Enabling Clinical Adoption of Omics: Fit-for-Purpose Validation and a Spatial Biomarker Case Study
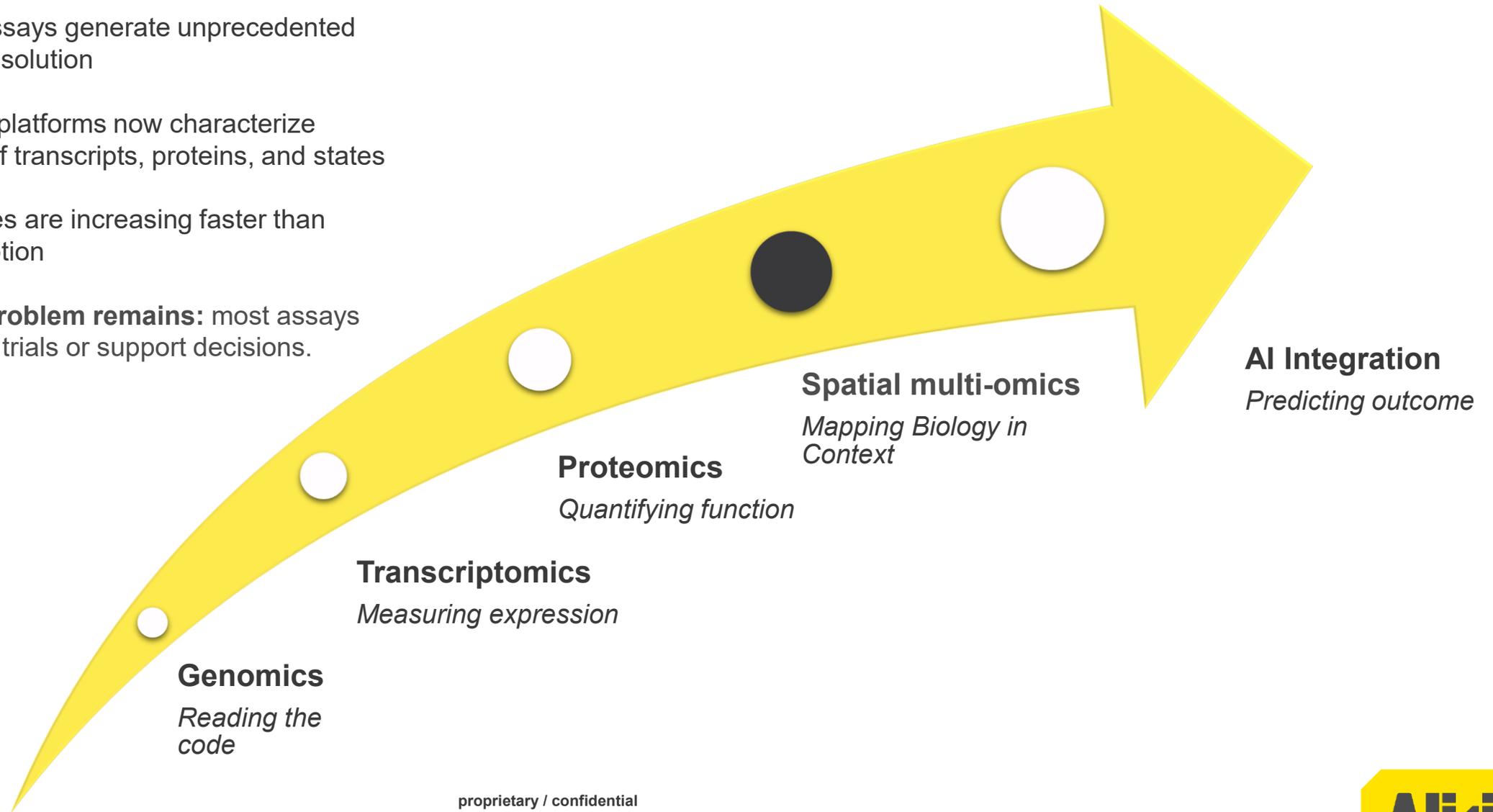
BIOANALYSIS

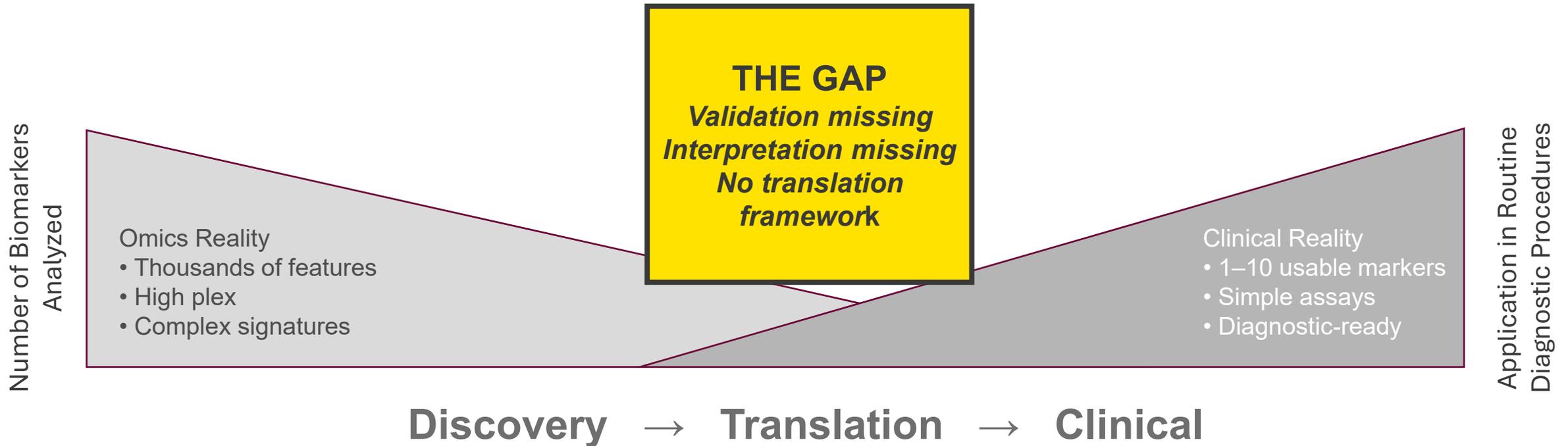we deliver
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The Omics Revolution: Converging Toward Spatially Resolved Biology

- High-plex assays generate unprecedented molecular resolution

- Multi-omics platforms now characterize thousands of transcripts, proteins, and states

-

- Data volumes are increasing faster than clinical adoption

- **But a key problem remains:** most assays never reach trials or support decisions.

AI Integration

Predicting outcome

Spatial multi-omics

Mapping Biology in Context

Proteomics

Quantifying function

Transcriptomics

Measuring expression

Genomics

Reading the code

The Gap Between Omics Innovation and Clinical Adoption

- Omics has outpaced our ability to validate and interpret biomarkers.

- Clinicians still rely on single-analyte diagnostics despite high-plex omics.

- Spatial biology provides mechanistic clarity but lacks standardized validation.

- Fit-for-purpose validation is essential for clinical adoption and regulatory credibility.

THE GAP
Validation missing
Interpretation missing
No translation framework

Number of Biomarkers Analyzed

Omics Reality
- Thousands of features
- High plex
- Complex signatures

Clinical Reality
- 1–10 usable markers
- Simple assays
- Diagnostic-ready

Application in Routine Diagnostic Procedures

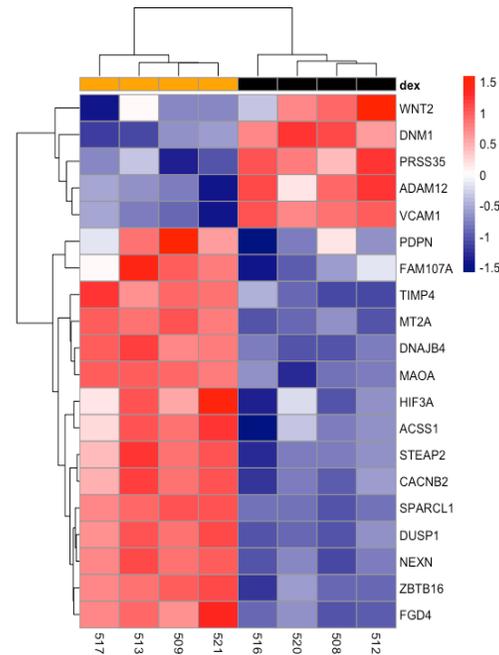**Discovery → Translation → Clinical**

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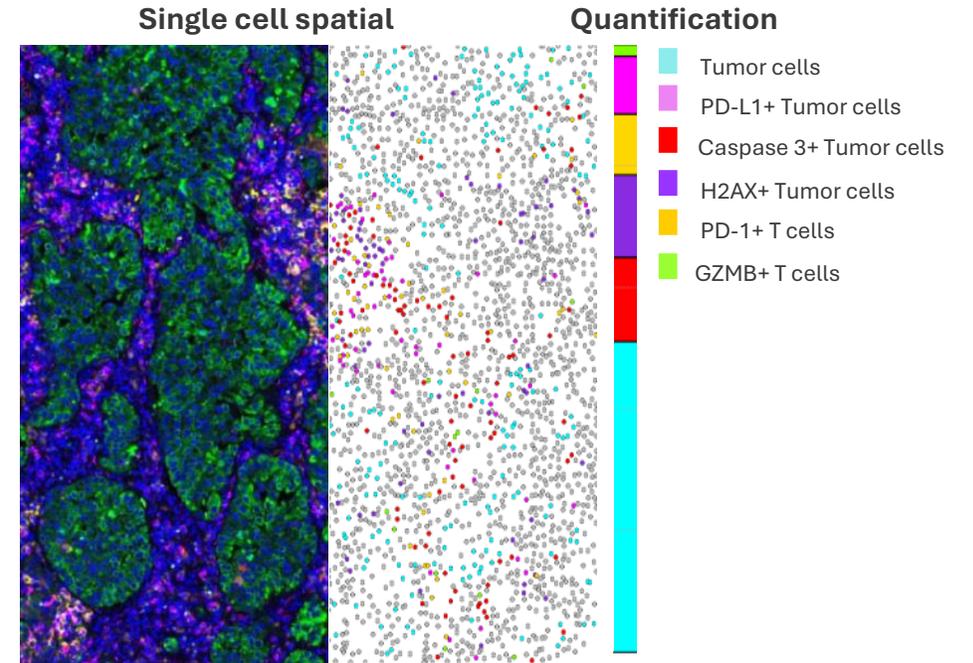# From Observation to Prediction: Spatial Reveals Where Biology Drives Outcomes

The heatmap captures transcriptional differences, but spatial single-cell phenotyping reveals how cell states organize and interact in tissue.

Quantification turns these patterns into predictive signals:

- Stressed or dying tumor regions
- Activated T-cell pockets
- Zones of immune suppression

Bulk

Single cell spatial

Quantification

- Tumor cells
- PD-L1+ Tumor cells
- Caspase 3+ Tumor cells
- H2AX+ Tumor cells
- PD-1+ T cells
- GZMB+ T cells

Spatial

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The Challenge: Classical Validation Does Not Match Omics Reality

Classical Assay
- One analyte at a time
- Linear calibration curves
- Homogenous samples
- Fixed QC rules

Spatial Assays
- Thousands of features simultaneously
- Non-linear spatial gradients
- Tissue heterogeneity
- AI segmentation variability
- Multi-layer QC needed (analytical, biological and computational)

|	Area Classification	Cell Typing		Spatial Structures
Core Readout	Identify Tissue compartments (tumor, stroma...)	Distinguish immune vs. tumor or stroma populations		Detect organized multi-cells aggregates
Spatial Features Category	Area Region	Cellular Distribution	Cellular Interactions	TLS structures
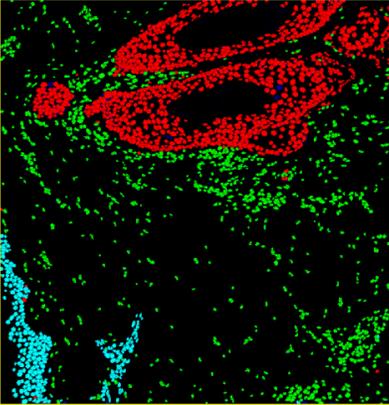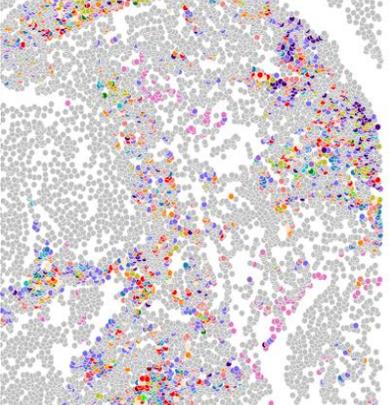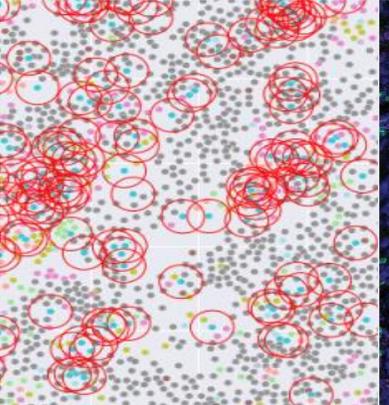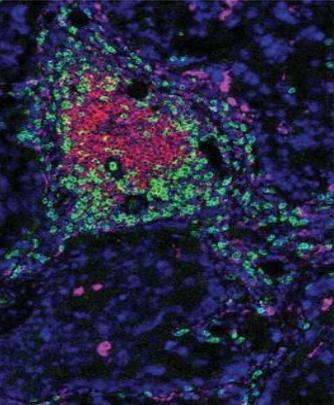
Spatial Validation Workflow
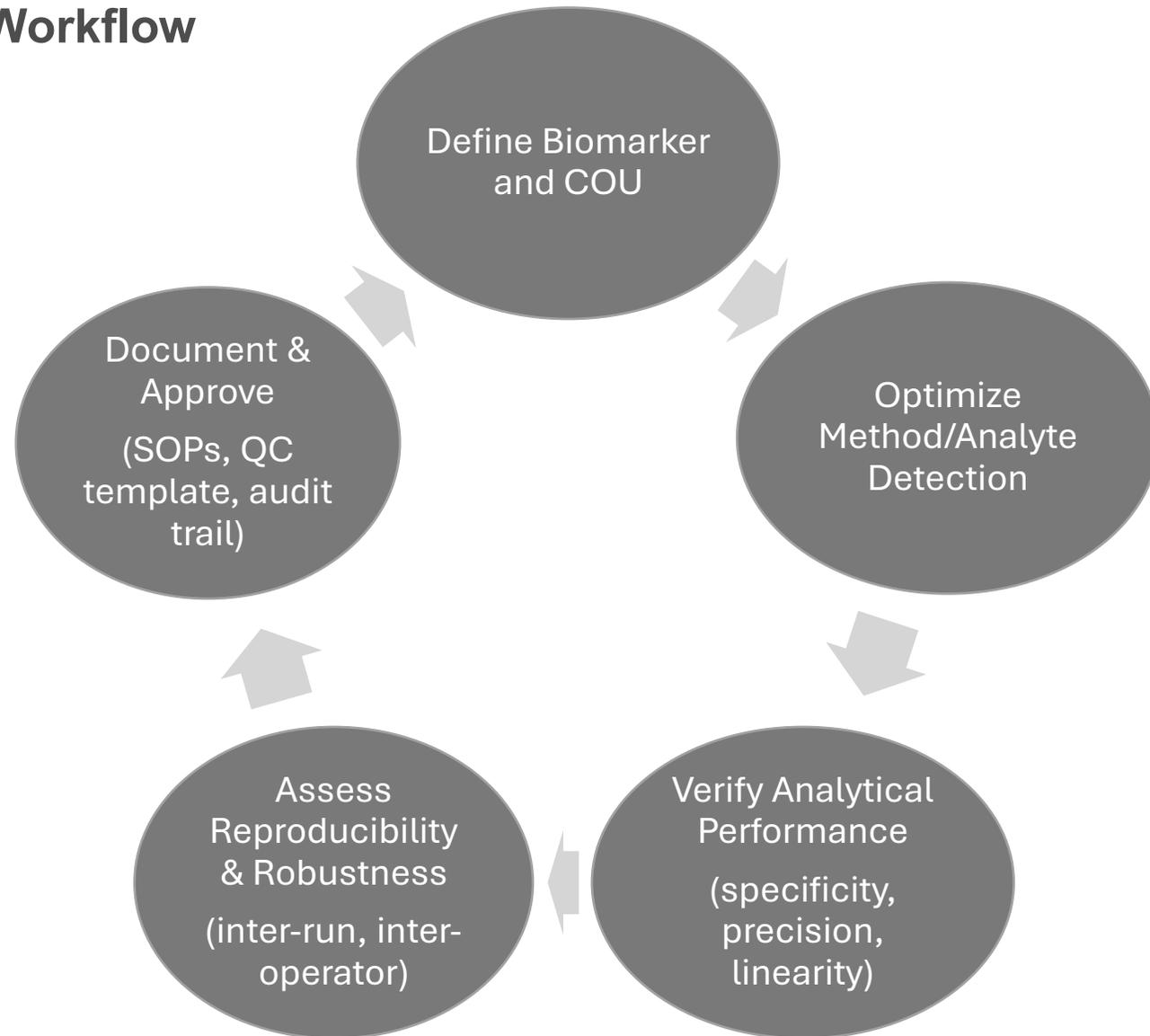
Fit-for-purpose applied to spatial QC

Quality is engineered across every layer from sample integrity to spatial metrics.

Once assays are qualified or validated, quality is continuously engineered across study execution.

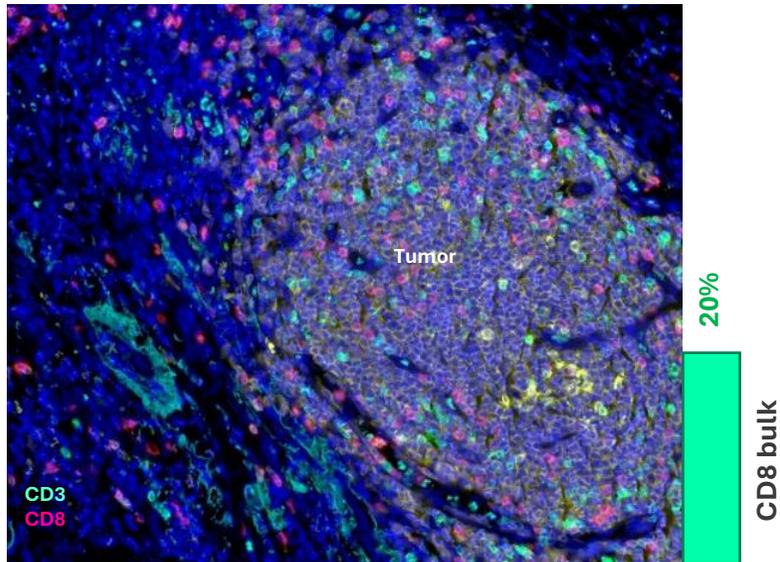## Study Design
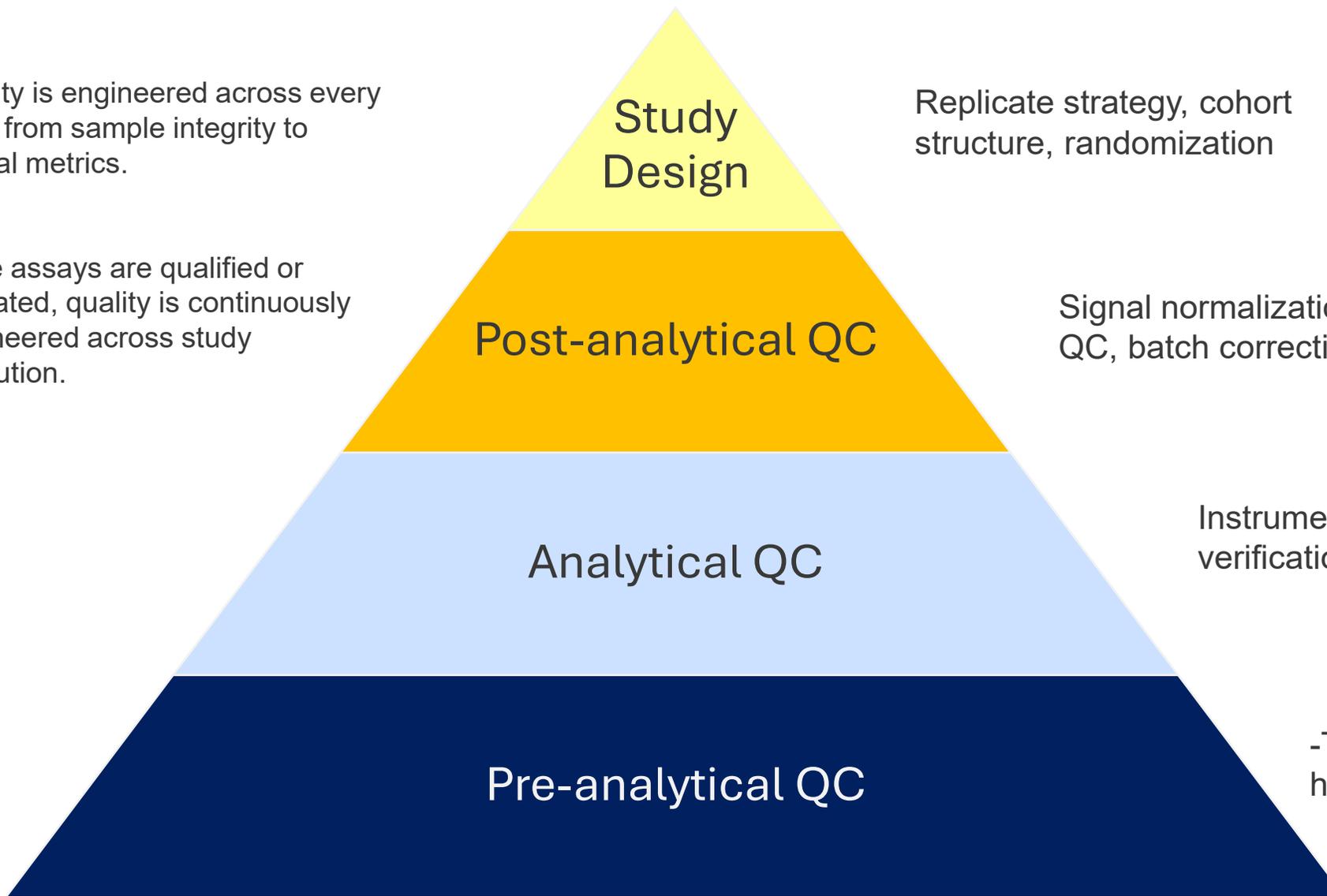
Replicate strategy, cohort structure, randomization

Post-analytical QC

Signal normalization, segmentation QC, batch correction

Analytical QC

Instrument qualification, panel verification, replicate ROIs

Pre-analytical QC

-Tissue integrity, orientation, histology review, control tissues

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Spatial Resolves Neighborhood

Immune Inflamed

CD3
CD8

Tumor

20%

CD8 bulk

Immune Excluded

Tumor

CD3
CD8

18 %

CD8 bulk

Immune Desert

Tumor

CD3
CD8

10 %

CD8 bulk
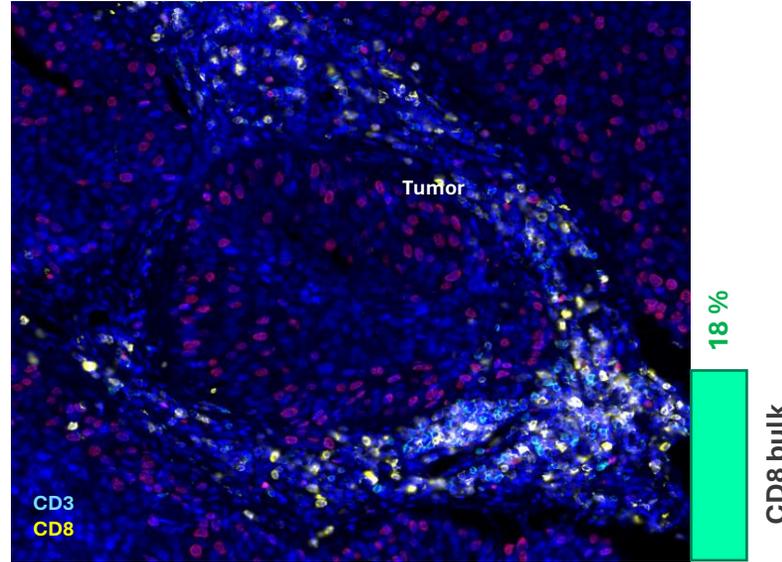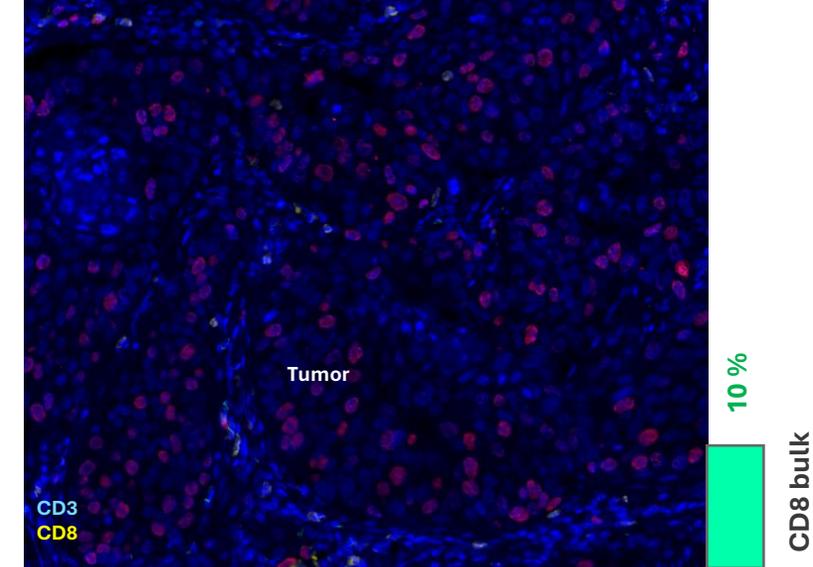
Neighborhood architecture outperforms bulk abundance for response stratification.

Impact on Targets and Biomarkers

From Bulk Signals to Spatial Context

- Target Refinement: Confirm signaling within niche-enriched zones.

- Biomarker Precision: Spatial signatures outperform bulk abundance metrics by linking function to microanatomy.

Translational & Clinical Impact

- Patient Stratification: Group patients by niche activation and immune cell density patterns.

- Pharmacodynamic Readouts: Quantify therapy-driven changes in niche size, cell proximity, and co-localization dynamics.
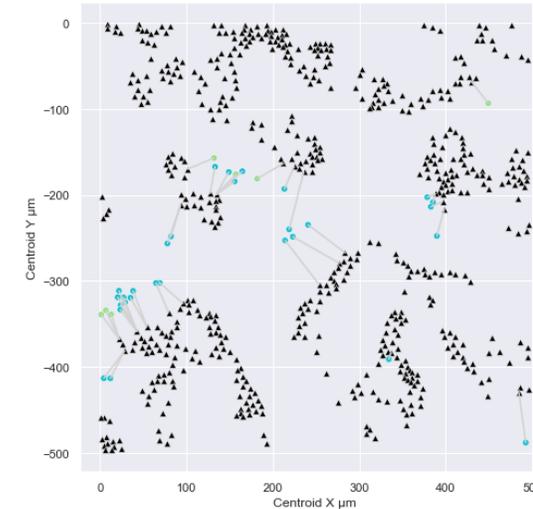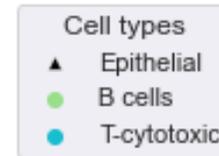

Non-Responder
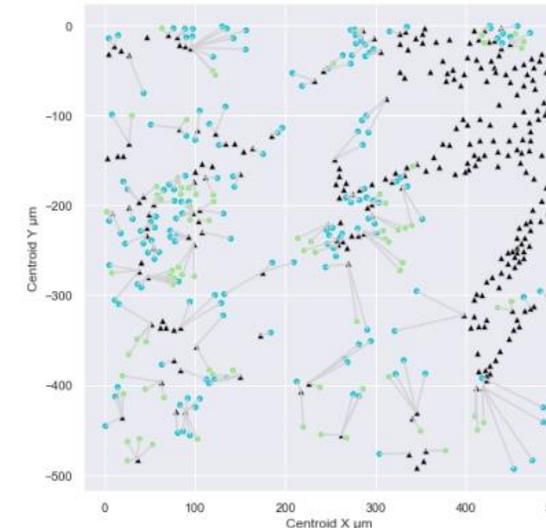
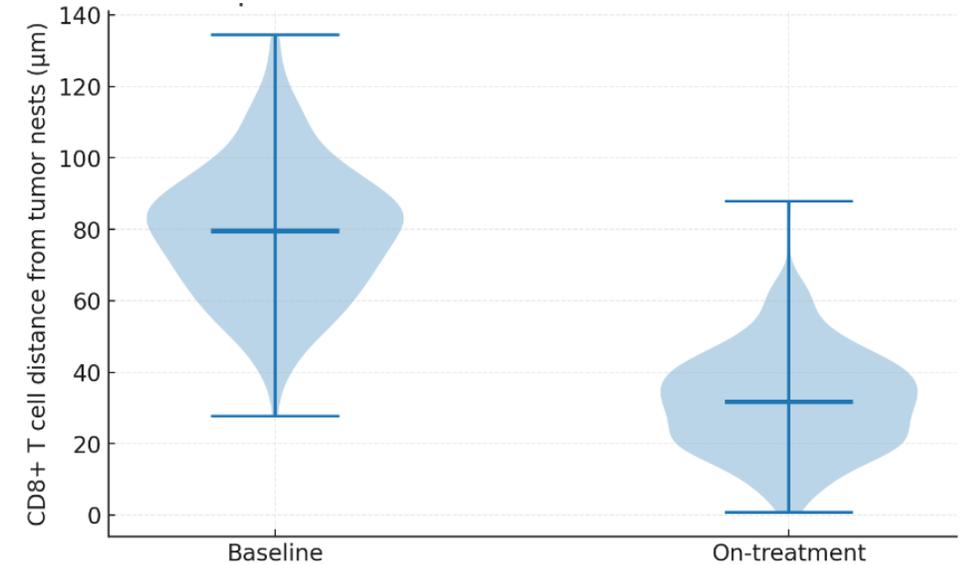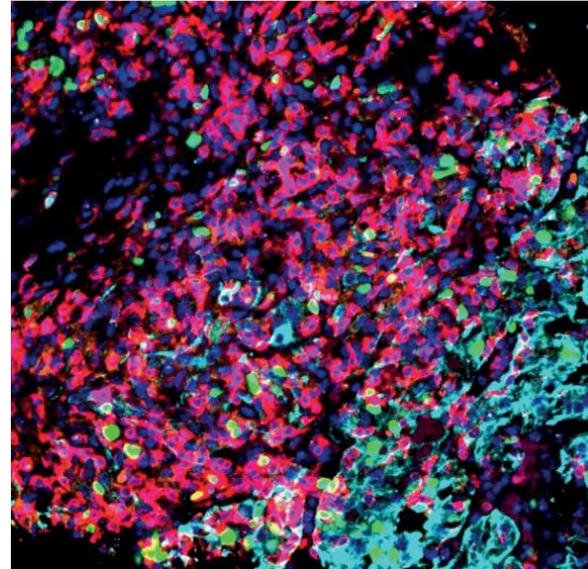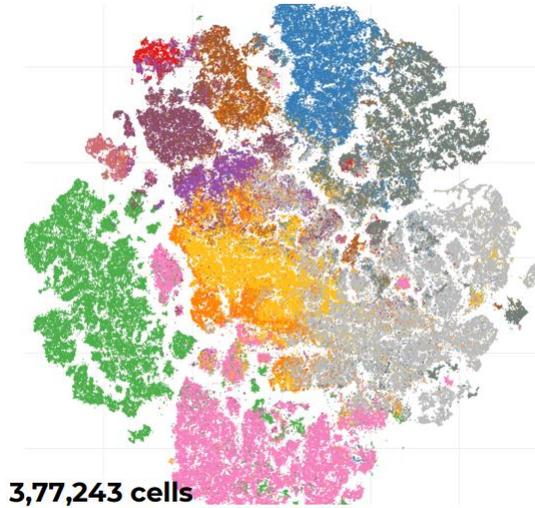Responder

Biomarker Precision

- The microenvironment drives biology ⇨ Predictive Biomarkers

- See biology where it happens

- Measure real interactions quantifies neighbors, distances, and contact frequency.

- Localize pathways & targets: maps to specific niches/compartments.

- Stronger biomarkers: spatial signatures (niche density, co-occurrence, exclusion, NND) often outperform simple counts.
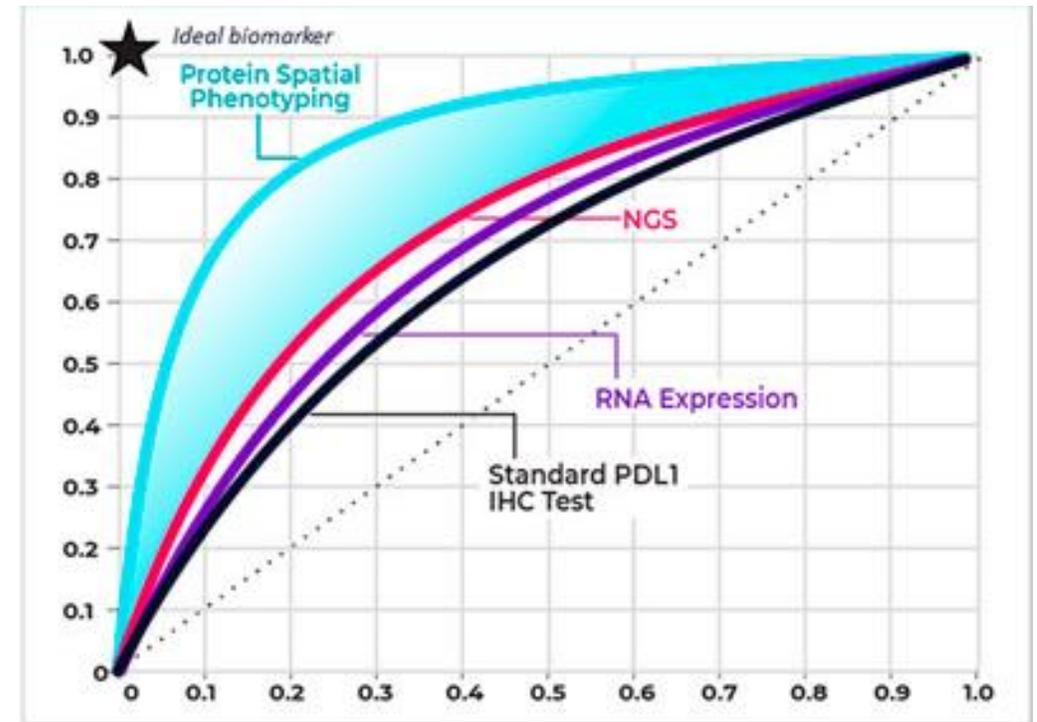
Comparison of different predictive biomarker testing assays for PD-1/PD-L1 checkpoint inhibitors response: a systematic review and network meta-analysis. Front. Immunol., 2023

Case Study: Spatial Architecture Predicts Immunotherapy Response
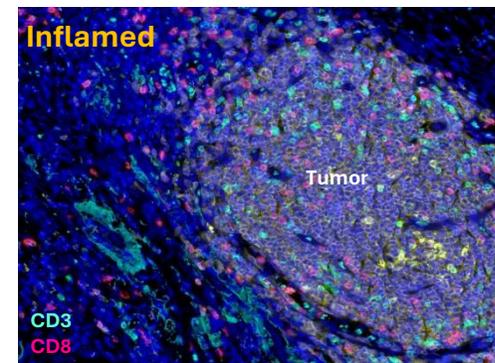
Responder

3,77,243 cells

- Paired biopsies profiled with spatial transcriptomics & multiplex proteomics
- Spatial proximity metrics differentiate responders better than bulk values
- CD8–tumor interactions are key predictors

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Spatial Immune Niches Predict Responders

These maps define arm enrichment strategies: patients stratified into *inflamed*, *excluded*, *cold* tumors

Eligible for PD-1/PD-L1 therapy

Feature	Inflamed	Excluded	Cold
% CD3+ cells	25%	22%	8%
% CD8+ cells	18%	15%	3%
CD8+ inside tumor core	High (70%)	Low (10%)	Very low (≤5%)
CD8–tumor mean NN distance	Short (5–10 μm)	Long (25–40 μm)	Very long (>50 μm)
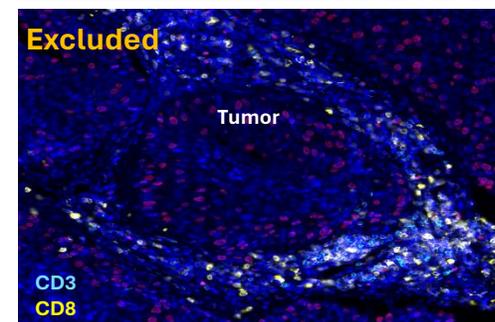
Combination with stromal/angiogenic modulators
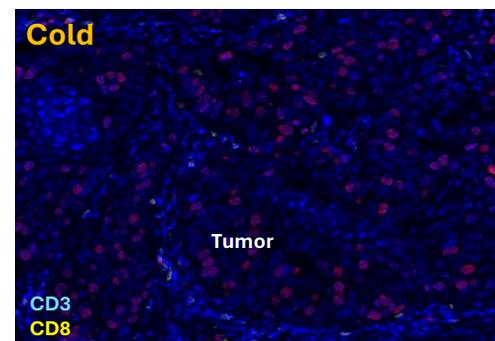
Consider novel IO or reprogramming approaches

Spatial PD-L1/CD8 architecture differentiates responders vs non-responders."

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Case Study: Key Findings

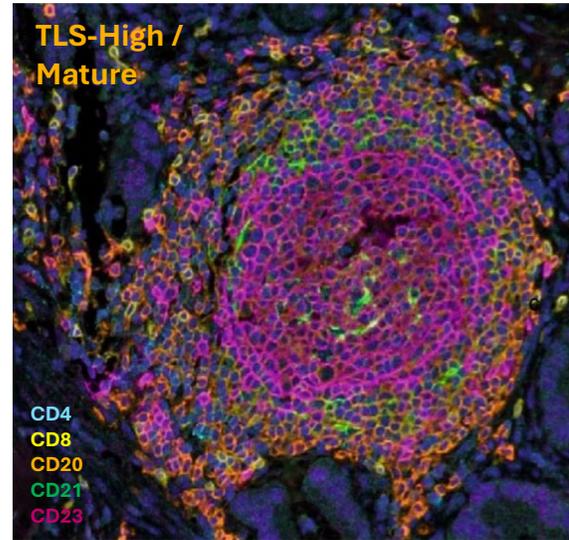These maps define arm enrichment strategies: patients stratified into TLS-high (mature) and TLS-immature/absent tumors.

Feature	TLS-High	TLS-Immature
TLS density	>5 TLS/slide	1–4 TLS/slide
TLS maturity	Mature (CD20/CD21/CD23+)	Partial
B-cell zone	Organized	Sparse
Survival association	OS ↑↑	OS ↑

TLS = tertiary lymphoid structures

TLS-High / Mature

CD4
CD8
CD20
CD21
CD23

Eligible for PD-1/PD-L1 ± CTLA-4 therapy.

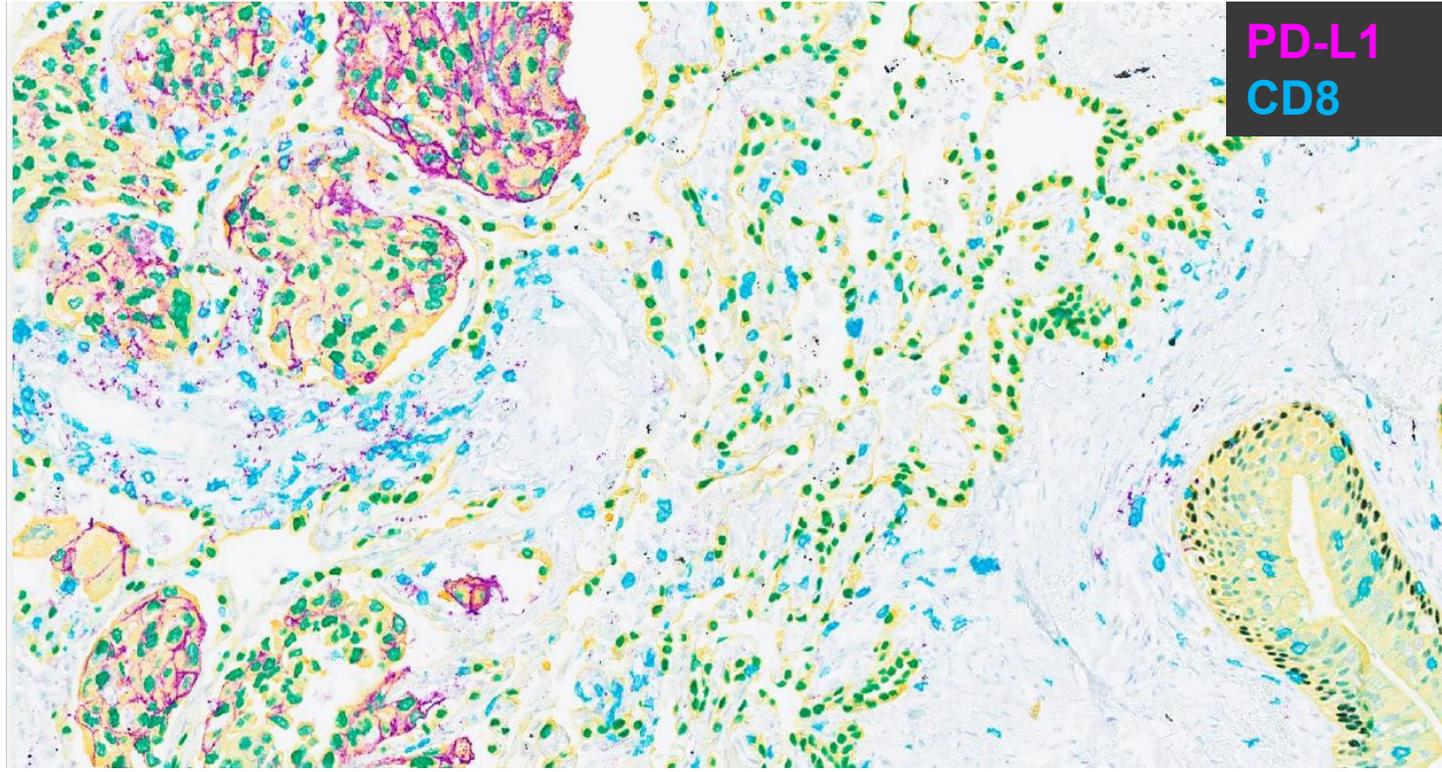**TLS-Immature / Absent**

CD4
CD8
CD20
CD21
CD23
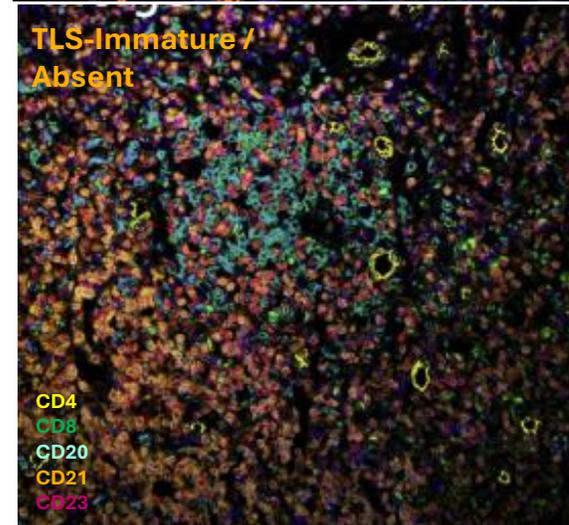
Direct to IO-alternative or TLS-inducing therapies.

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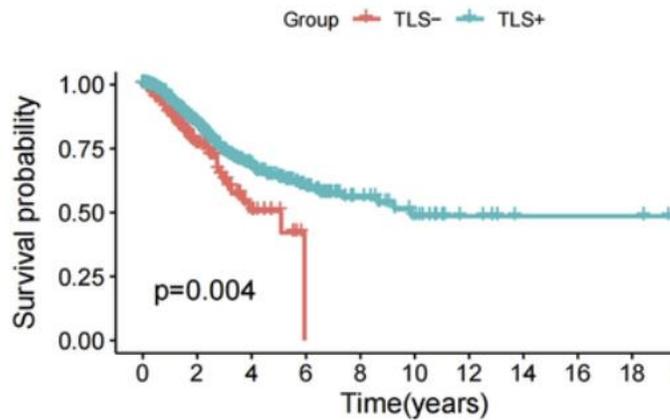
Translational Impact: From Discovery to Decision

Context: Translational immuno-oncology study using mIF platforms to evaluate PD-L1/CD8* spatial relationship in Lung cancer
Outcome: Stable PD-L1/CD8 ratios across batches supports PD response modeling.

PD-L1
CD8

Lung Carcinoma

*Relative abundance or density of PD-L1–positive cells compared to CD8–positive cells in a given area.

Metric	Acceptance Criteria	Observed Value
Specificity	Signal localized to expected compartments; minimal background	Confirmed via isotype & IHC cross-check
Precision	%CV ≤ 20% across 3 precision runs (same analyst/instrument/day)	13%
Reproducibility	%CV ≤ 25% across operators and days (same protocol)	18% 2 operators, 3 days
PD-L1/CD8 Ratio Variability	≤ 20 % variance between runs	Achieved 14%

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Roadmap to Clinical Adoption

Analytical Validation

Establish precision, accuracy, specificity, sensitivity, and QC thresholds.

Biological Interpretation

Link molecular signals to cell states, pathways, and tissue context.

Clinical Relevance

Demonstrate association with mechanism, response, or exposure.

Operationalization for Trials

Standardize workflow, QC, reporting, and sample-to-answer timelines.

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Why Mechanism Matters: FDA Opens Pathway for Mechanistic Biomarkers

Regulators Are Prioritizing Mechanism-Based Evidence
Especially in rare or individualized therapies

- **Why it matters for spatial biology**
  - Spatial uniquely visualizes MoA *in situ*
  - Shows pathway activation, cell–cell interactions, niche shifts
  - Provides the mechanistic evidence FDA now recognizes

- **Why fit-for-purpose validation matters**
  - Mechanistic biomarkers only work if the data is validated for the intended COU

FDA's New Plausible Mechanism Pathway

Authors: Vinay Prasad, M.D., M.P.H., and Martin A. Makary, M.D., M.P.H.   Author Info & Affiliations

Abstract

Personalized therapies hold tremendous promise but challenge traditional models of drug and biologic development. The FDA outlines a path to market entry for products where a randomized trial is not feasible.

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Closing

- Omics must be validated proportionally to purpose

- Spatial enables mechanism-based decision-making

- Integrated multi-omics accelerates clinical adoption