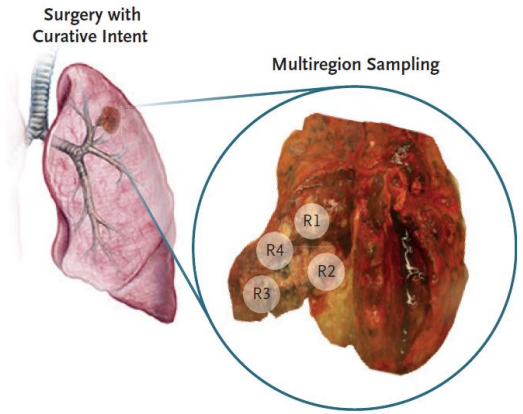
Sure….. integrate immune markers into Prognosis

- Its not as easy as you think
- Consider the genomic, i.e. mutations (SNV), copy number abberations, neoantigens, clonality, subclonality, evolution, and then how these spatially relate to each other.

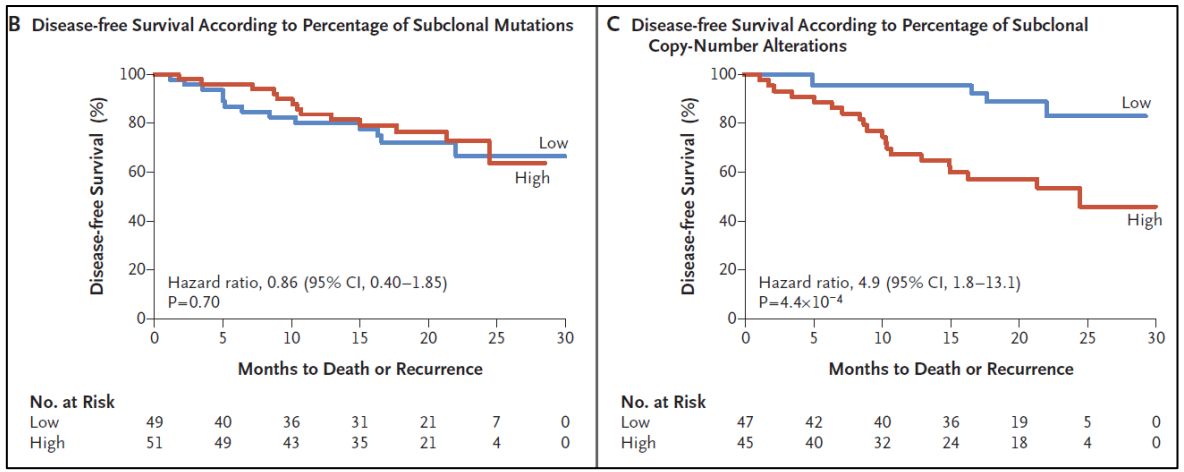
Immunological/Pathological/Prognosis

- Intratumoral Heterogeneity and Chromosomal Instability



Somatic mutations, SNV and CAN measured as a percentage of the genome affected by such alterations, classified as clonal (present in all cancer cells) or subclonal (present in a subset of cancer cells)

- 30% of somatic mutations were subclonal
- 48% of CNA were subclonal
- SCC > Adeno for clonal but ND in subclonal or within Ad subtypes
- **POOR PROGNOSIS: Tumors with higher proportion of subclonal CNAs, not subclonal mutations**



Patients with early-stage tumors with high levels of copy-number heterogeneity may represent a high-risk group who may benefit from close monitoring and early therapeutic intervention during follow-up.

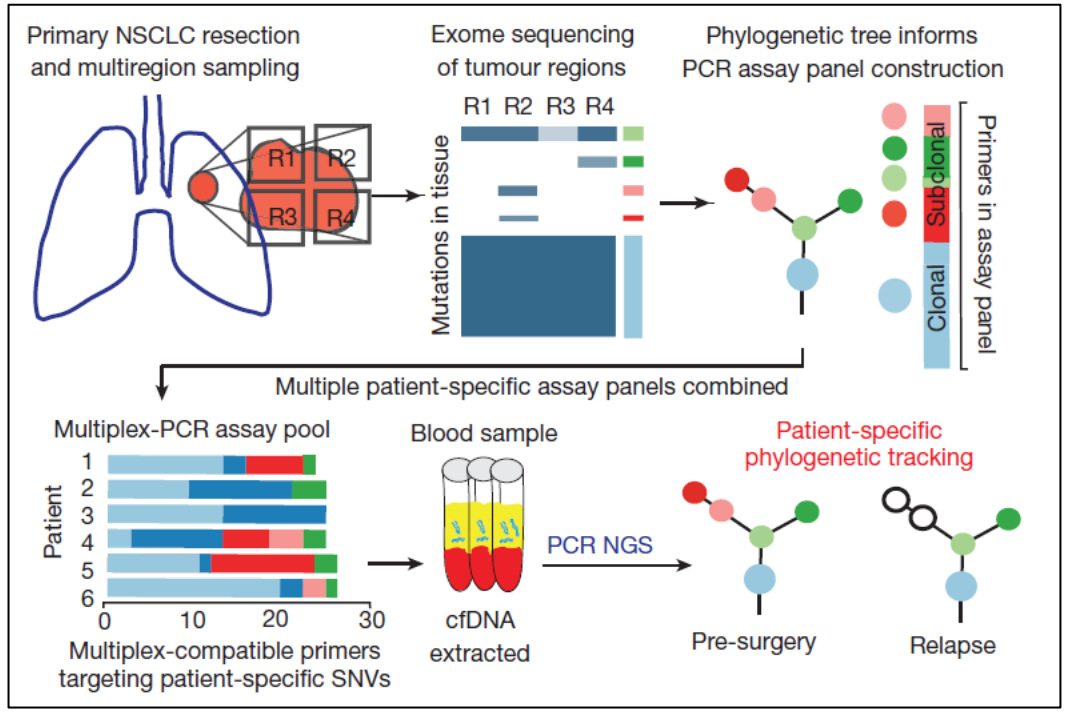
Take home: Capturing tumors prior to subclonal diversification requires earlier detection and screening.

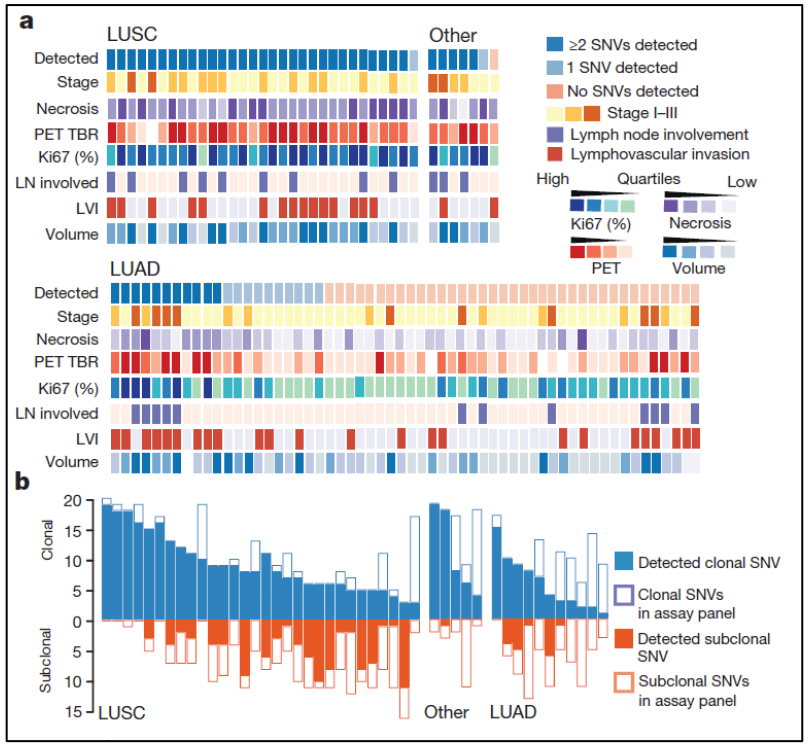
Tracking the Evolution of Non–Small-Cell Lung Cancer

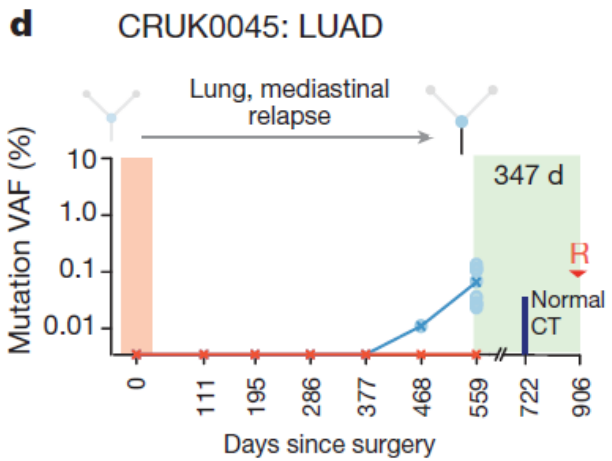
N Engl J Med 2017;376:2109-21.

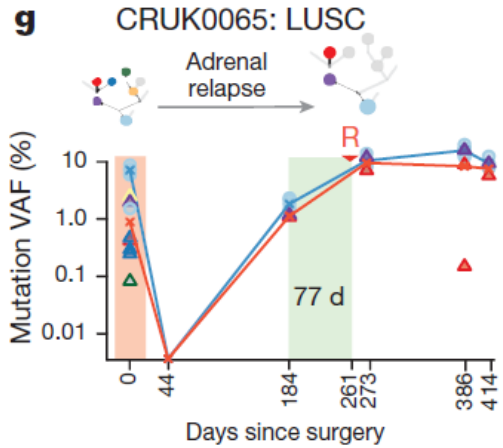
Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution

25 MAY 2017 | VOL 545 | NATURE | 447





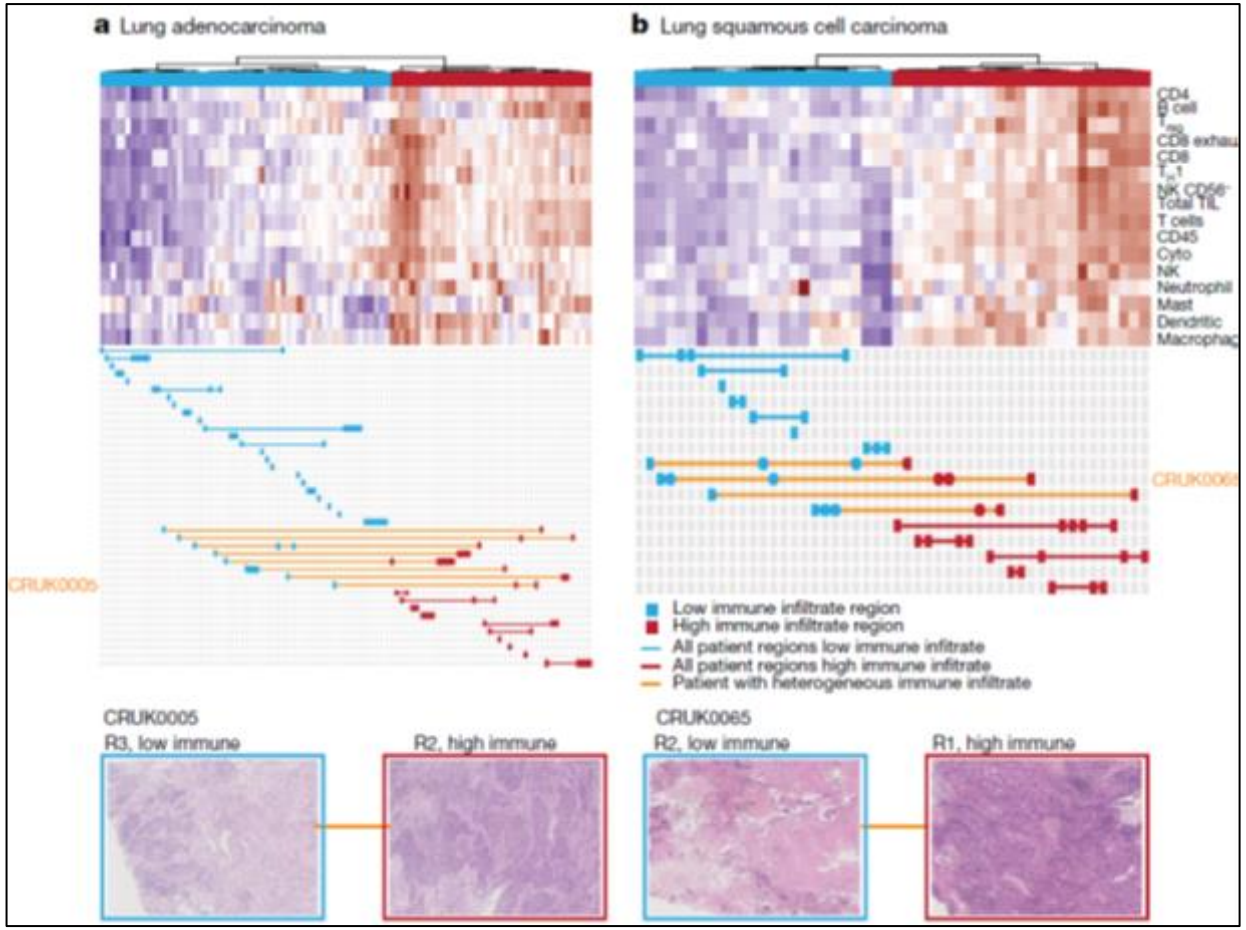


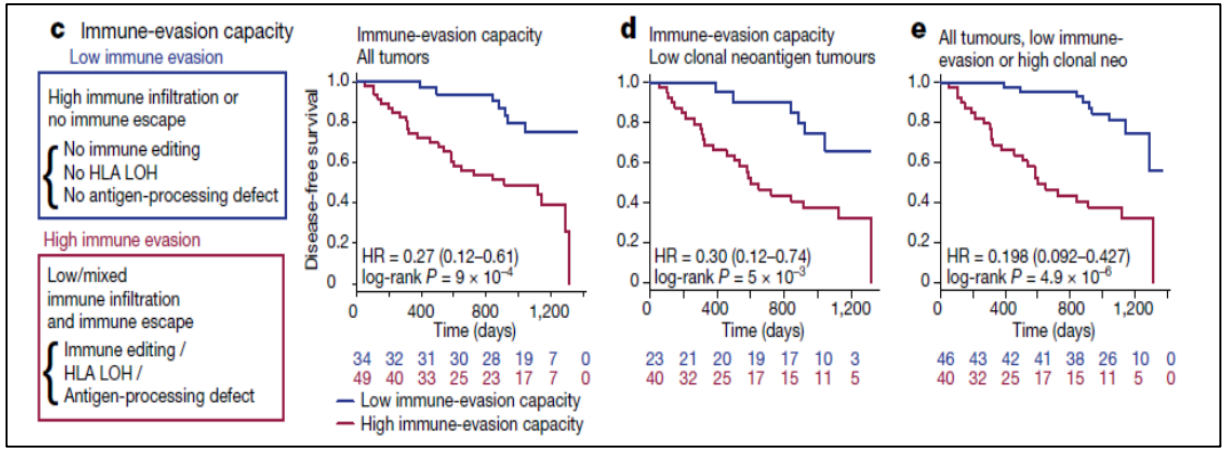


Neoantigen-directed immune escape in lung cancer evolution

28 MARCH 2019 | VOL 567 | NATURE | 479

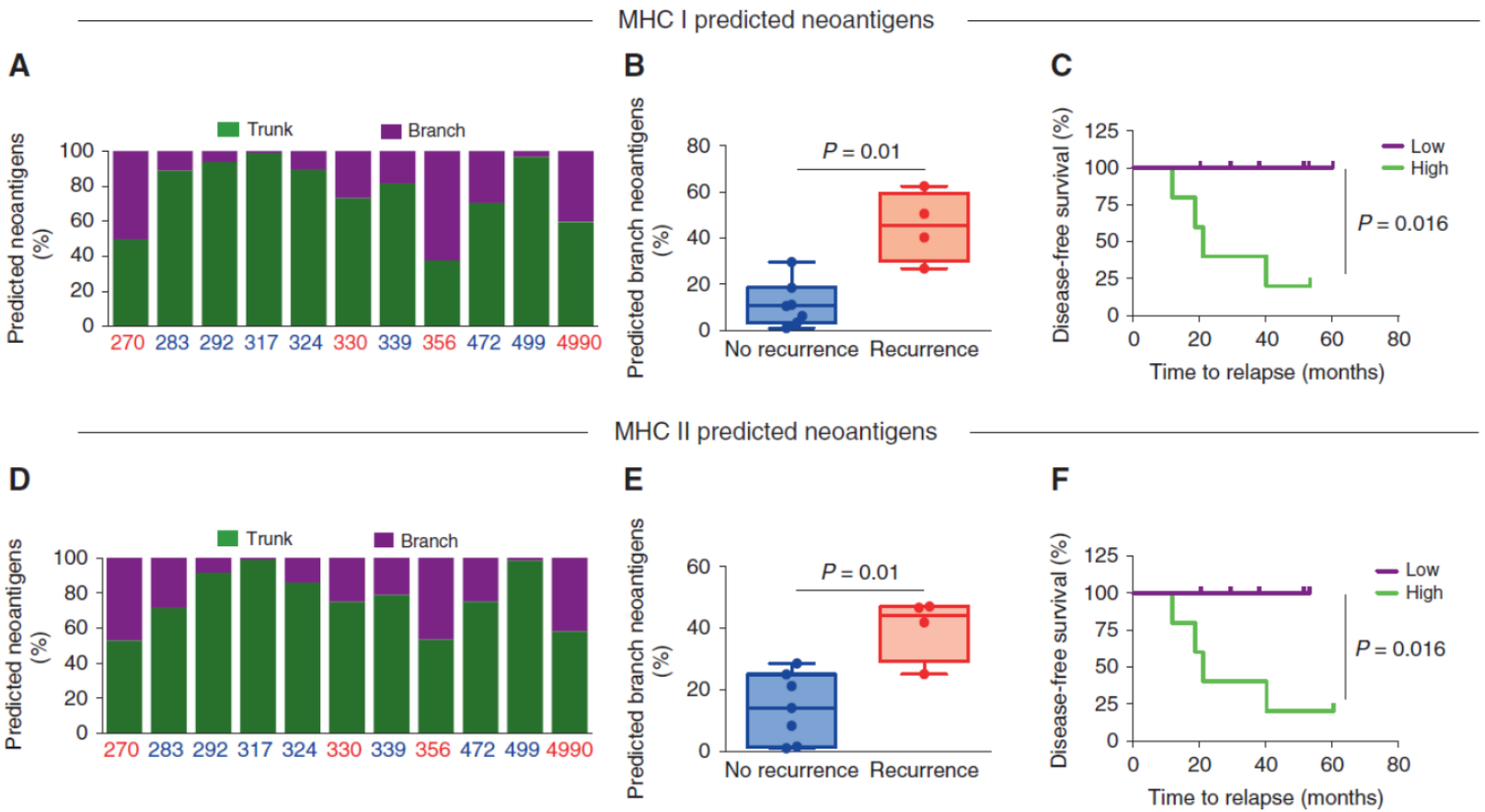
- Immune heterogeneity in tumors is dictated by immunologic sculpting, immunoediting, and immune escape and is visible at the levels of DNA (mutation, copy number, genetic heterogeneity), RNA (expression), and the epigenome (promoter hypermethylation).
- Immune infiltration and tumor mutational burden (TMB) can vary within the same tumor, with 28% of samples demonstrating immunologic heterogeneity and 21% of samples harboring TMB heterogeneity.
- Neoantigen-producing mutations were more likely to be located in areas of subclonal copy number loss compared to non-neoantigen mutations.
- Immunologically cold tumors
  - **more** ubiquitously expressed clonal neoantigens,
  - **HLA loss of heterozygosity** is present and is a mode of immune evasion.
  - **Epigenetic neoantigen repression**, with neoantigenic mutations much more likely to have **DNA promoter hypermethylation** compared to the same genes lacking neoantigenic mutations.





TCR Repertoire Intratumor Heterogeneity in Localized Lung Adenocarcinomas: An Association with Predicted Neoantigen Heterogeneity and Postsurgical Recurrence

July 21, 2017; DOI: 10.1158/2159-8290.CD-17-0256



What about immune gene signatures?

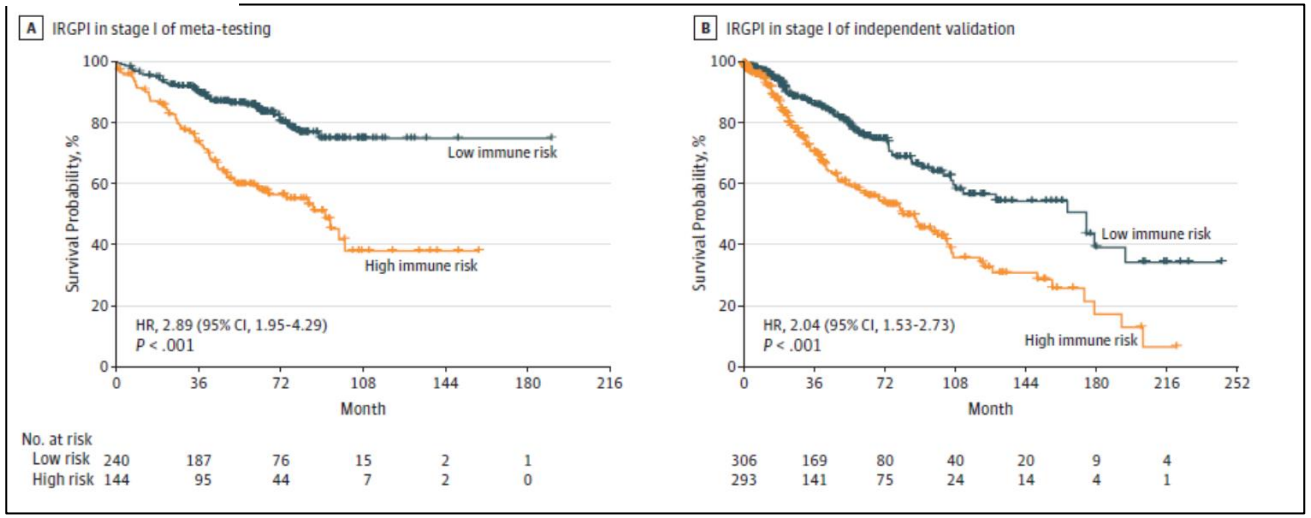
Development and Validation of an Individualized Immune Prognostic Signature in Early-Stage Nonsquamous Non–Small Cell Lung Cancer

JAMA Oncol. 2017;3(11):1529-1537. doi:10.1001/jamaoncol.2017.1609

In silico construction of immune gene risk signature using 25 immune related genes

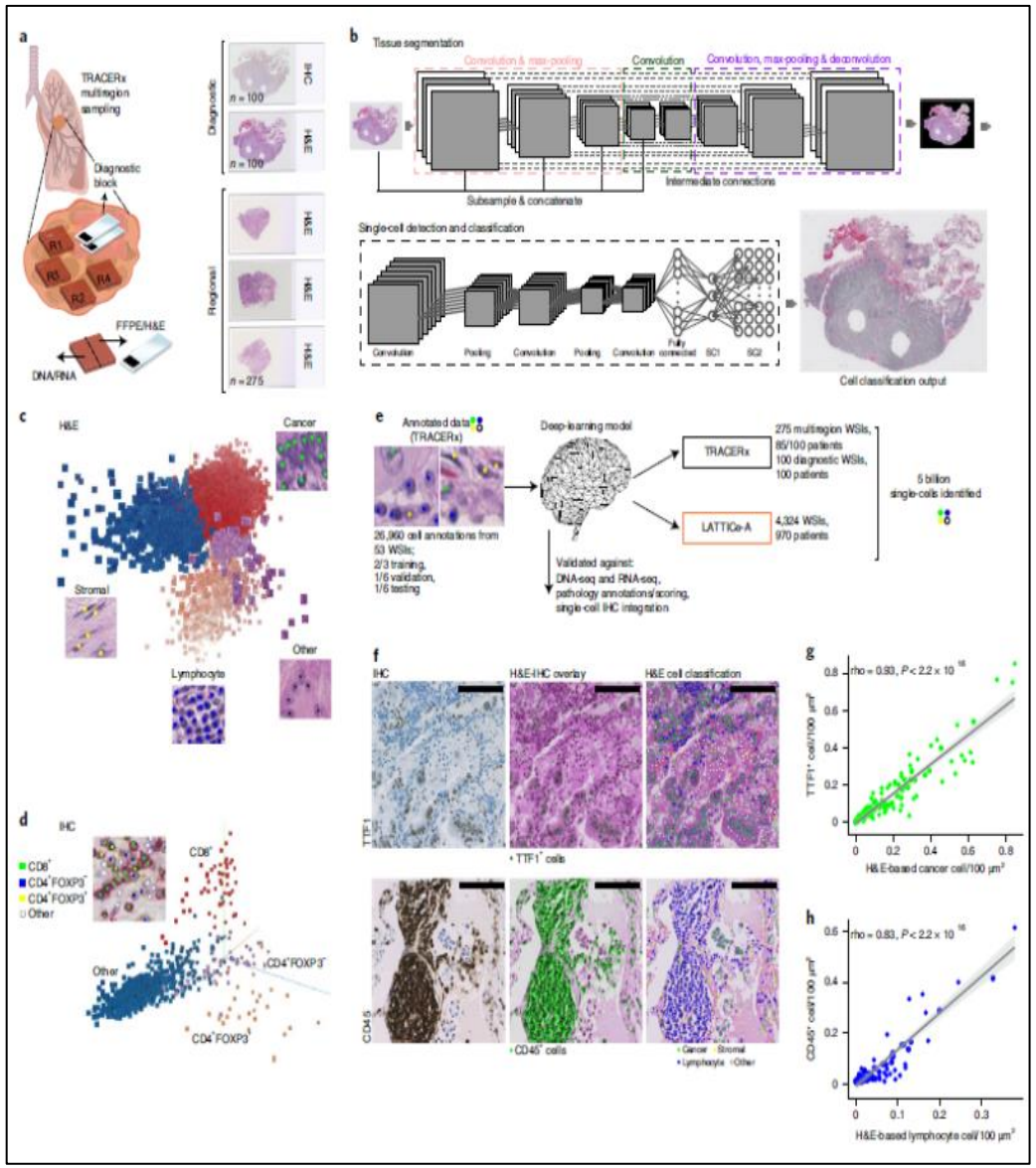
- Cytokines, cytokine receptors, and genes related to the T-cell receptor signaling pathway, B-cell antigen receptor signaling pathway, natural killer cell cytotoxicity, and antigen processing and presentation pathways.

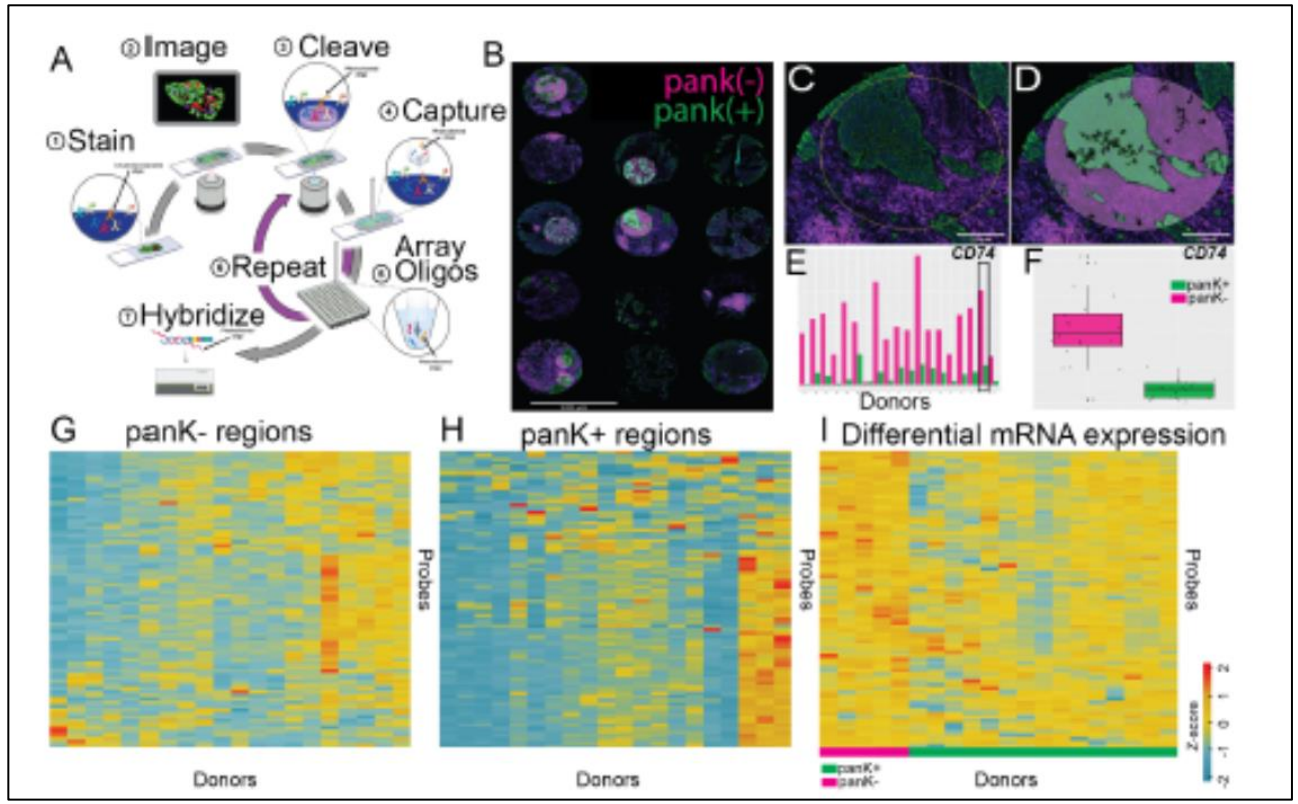
C-index 0.64 which isn't that great



Geospatial immune variability illuminates differential evolution of lung adenocarcinoma

NATURE MEDICINE | VOL 26 | JULY 2020 | 1054–1062 | www.nature.com/naturemedicine





Immunotranscriptomics of Blood and Prognosis