically significant GSEA analysis (FDR ≤ 0.05) showing a significant overlap between two groups.

Supplementary Figure 14: Transcriptomic signatures associated with recurrence in NAT tissue following adjusting for clinical covariates. (A, B) volcano plots of differentially expressed genes (FDR <0.2) between subjects with recurrence and without recurrence in old and young patients in the NYU cohort, respectively. (C) heatmap of canonical pathway analysis based on Ingenuity Pathway Analysis (IPA) comparing recurrence vs. no recurrence groups in old and young patients within the NYU cohort. Yellow shows upregulation of pathways, and blue shows downregulation. Similar analysis pattern in (D-F) TCGA cohort.

Supplementary Figure 15: MEGENA based co-expression network analysis of normal adjacent tissue samples (NAT) in the NYU cohort. Sunburst plots show genes co-expression modules identified by MEGENA analysis that are associated with recurrence in (A) old and (B) young patients. Red shows upregulation of module, and blue downregulation of module. Major modules are highlighted: (A) Modules associated with recurrence in older patients include immune-related

(M151), ECM remodeling (M155), and cytokine/AP1-ATF2 (M168) modules. (B) Modules associated with recurrence in younger patients include enrichment of ECM/matrisome (M164) and transcriptional regulation (M604).