Building Cancer Digital Twins for Precision Oncology

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Complex diseases such as cancers are driven by a complex cell ecosystem

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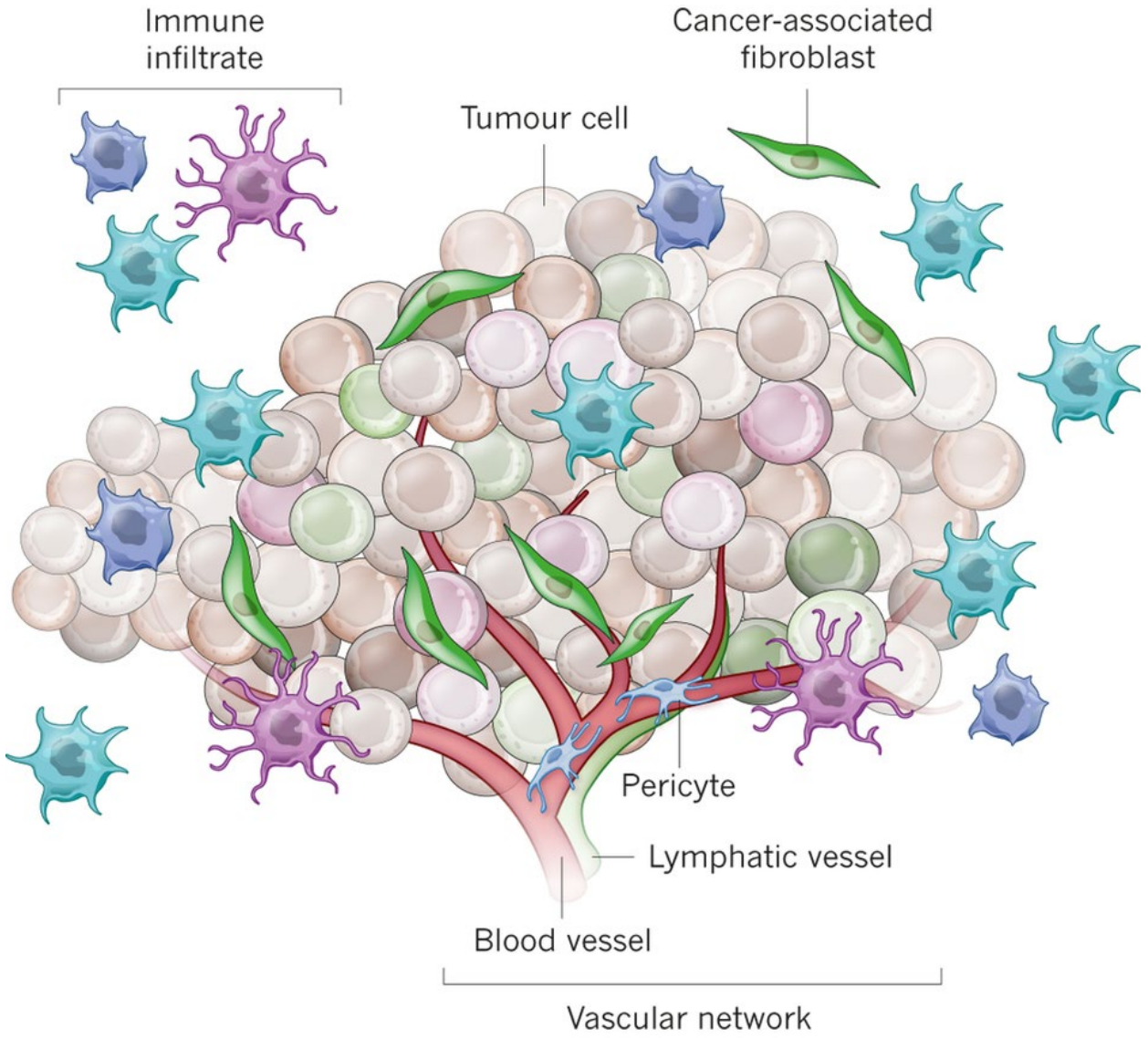


Can we build mechanistic simulations of tumors so as to test effect of therapies before treating a patient with cancer ?

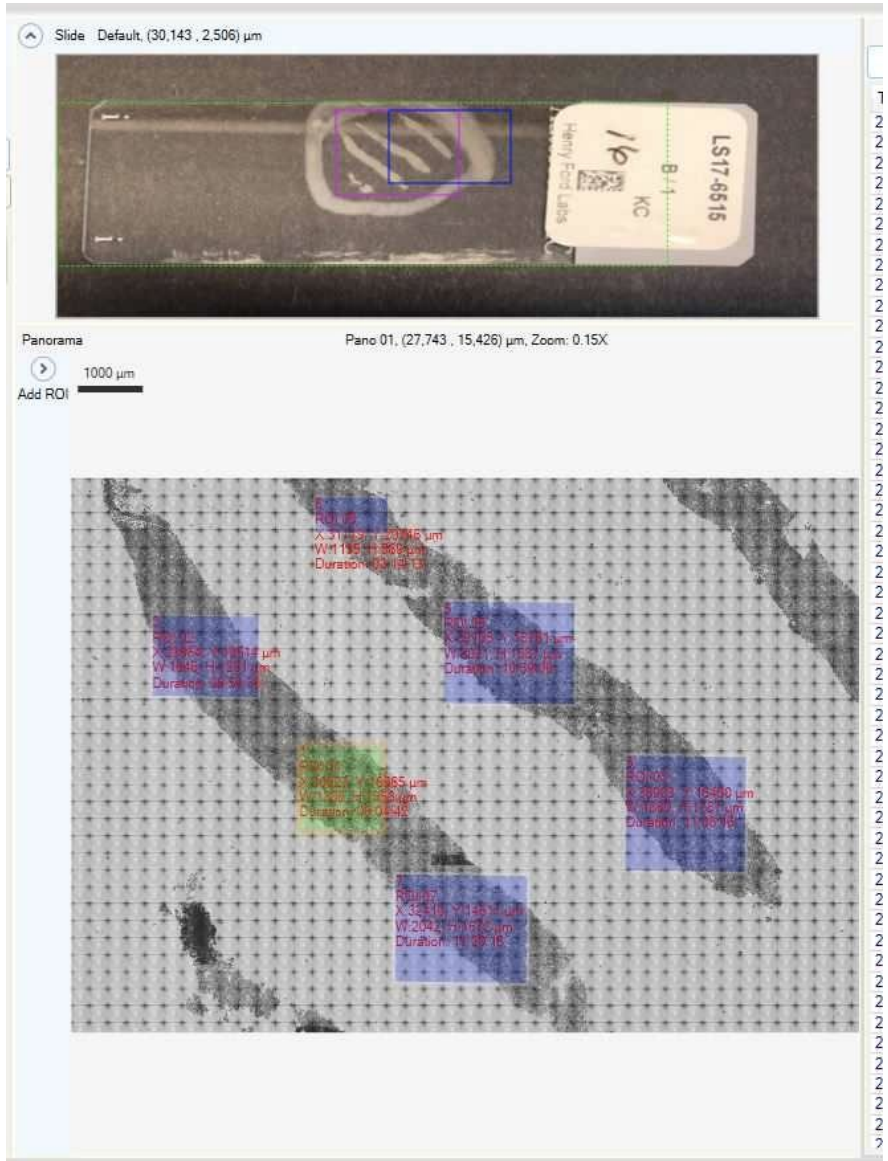
Spatial proteomics and transcriptomics to interrogate tissue architecture

CODEX/Phenocycler

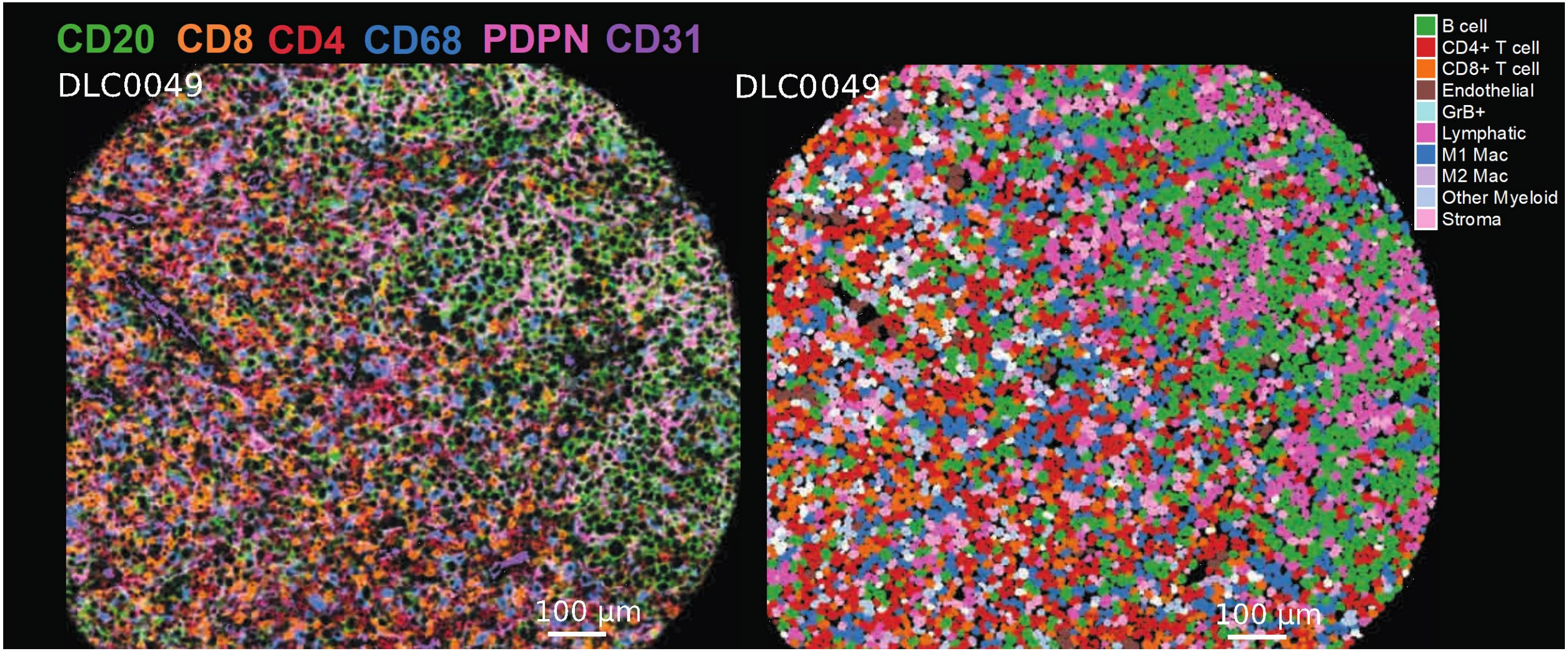
Hyperion/imaging mass cytometry

Nanostring CosMX

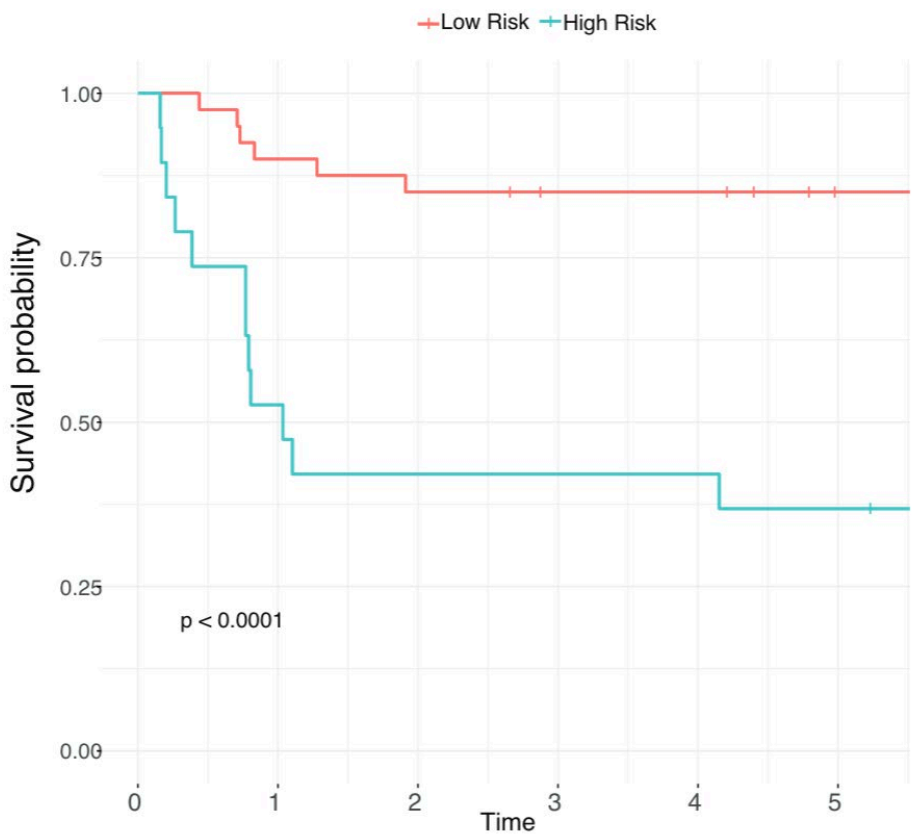
Tissue slides & tissue microarrays



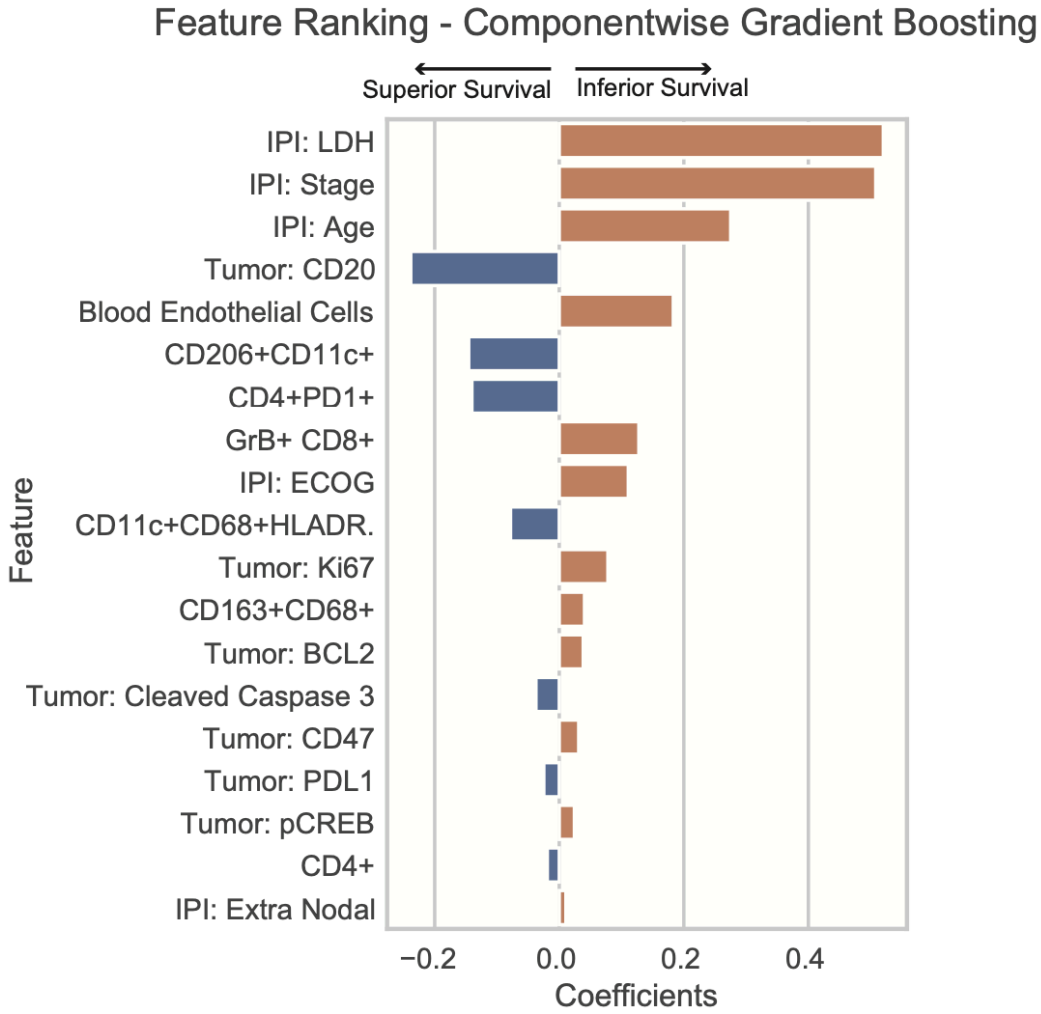
Each cell now has a specific identity



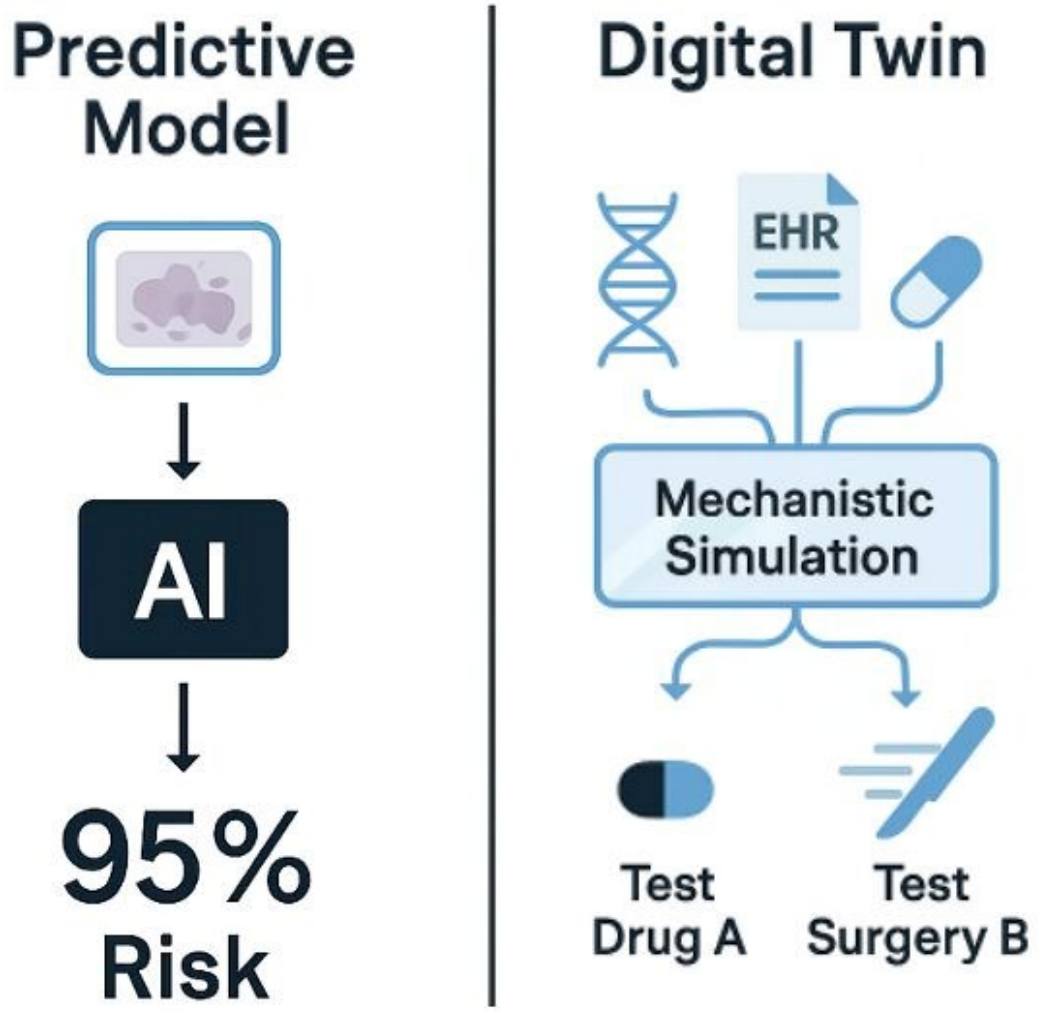
Machine learning (XGBoost) model predict survival upon R-CHOP and identifies key predictive factors



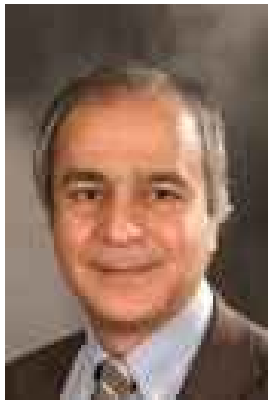
Predictions in test set independent from training set



From spatial data to tumor digital twins



Spatial analysis of early-stage lung adenocarcinoma



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Low dose CT detects smaller more curable lung cancers

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

The aggressive and heterogeneous nature of lung cancer has thwarted efforts to reduce mortality from this cancer through the use of screening. The advent of low-dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages. The National Lung Screening Trial (NLST) was conducted to determine whether screening with low-dose CT could reduce mortality from lung cancer.

METHODS

From August 2002 through April 2004, we enrolled 53,454 persons at high risk for lung cancer at 33 U.S. medical centers. Participants were randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732). Data were collected on cases of lung cancer and deaths from lung cancer that occurred through December 31, 2009.

RESULTS

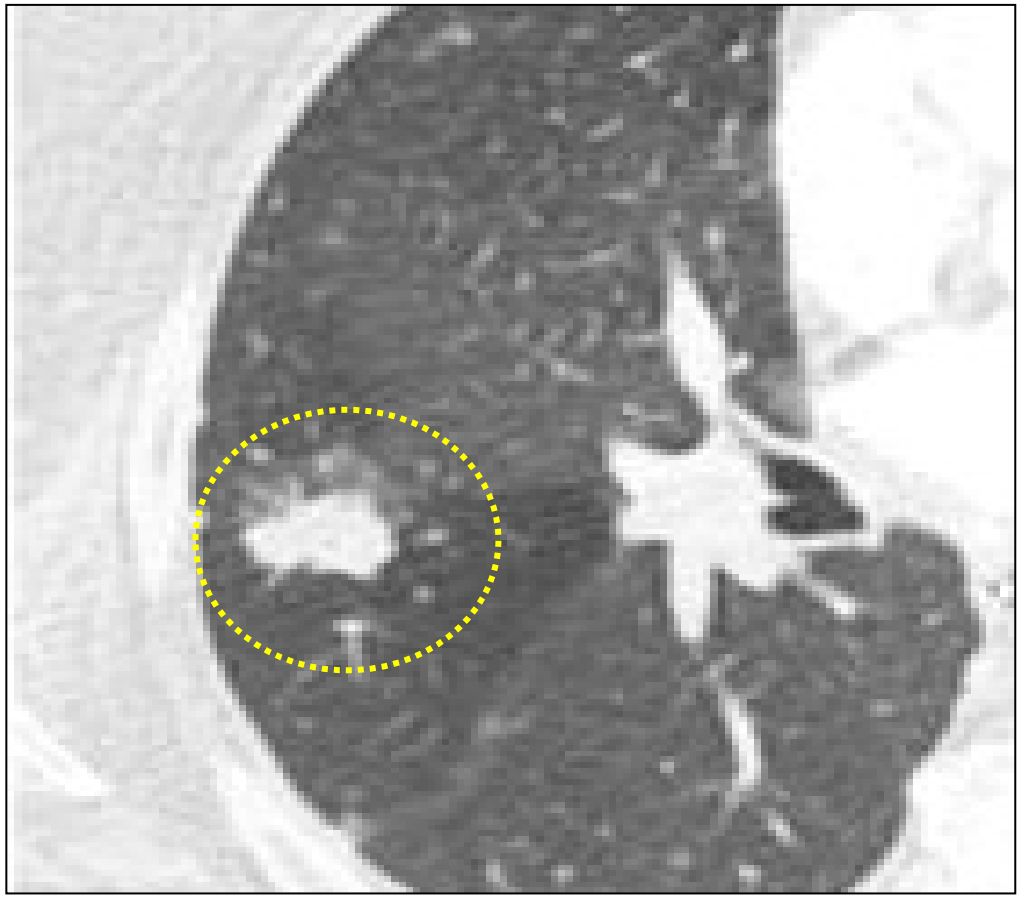
The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false positive results. The incidence of

The members of the writing team (who are listed in the Appendix) assume responsibility for the integrity of the article. Address reprint requests to Dr. Christine D. Berg at the Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd., Suite 3112, Bethesda, MD 20892-7346, or at bergc@mail.nih.gov.

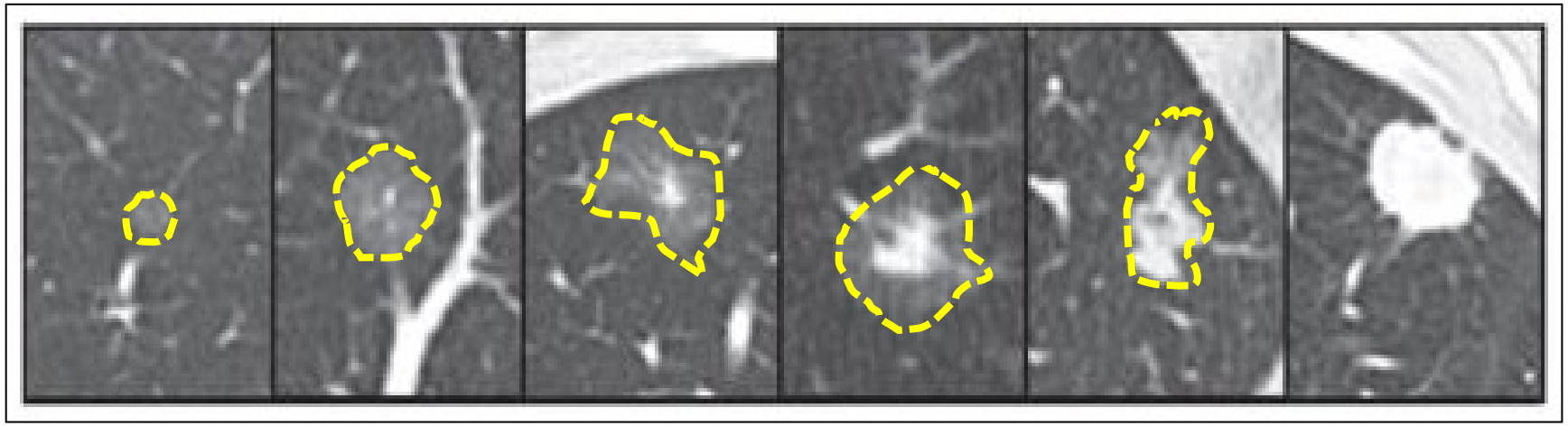
*A complete list of members of the National Lung Screening Trial research team is provided in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1102873) was published on June 29, 2011, at NEJM.org.

N Engl J Med 2011;365:395-409.



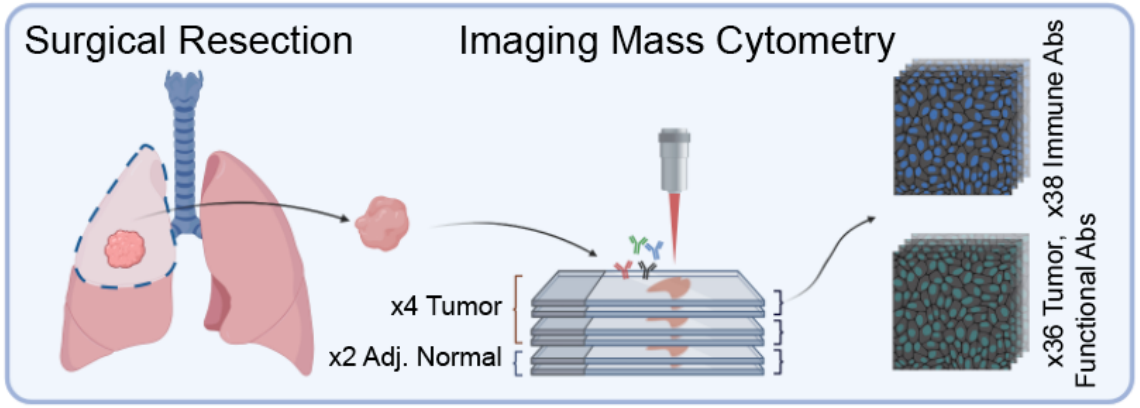
Radiographic progression to Lung Adenocarcinoma (LUAD



Pure Non-Solid → Part Solid → Solid

Godoy, M et al
Current Opinion in Pulmonary Medicine. 18(4):304-312, July 2012.

Using IMC for deep characterization of lung adenocarcinoma (LUAD) initiation and progression



Radiological Phenotype

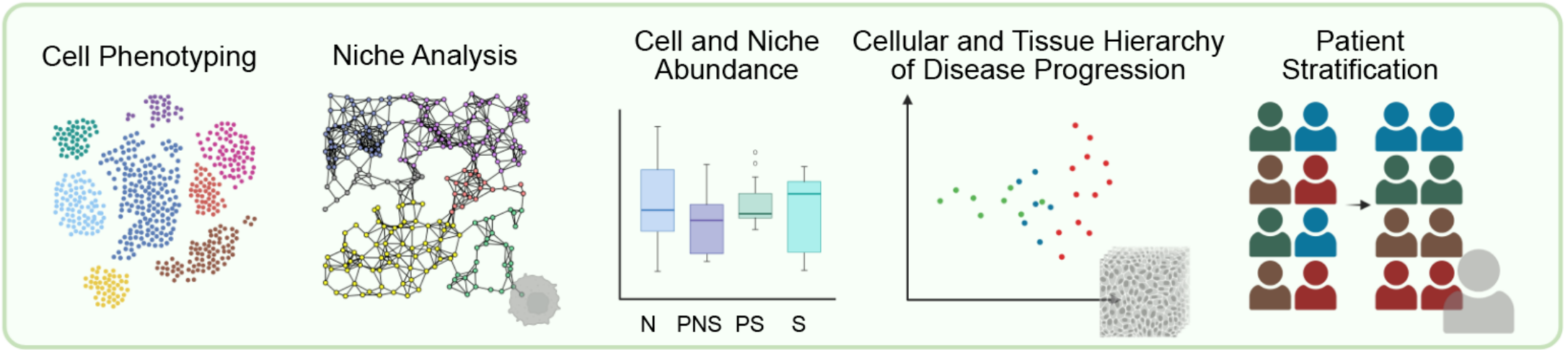
Initiation Progression

χ^2 **value**: 17.83
p-value: 0.0013

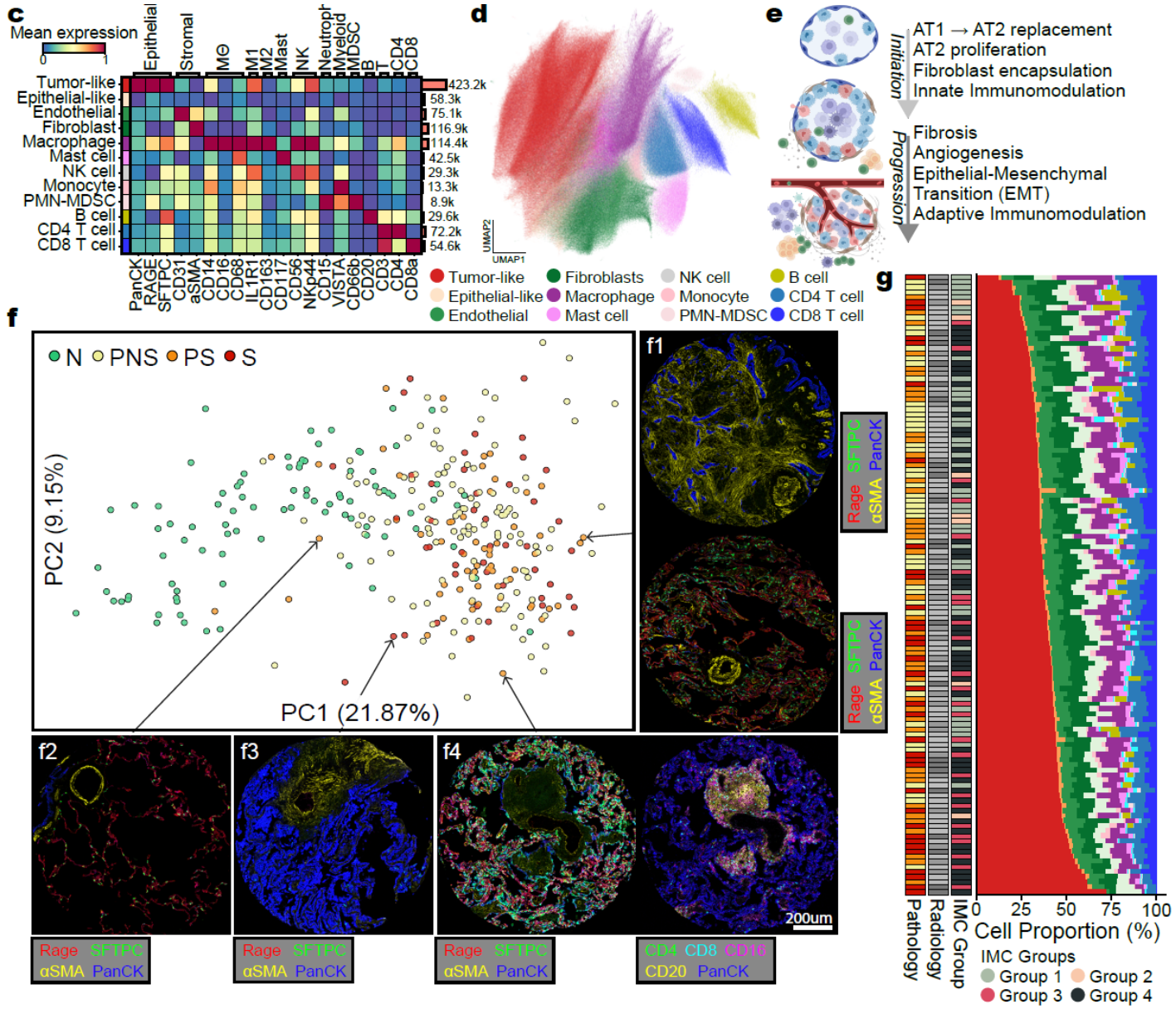
Histological Phenotype	N	PNS	PS	S	Unk.	Total
N	98					~~(Matched)~~
AIS		24	9	7	4	44
MIA		30	10	4	0	44
iAC		8	12	13	2	35
Total	~~ ~~	62	31	24	6	**123**(98)

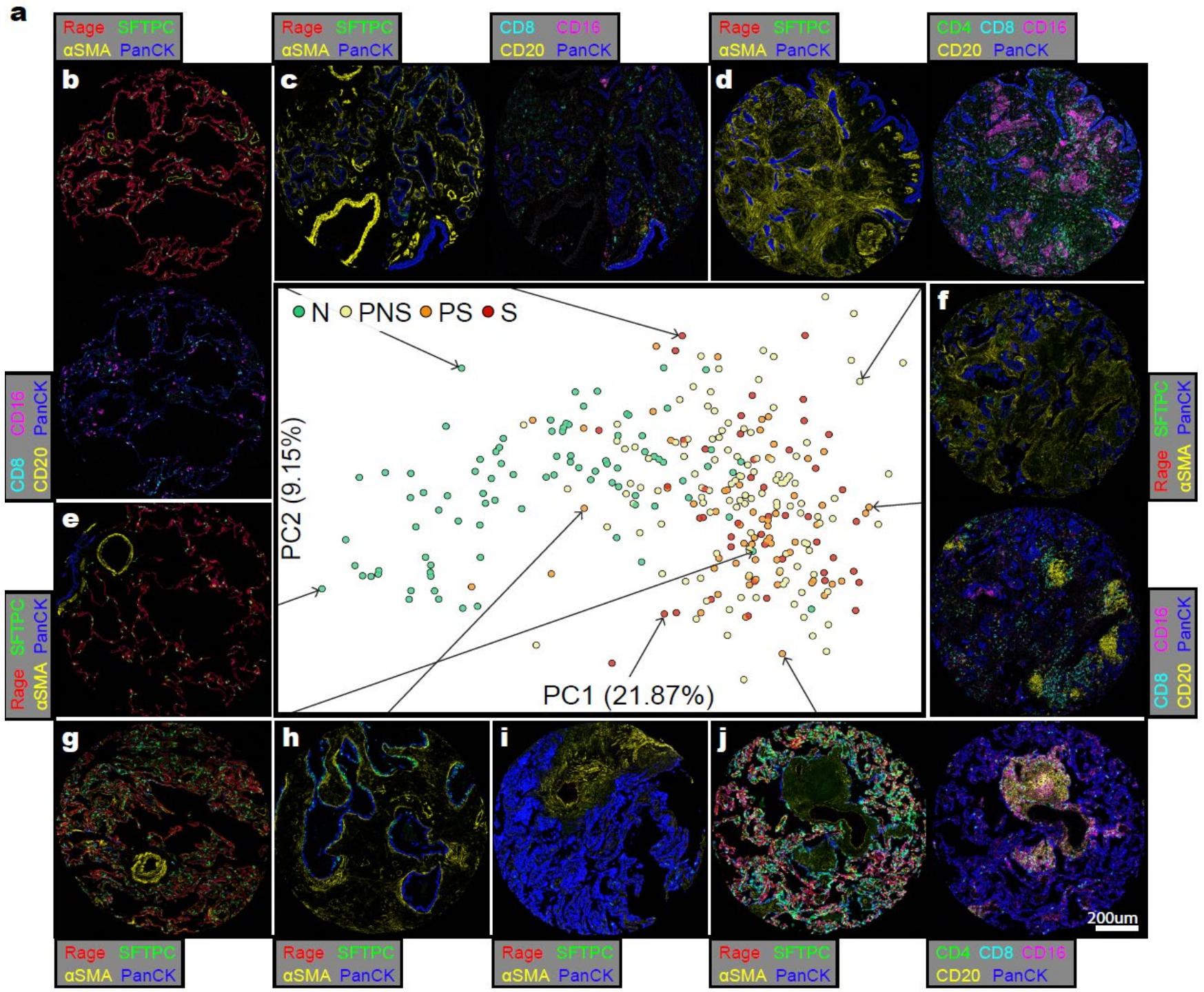
Initiation

Progression



Study Overview





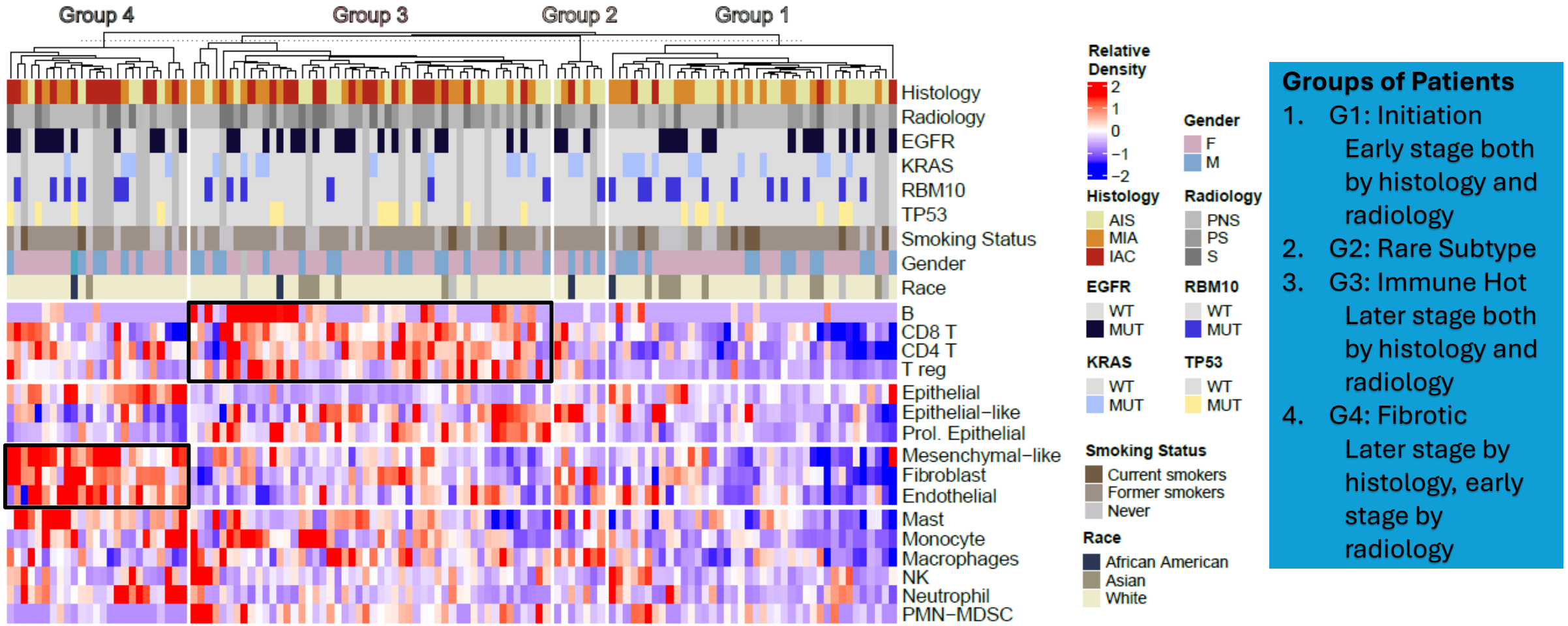
Incredible Extent of Inter-tumor Molecular Heterogeneity

- **PC1** captures normal – tumor variation
- **PC2** captures stromal and immune variation
- **Epithelial, Stromal, and Immune** variation
- **Molecular variation** does not correlate well with principal **clinical variation**

Is there a better way to simplify these heterogeneity for a more precise diagnosis?

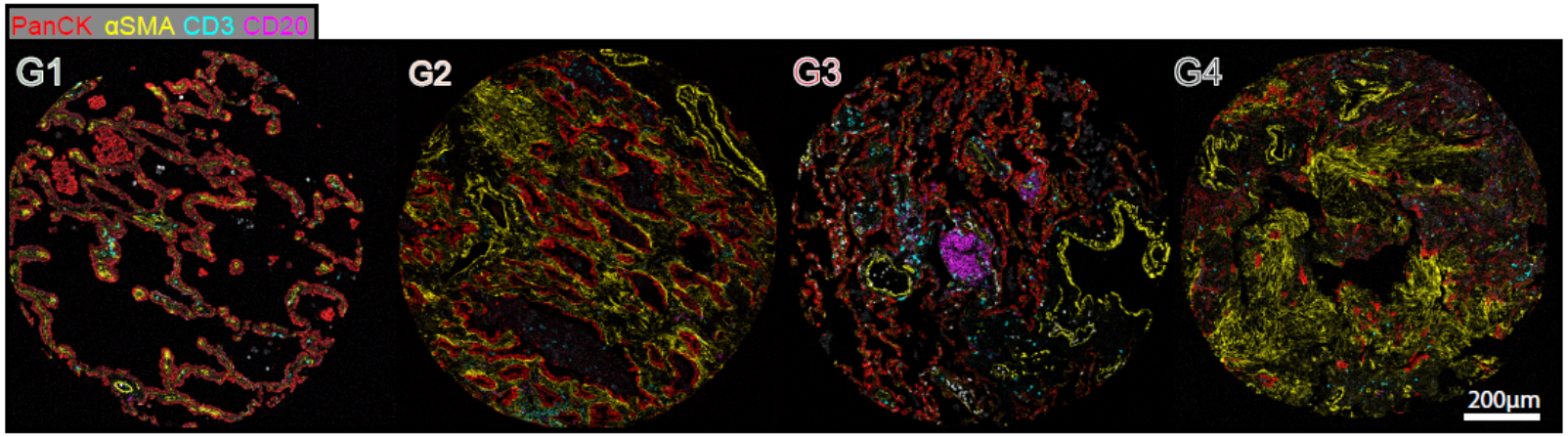
Unpublished material, Manuscript submitted

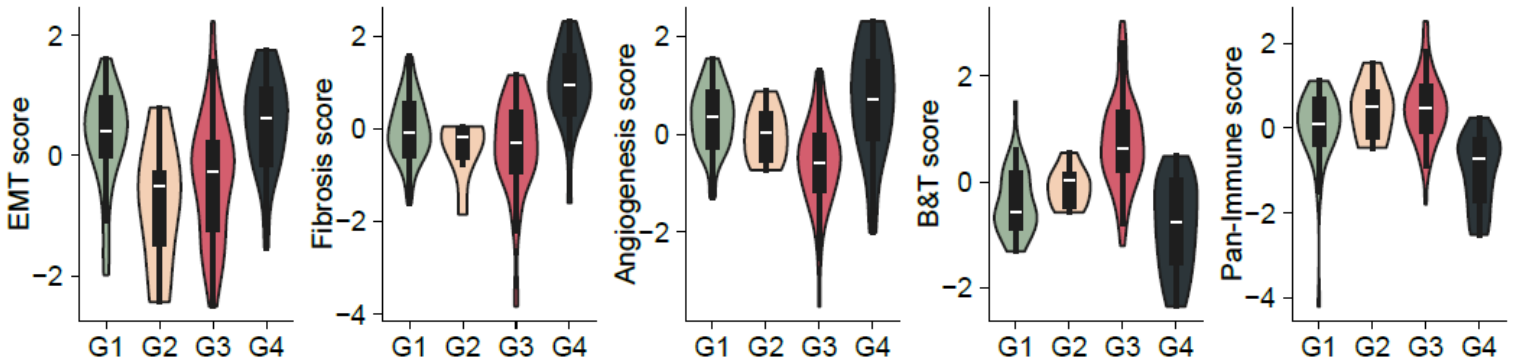
Patient Stratification into 4 groups based on IMC

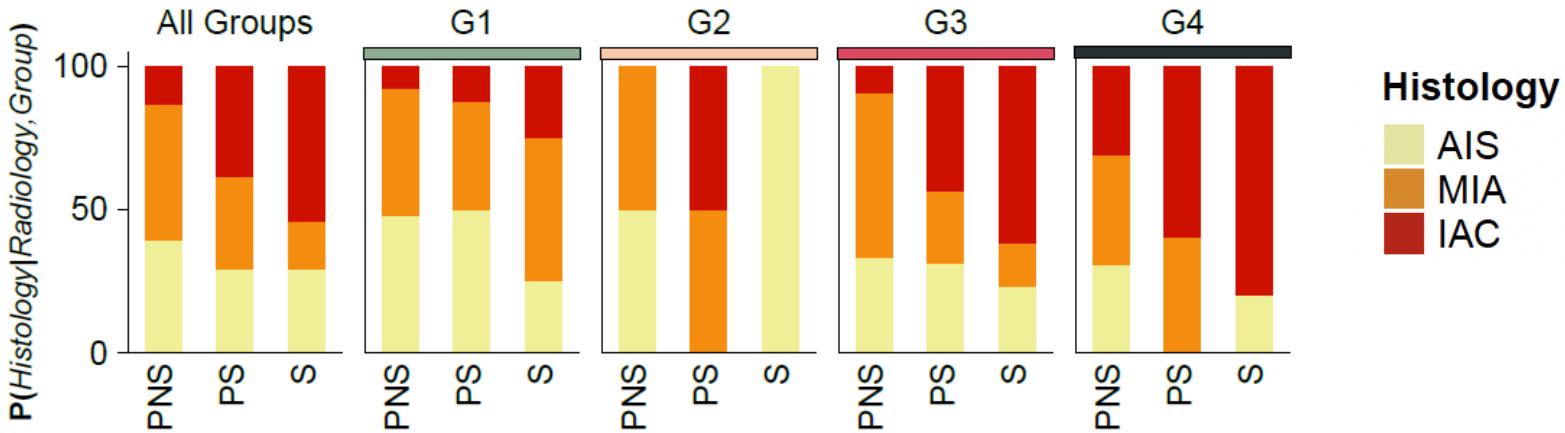


Groups of Patients

1. G1: Initiation
   Early stage both by histology and radiology
2. G2: Rare Subtype
3. G3: Immune Hot
   Later stage both by histology and radiology
4. G4: Fibrotic
   Later stage by histology, early stage by radiology







Groups of Patients

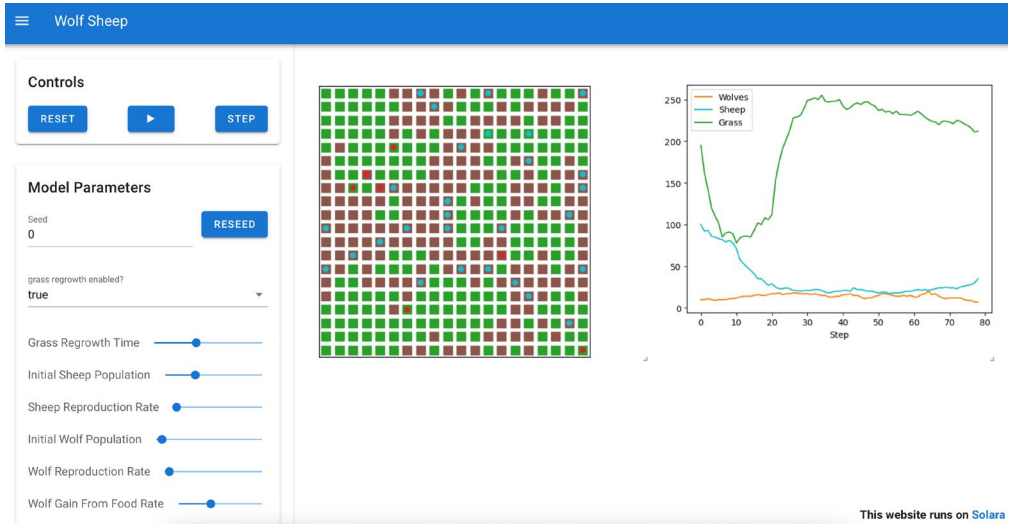
1. G1: Initiation
2. G2: Rare Subtype
3. G3: Immune Hot
4. G4: Fibrotic

Understanding Risk of Fibrotic LUADs

- High fibrosis, angiogenesis, EMT
- **Low Immune score** in general
- **25% increased risk** of **invasive adenocarcinoma** compared to other patients

Agent-Based Model (ABM) of the LUAD Microenvironment

Core idea: simulate dynamics by tracking individual agents (cells, niches, stromal nodes) that follow localized rules; system-level behavior emerges from their interactions.



Why use ABM for cancer

- Preserves spatial heterogeneity (immune exclusion, CAF cuffs, TLS pockets) absent in ODEs or bulk averages.
- Easily toggles mechanisms (matrix stiffness, suppression, chemotaxis) one at a time.
- Generates movies/plots that can map back onto multiplex images or histology.

What ABM lets us test

- Scenario sweeps (baseline vs interventions).
- “What-if” manipulations (remove CAF ring, boost TLS quality, block PD-1).
- Hypothesis vetting prior to wet-lab or clinical trials.

Agent based modeling for early lung cancer

- **Agents & colors:** Tumor (pink), CAF/αSMA (gold), CD8 (blue), CD4 (teal), Treg (purple), macrophage (gray), TLS node (green).

- **Key rules:** chemotactic movement damped by ECM; CD8 kill = base × MHC × (1 − PD-L1 penalty) × (1 − local suppression); EMT rises with TGFβ/ECM; TLS quality drifts down.

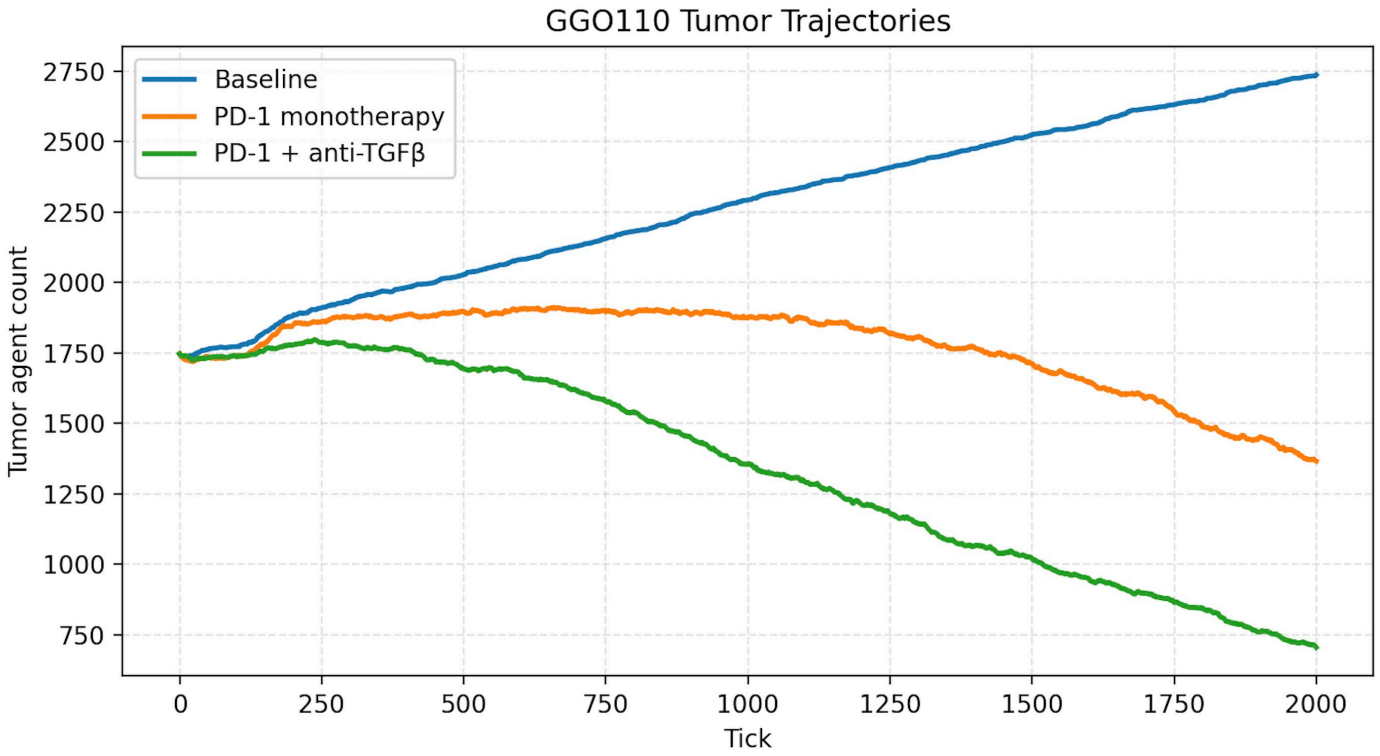
- **Preset:** 1 mm² window, 2,000 ticks (~33 h), G4 counts (1,200 tumor, 700 CAF, 300 TAM, 250 CD8, 200 CD4, 80 Treg, 1 TLS).

- **Intervention knobs:** anti-TGFβ (softens CAF ring, lowers EMT), PD-1 (restores CD8 function), optional TAM/TLS/Treg modifiers.

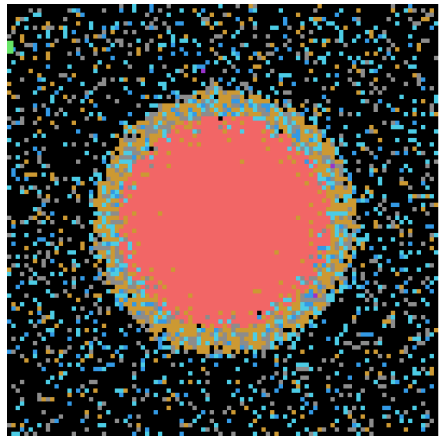
Mechanistic parameters

Mechanism	Baseline Setting	Anti-PD1 Effect	Anti-TGFβ Contribution
CD8 kill probability	0.15 × (MHC, PD-L1, activation, exhaustion)	+0.02 bonus; exhaustion increment ×0.7	NA
CD8 chemotaxis penalty	ecm_penalty × ECM (Group 4 baseline 0.52)	NA	Penalty scaled by 0.4 (easier infiltration)
Tumor proliferation	0.03 × (1 − EMT)	NA	NA
EMT drift	0.02 × (TGFB + ECM), clamped 0–1	NA	Drift multiplier 0.5 (less EMT gain)
CAF ECM deposition	0.02 × activation	NA	Multiplier 0.6
CAF TGFB secretion	0.03 × activation	NA	Multiplier 0.5
Suppressive background	0.05	NA	NA
CD8 step probability	1.0 toward CXCL9/10	NA	NA
Grid / scheduler	100 × 100 lattice; move → interact → update	NA	NA
Initial seeding	Patient counts × 0.5 (--tumor-scale 0.5)	NA	NA

Simulating baseline (no treatment), anti-PD1 and combo anti-PD1+anti-TGFbeta

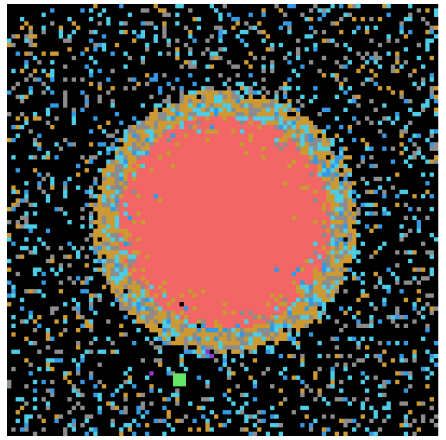


Baseline



Tumor
CAF/alphaSMA
CD8 T
CD4 T
Treg
Macrophage
TLS node

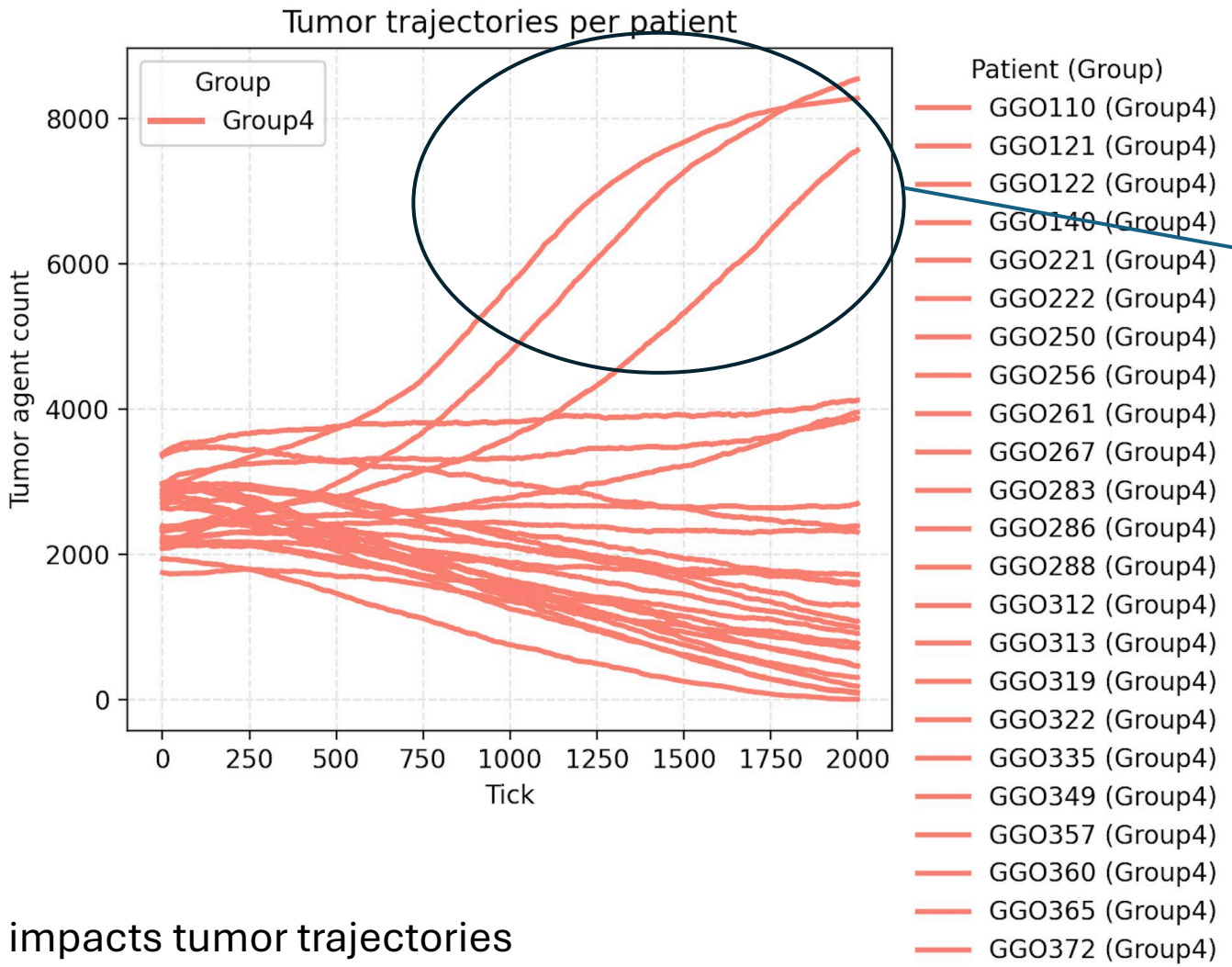
Combo anti-PD1 + anti-TGFbeta



Tumor
CAF/alphaSMA
CD8 T
CD4 T
Treg
Macrophage
TLS node

Data shown for 1 case (GGO110), with initial tumor composition matching spatial measurements, and assuming continuous dosing

Most (but not all) Group 4 patients predicted to respond to combo treatment

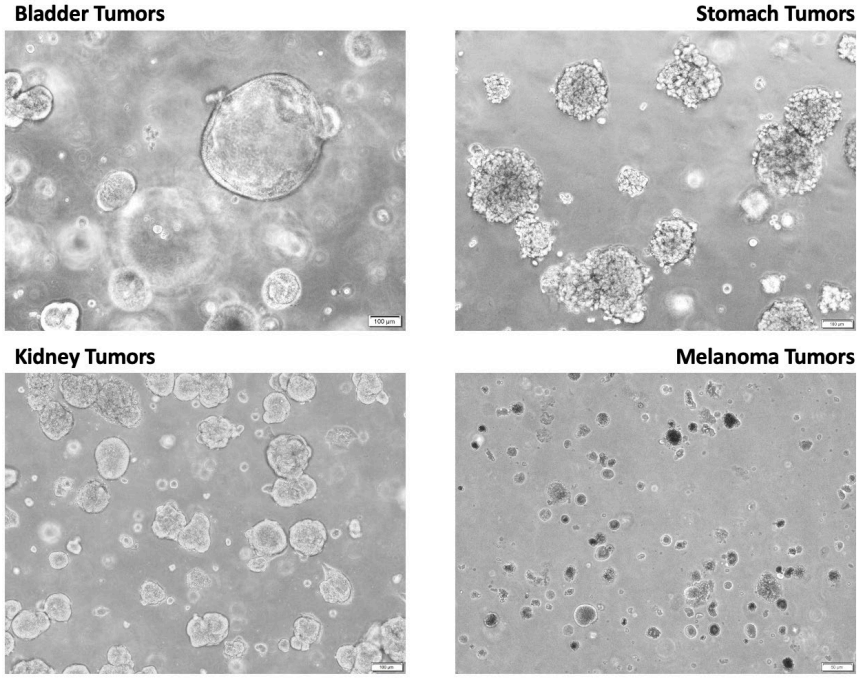


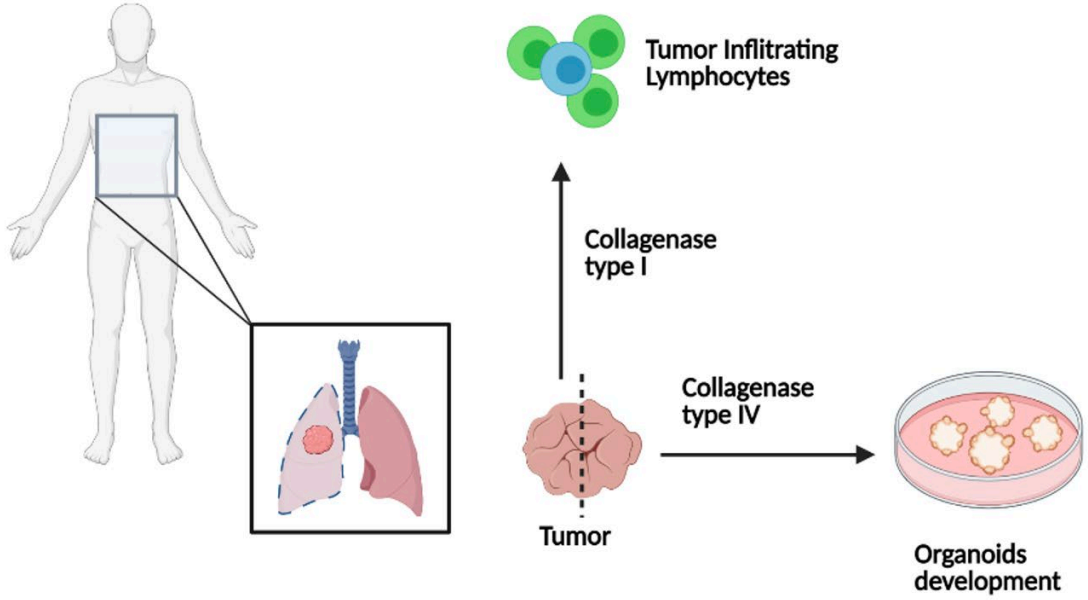
These tumors have near 0 CD8 T cells at baseline

Initial tumor composition impacts tumor trajectories

More work needed

- **Model improvement via parameter exploration/measurement**
- **Further validation (tumor organoids in co-cultures)**





TILs isolation and organoids generation from the same tumor biopsy.

Podaza et al, in press

Questions ?