

Beyond Diagnosis: AI to Transform Clinical Samples into Personalized Therapies

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Agenda

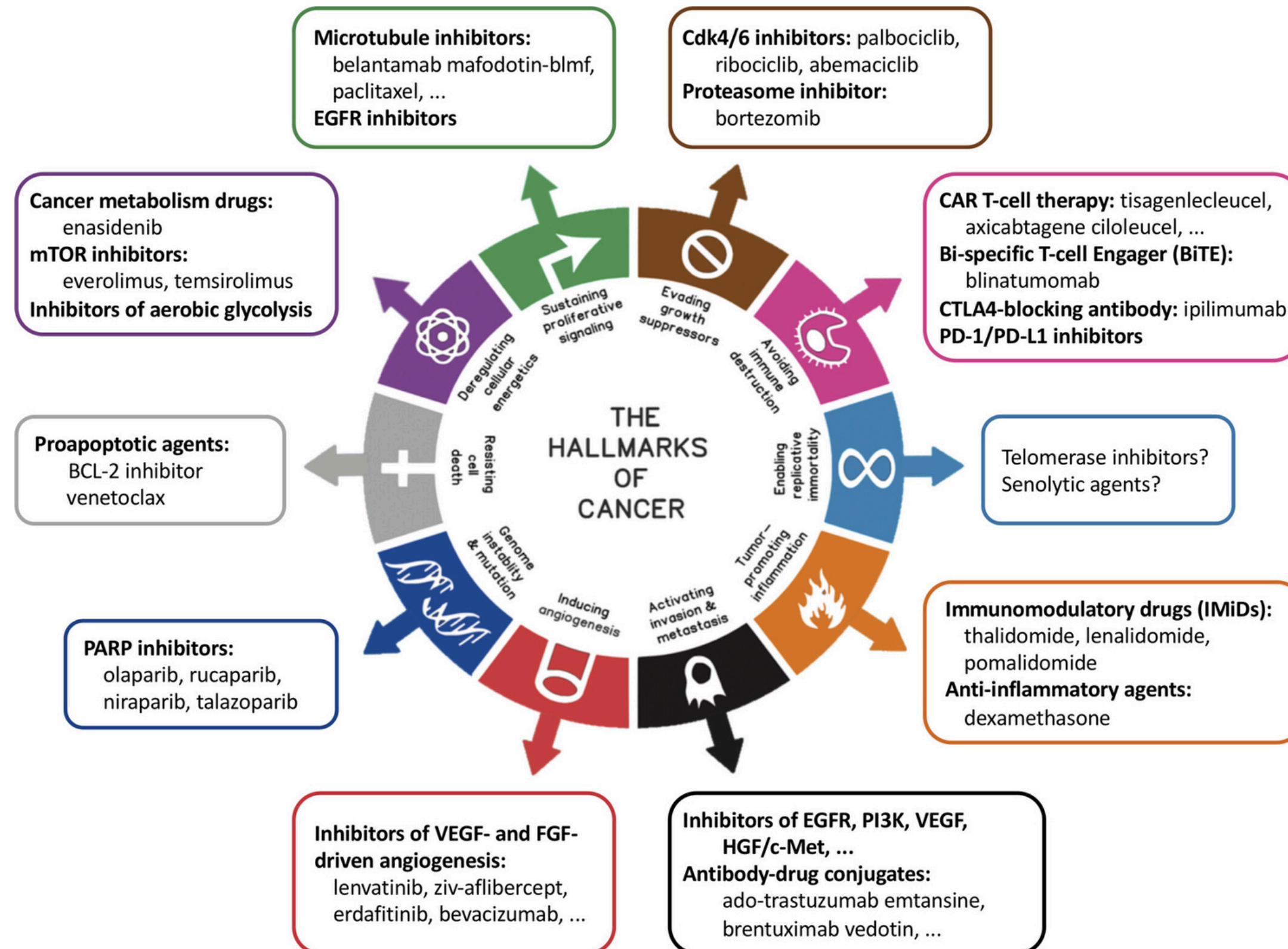
1. The reality today
2. One sample, many decisions
3. The Opportunity
4. Subtype and pathway characterization
5. Understanding the tumor microenvironment
6. Tumor mutational profile
7. Immunogenicity prediction
8. Individualized Cancer vaccines: A future alternative?
9. An integrated diagnostic and therapeutic approach
10. Limitations & future perspectives



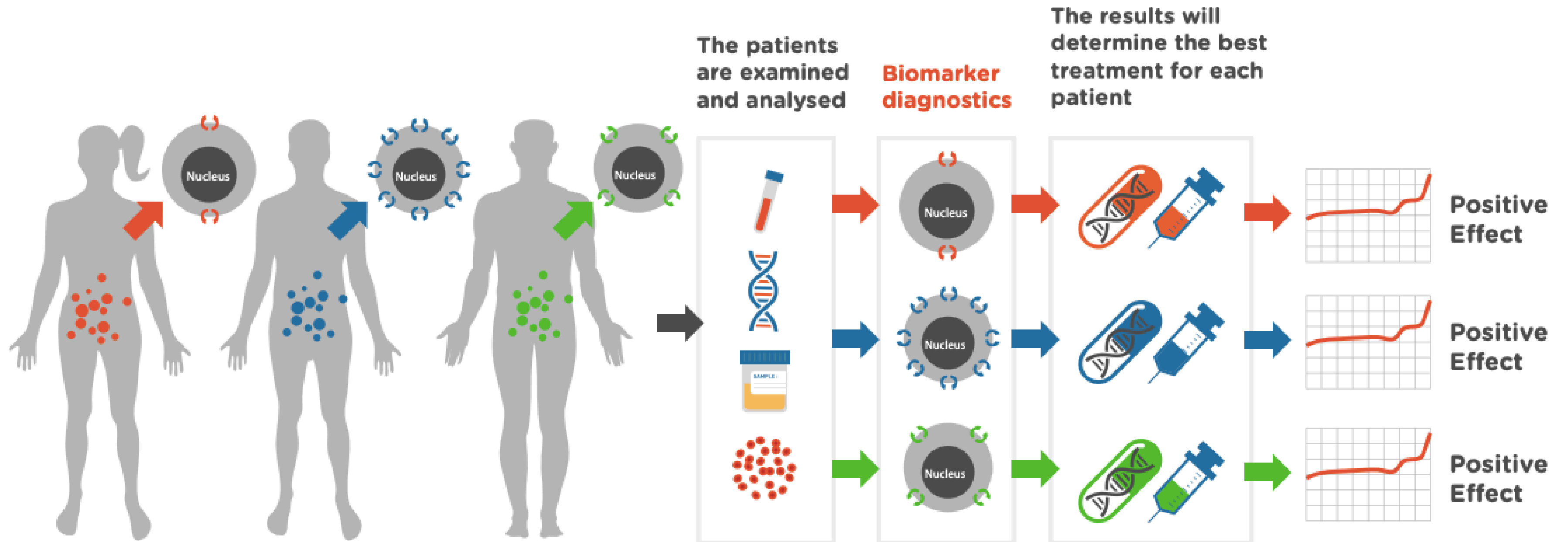


1. The reality today

Druggable genome and precision medicine in cancer: current state



The Personalized Medicine Approach





2. One sample - Many decisions

The Clinical Scenario

At the start, we only have one biopsy with many unknowns, and therapeutic decisions depend on multiple biological dimensions

Patient Journey starts (Day 0): Patient comes to a consult with a lung node and high suspicion of malignancy. The node is biopsied and sent to the pathologist

Piece 1 Arrives (Day 5): Pathology confirms it is Adenocarcinoma..
The oncologist starts standard chemotherapy immediately

Piece 2 Arrives (Day 14): IHC for PD_L1 testing comes back negative. ICI Is not indicated.

Piece 3 Arrives (Day 45): Molecular testing results show an EGFR mutation. The doctor switches to a targeted inhibitor (Osimertinib)

The Result: The patient suffered side effects from the initial treatment, and the healthcare system paid for a drug that wasn't the best fit.



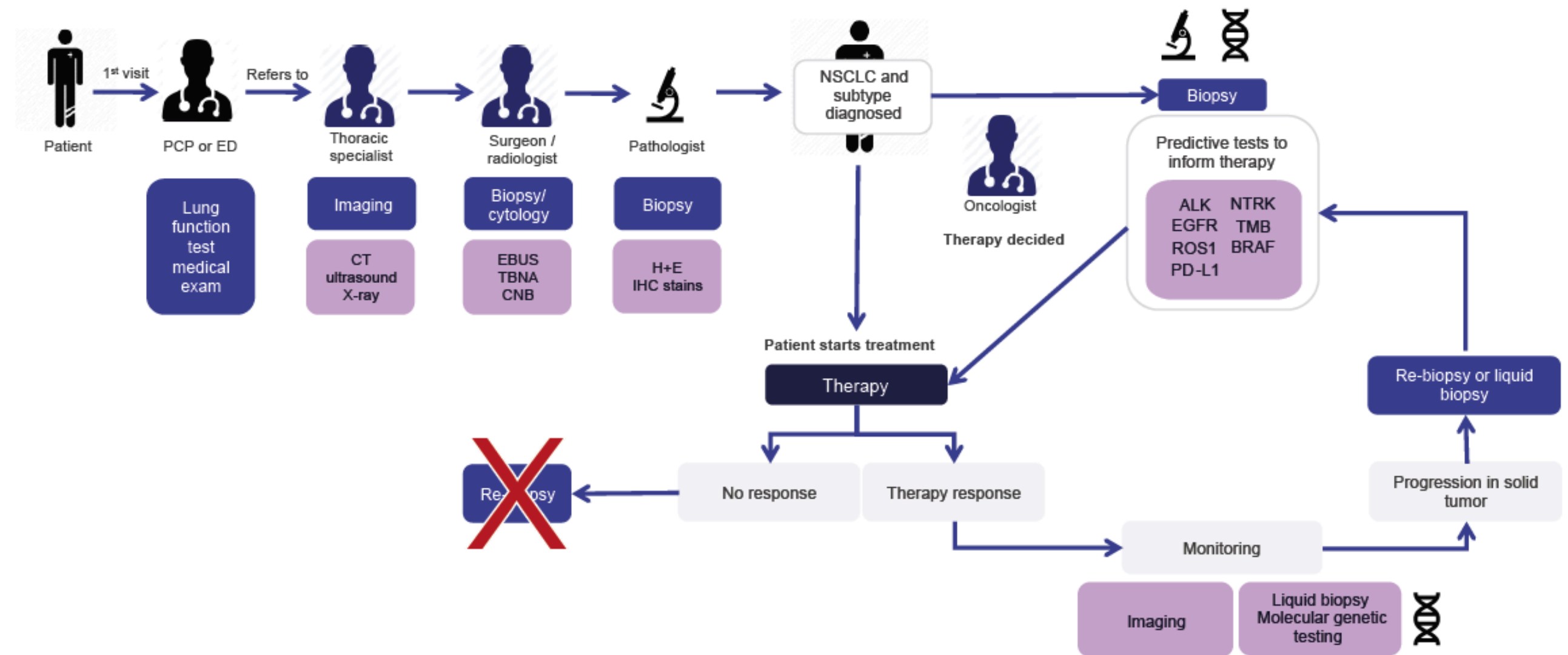
A piecemeal approach for patient diagnosis and treatment

Instead of having a "Holistic" view (Morphology + Lineage + Genetics) at the start, the doctor gets different pieces at different times

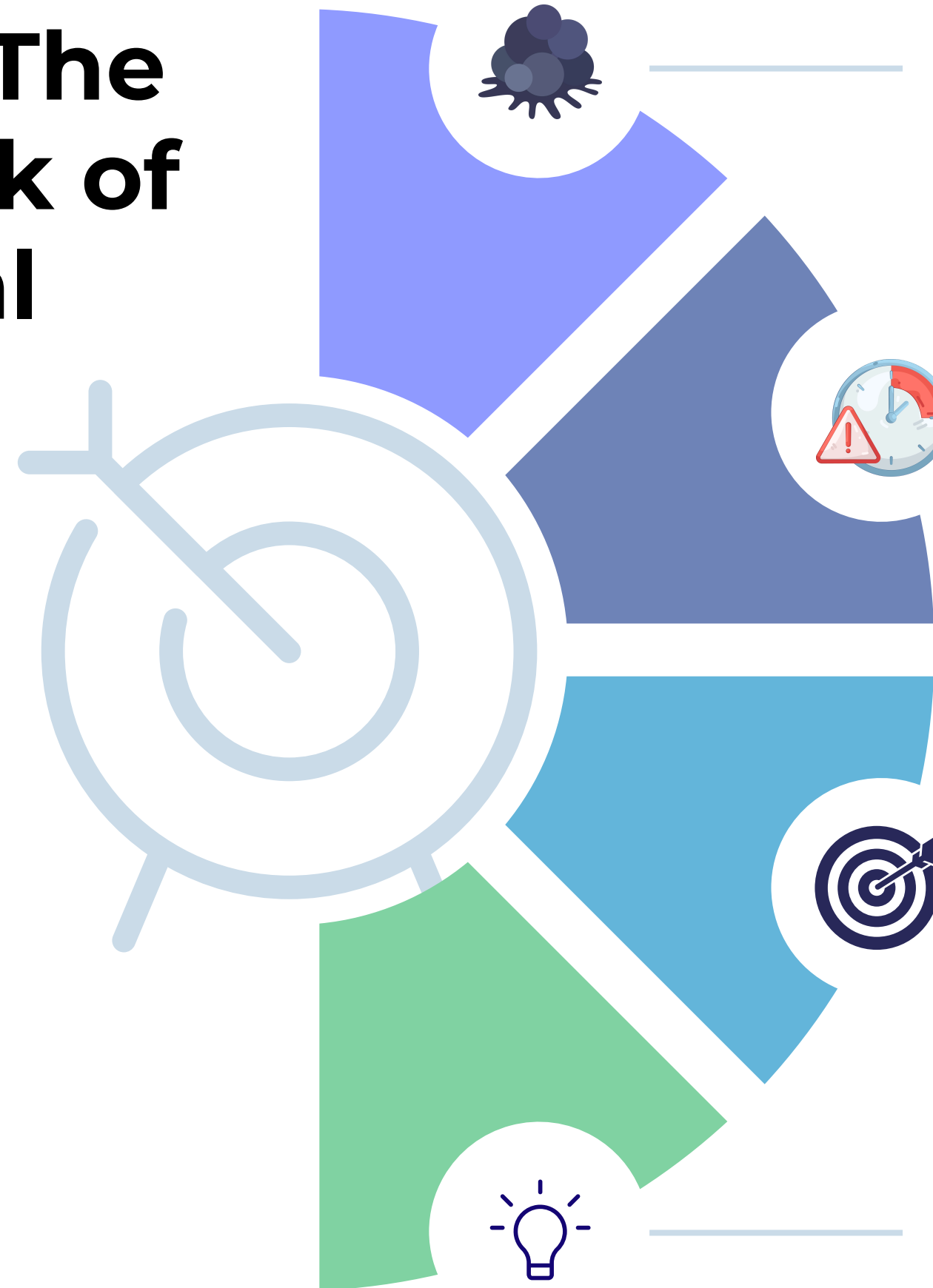
Multiple tests, separate outputs

Genomics, pathology, imaging, immunology
Reports not designed to speak to each other

Physicians are forced to **make decisions based on the "piece" they have** in front of them, often having to revise that decision later when a new piece arrives.



The Core Problem: The Bottleneck of Sequential Testing



Loss of Tissue

Repeated testing leads to "insufficient tissue" for critical profiling

Loss of Time

Sequential testing creates a significant time stack. Critical results arrive weeks later, delaying and often subverting optimal first-line therapy

Loss of Opportunity

Information arrives too late to influence the initial, critical therapeutic choices. Decisions become "piecemeal," based on partial truths, leading to non-ideal first-line treatment.

Loss of Discovery

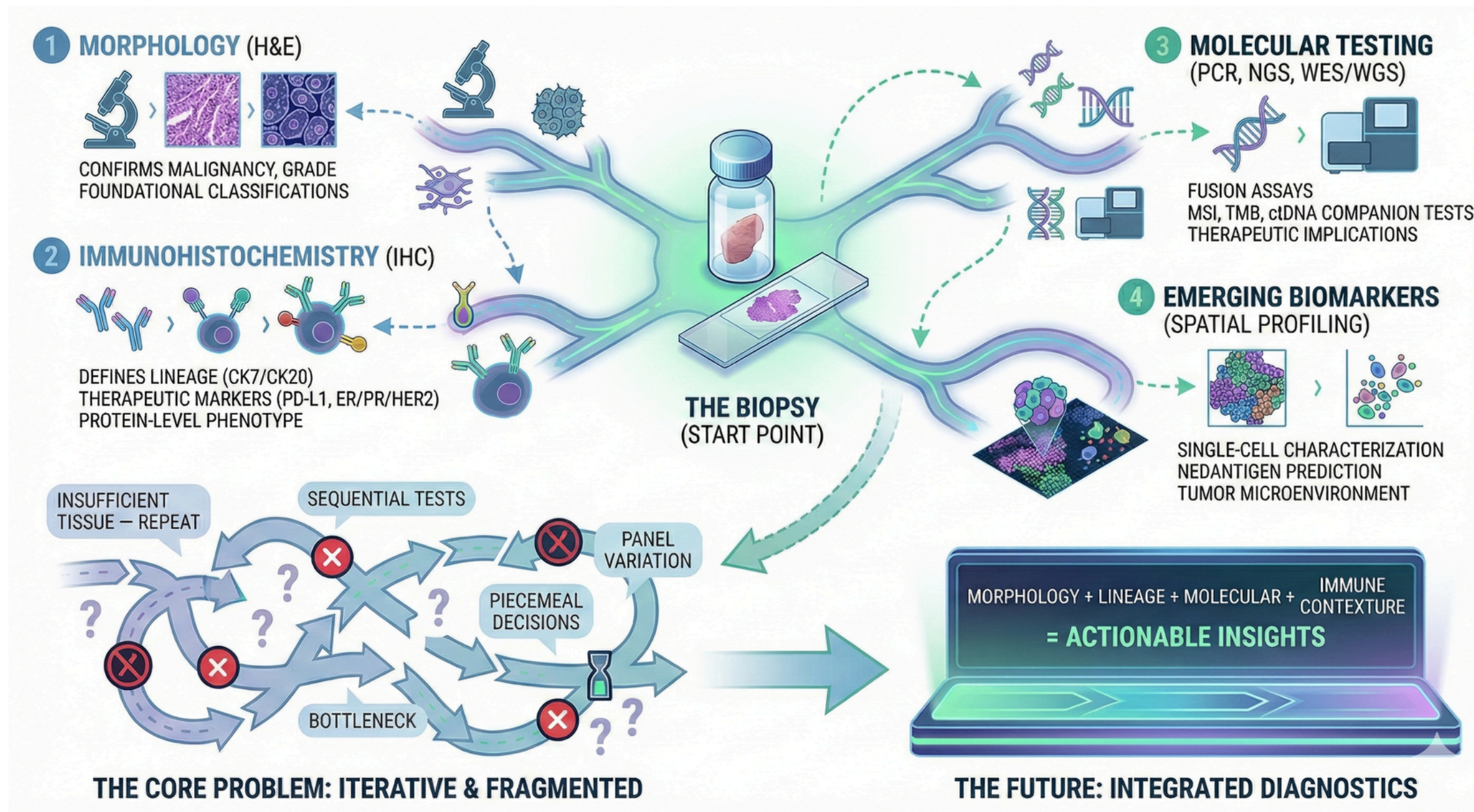
Heterogeneous testing, variable results, and siloed data prevent feedback into the learning loop. Actionable insights and novel biomarkers are lost due to non-requested and non-integrated information.



3. The Opportunity

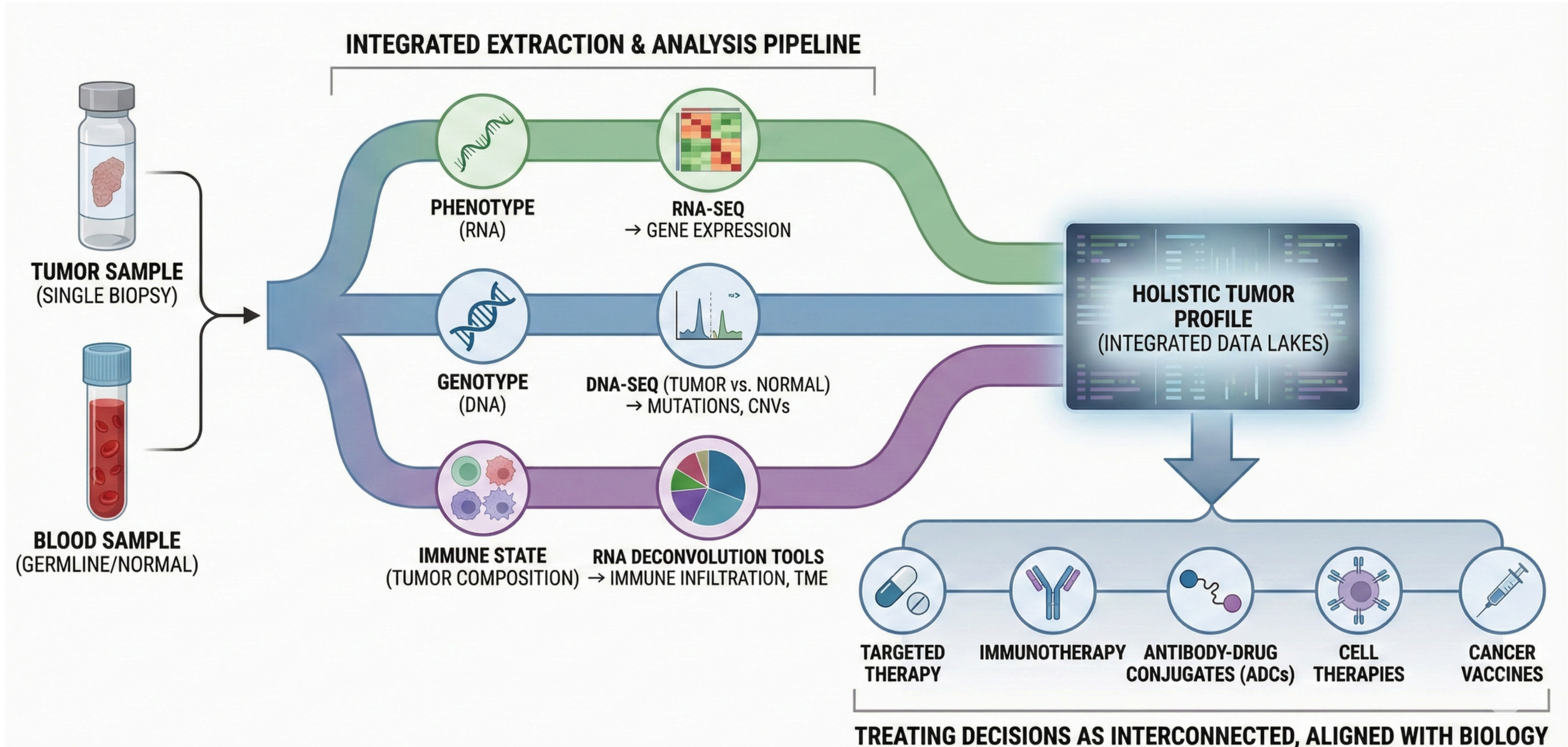
From fragmented testing to integrated biological insight

Current workflows treat histology, genomics, and immune profiling as isolated processes. This results in diagnostic delays, incomplete biological understanding, and suboptimal first-line decisions



**Integrated reporting
transforms one biopsy into a
complete therapeutic map,
not a sequence of
disconnected tests**

Integrated multi-omics pipeline from a single sample

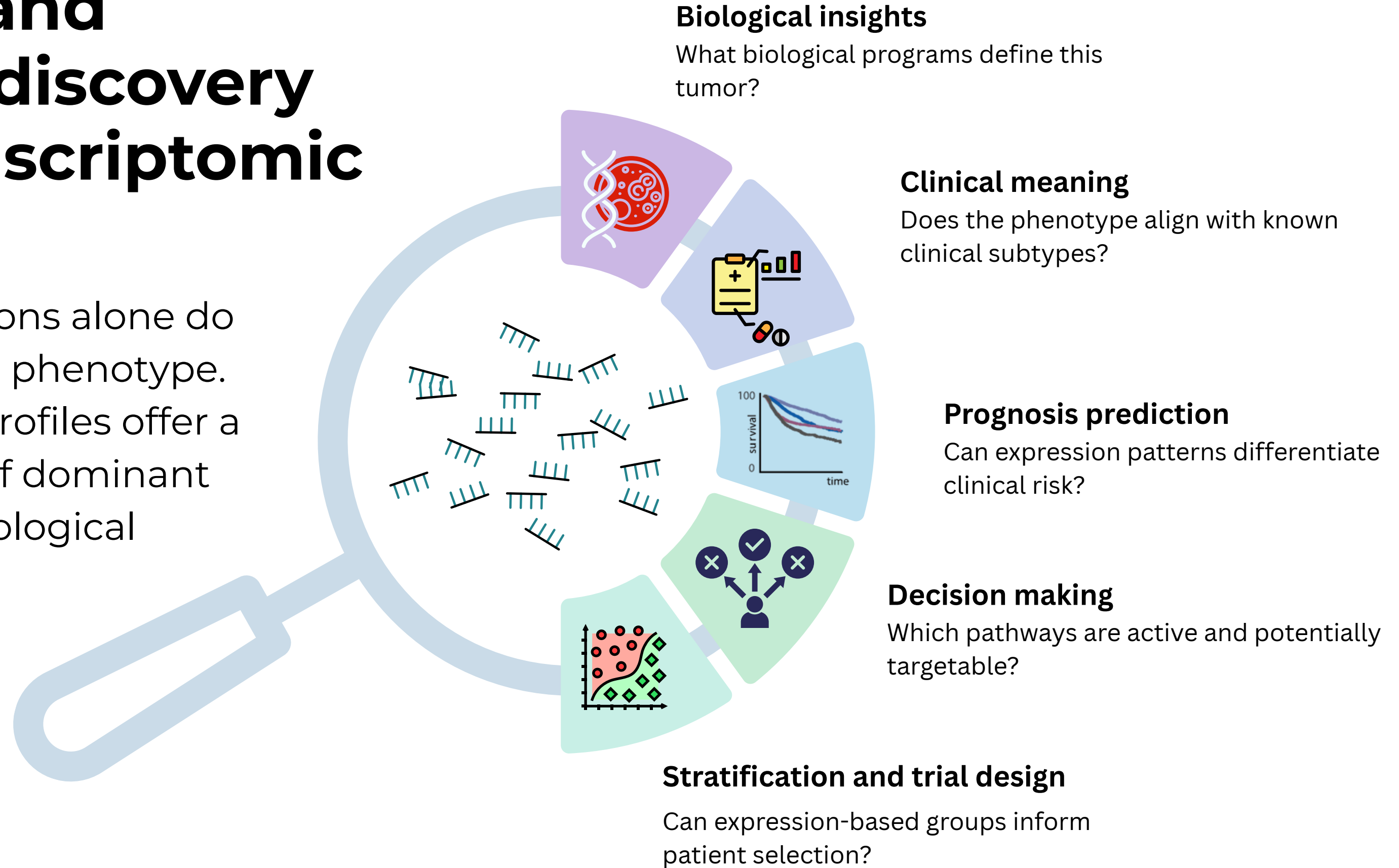




4. Subtype and pathway characterization

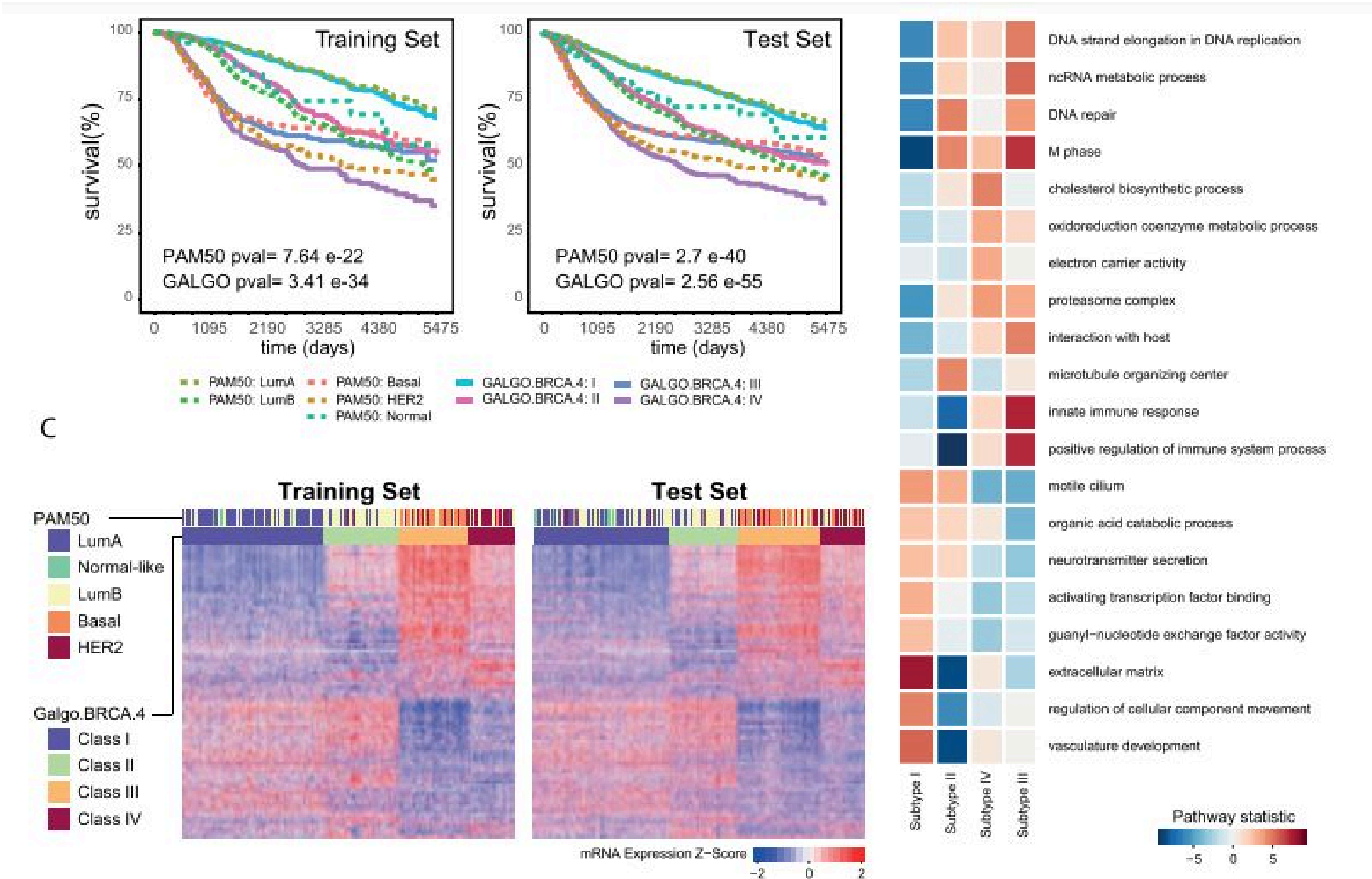
Subtype and pathway discovery from transcriptomic profiles

Genomic alterations alone do not define tumor phenotype. Transcriptomic profiles offer a functional view of dominant pathways and biological programs



Predicting clinically relevant subtypes from transcriptomic data

We applied evolutionary search methods to large-scale RNA datasets to identify expression patterns associated with clinical outcomes across multiple cancer types



Bioinformatics, 36(20), 2020, 5037–5044
doi: 10.1093/bioinformatics/btaa619
Advance Access Publication Date: 8 July 2020
Original Paper
OXFORD

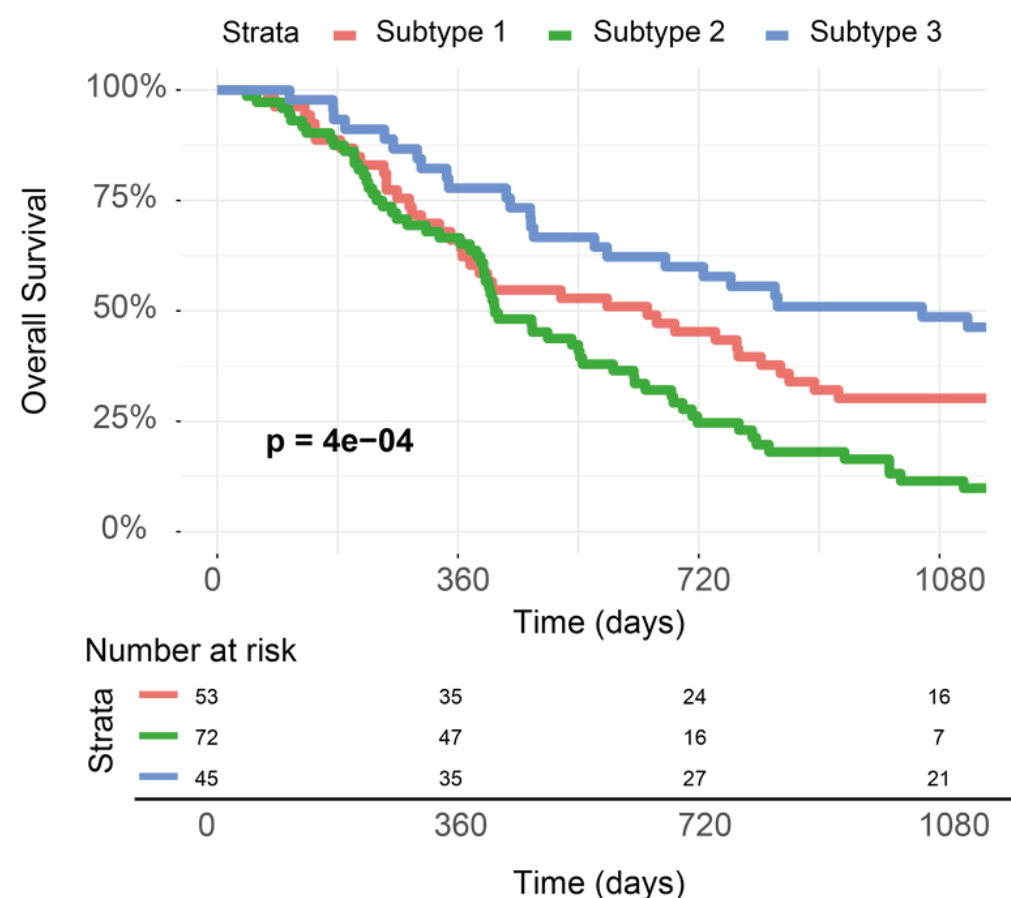
Gene expression
Galgo: a bi-objective evolutionary meta-heuristic identifies robust transcriptomic classifiers associated with patient outcome across multiple cancer types

Guerrero - Giménez et al 2020, Bioinformatics

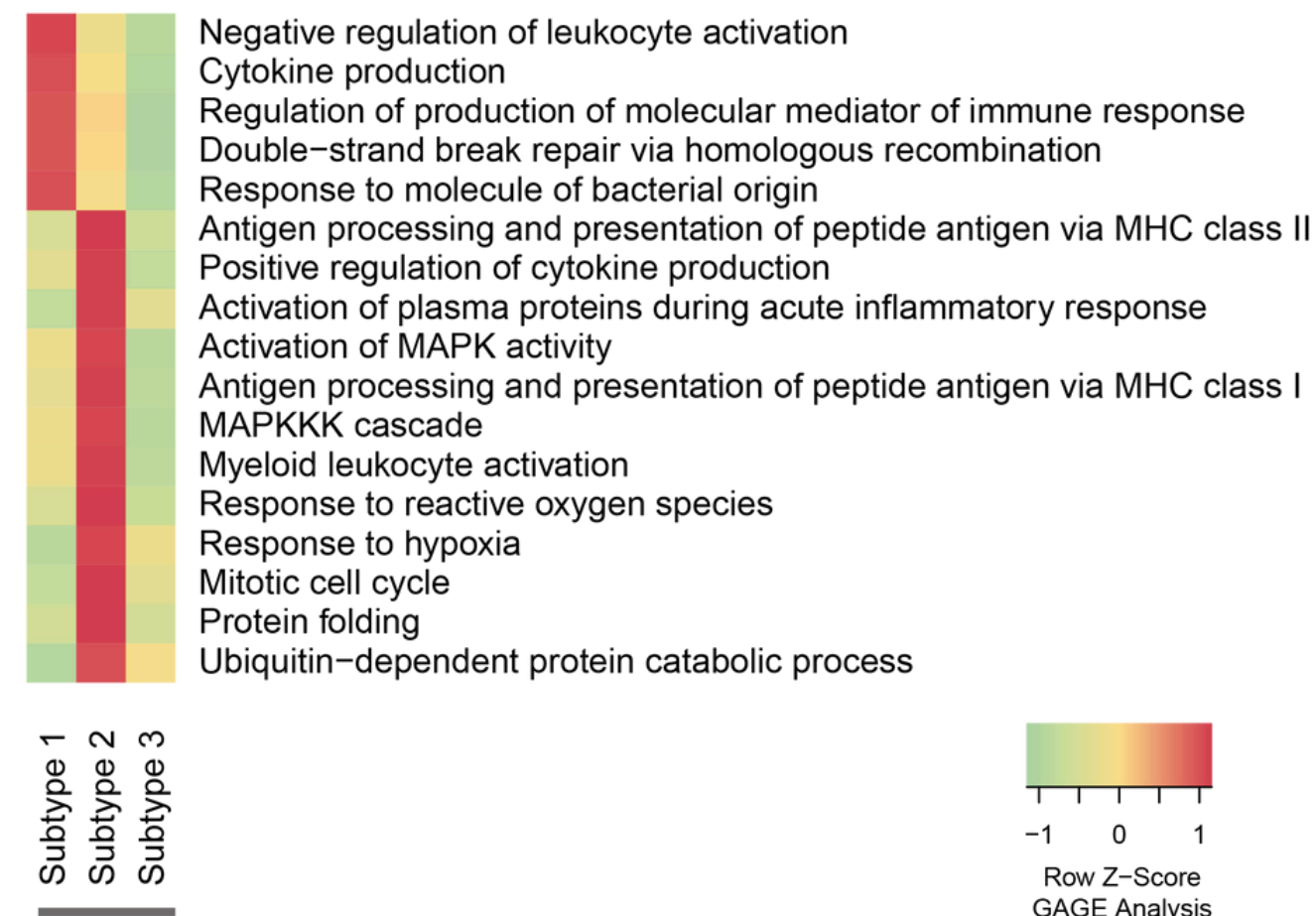
Subtype-specific biology in glioblastoma

In glioblastoma cohorts, transcriptomic subtyping identified groups with distinct biological programs and survival patterns, providing insight into disease heterogeneity.

SphereBio Glioblastoma Subtypes - Validation Set



Gene Set Enrichment Analysis by subtype



ASCO[®] ABSTRACT
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ASSOCIATION FOR CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER #482222

AI-driven transcriptomic classification of glioblastoma: Associations with survival and tumor microenvironment.

Juan Manuel Fernandez-Muñoz, Román Oberti, David A. Reardon, Francisco Quintana, Guido Nicolas Molina, Martin Eduardo Guerrero-Gimenez; SphereBio, Mendoza, Argentina; Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; SphereBio, Buenos Aires, Argentina

Fernandez-Muñoz et al 2025, ASCO Conference

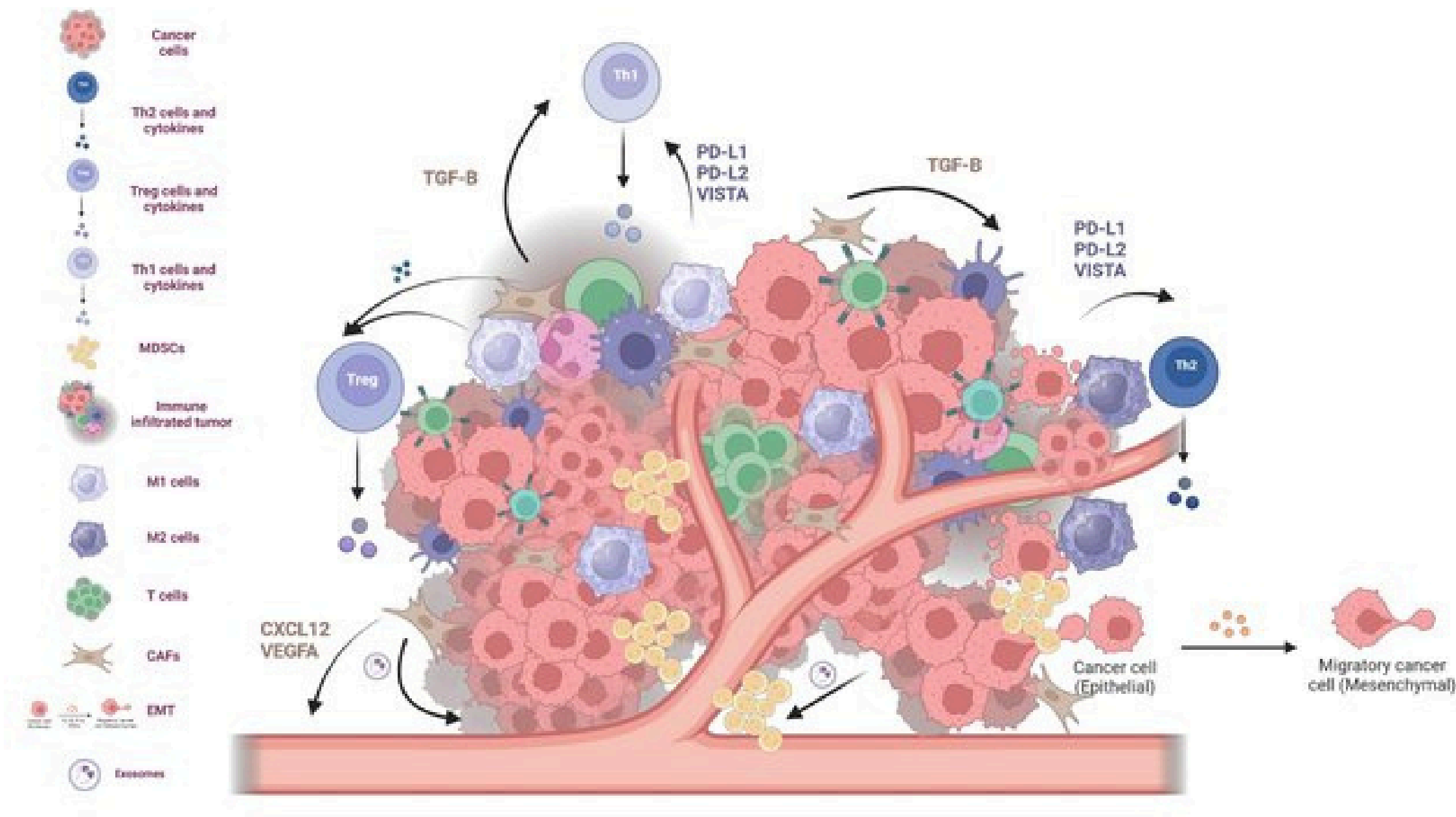
Gene set enrichment highlights processes including angiogenesis, immune response, and DNA repair, consistent with known glioblastoma hallmarks and offering hypotheses for therapeutic exploration.



5. Understanding the tumor microenvironment

The tumor microenvironment as a determinant of response

Tumors exist within a complex immune and stromal ecosystem.



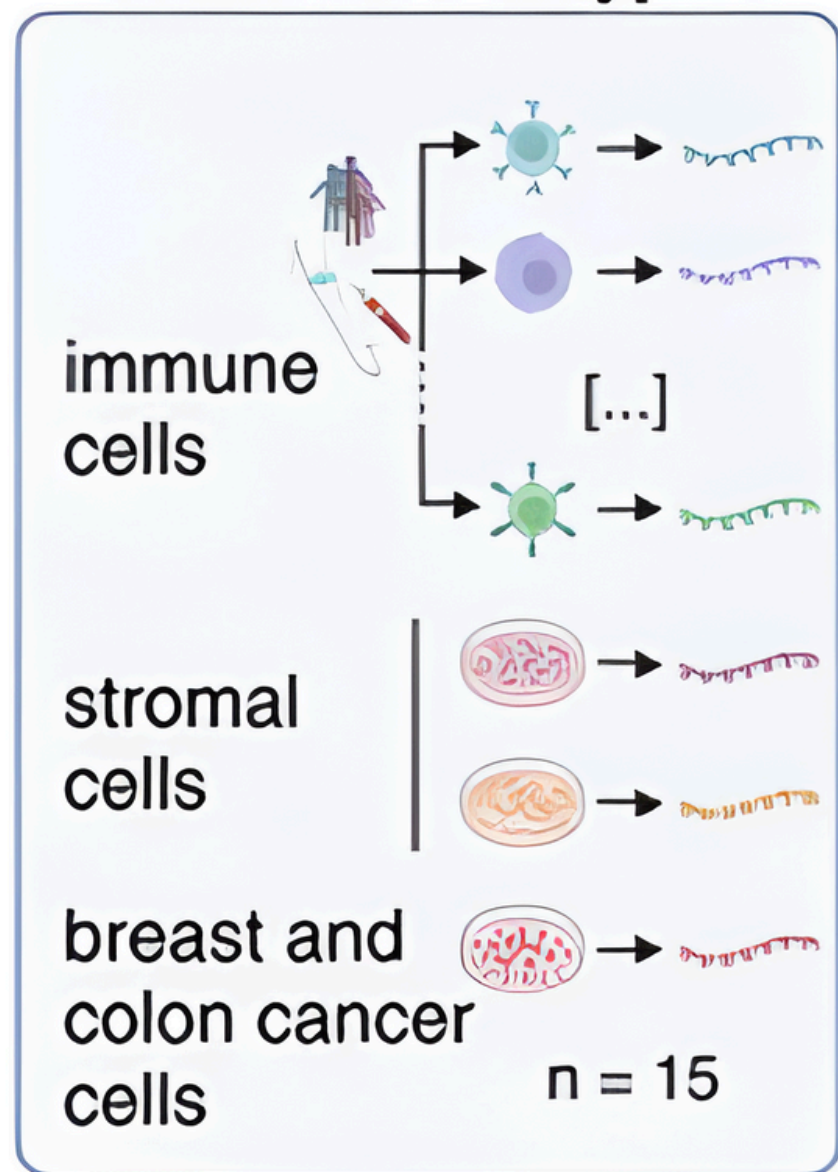
- Which cells are present?
- In what proportion?
- In which functional state?

The balance of effector, suppressive, and structural elements influences **progression, resistance, and therapeutic response.**

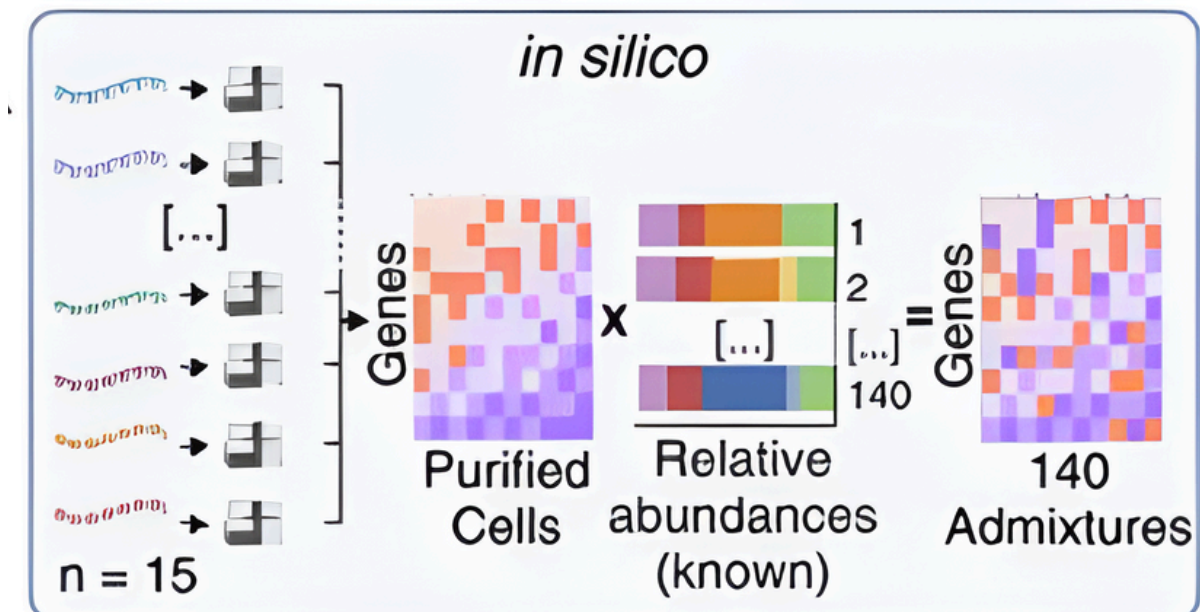
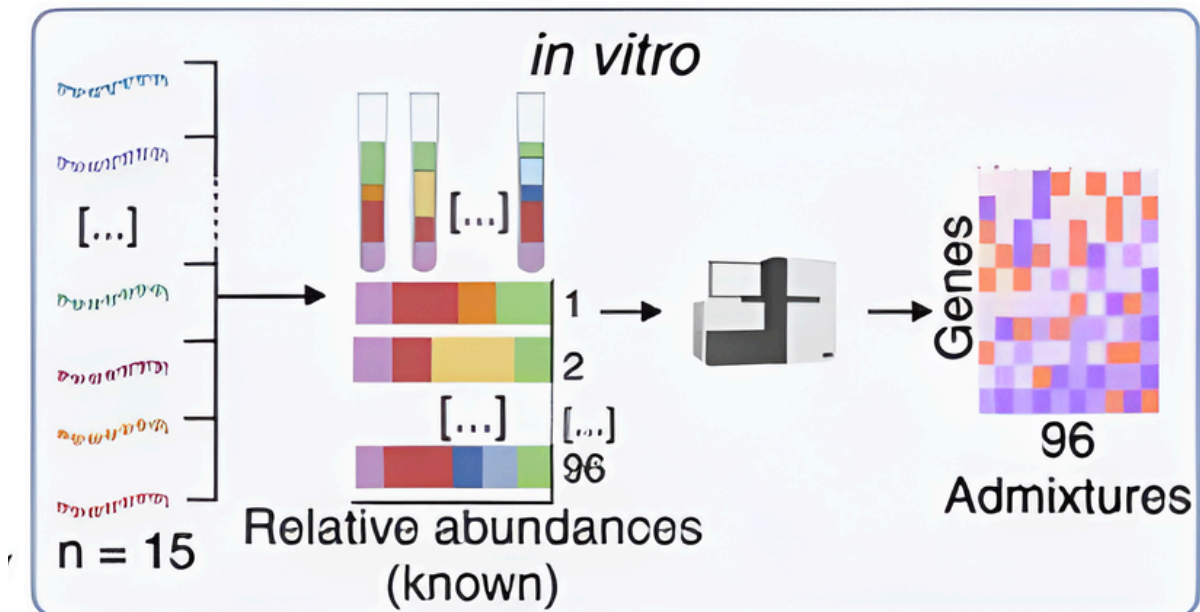
Inferring immune composition and state from expression profiles

Bulk transcriptomic data can be deconvolved to estimate the relative abundance of immune and stromal populations and infer functional states.

mRNA Generation from Purified Cell Types

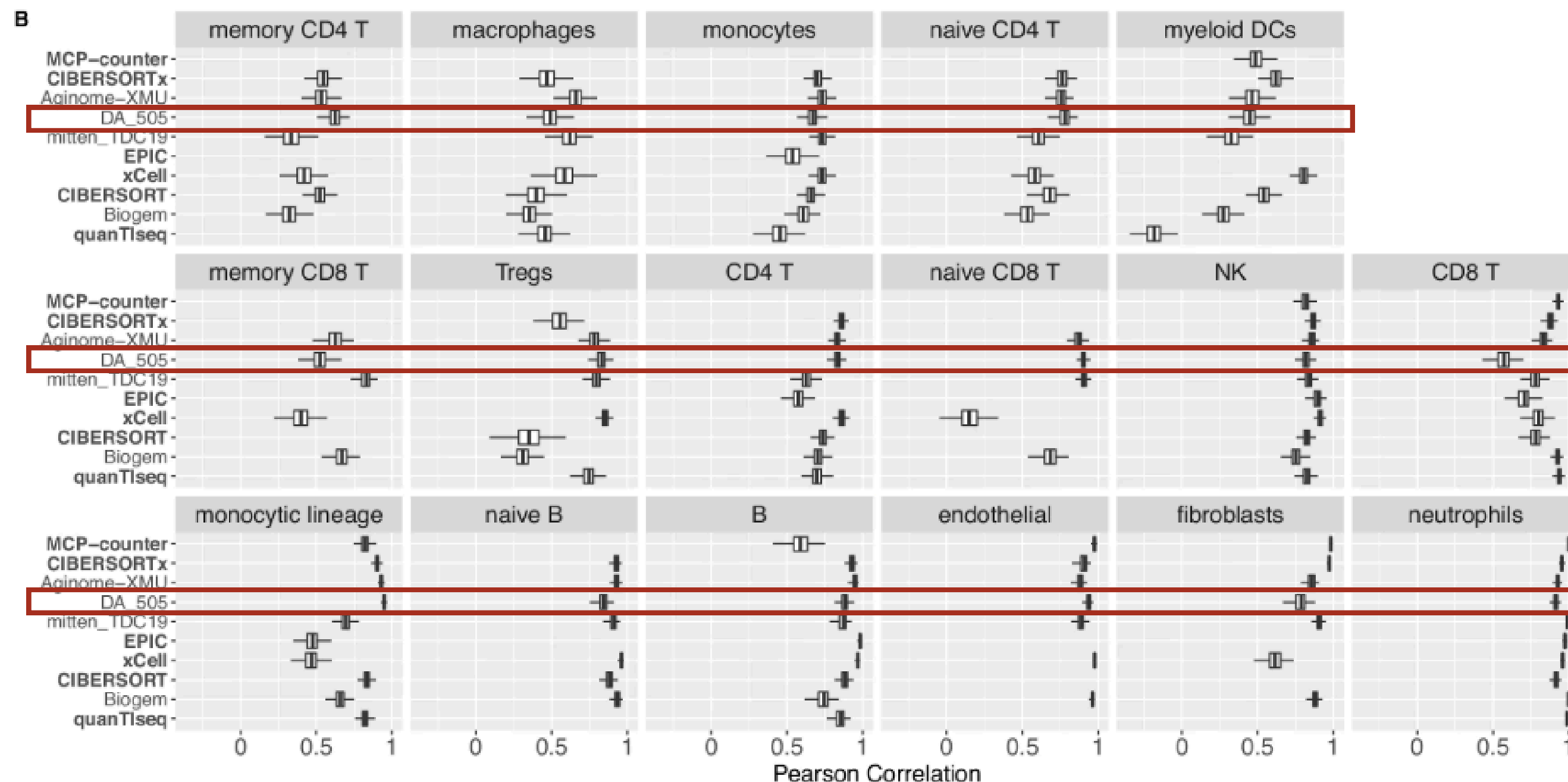


Admixture Generation



Community assessment of methods to deconvolve cellular composition from bulk gene expression

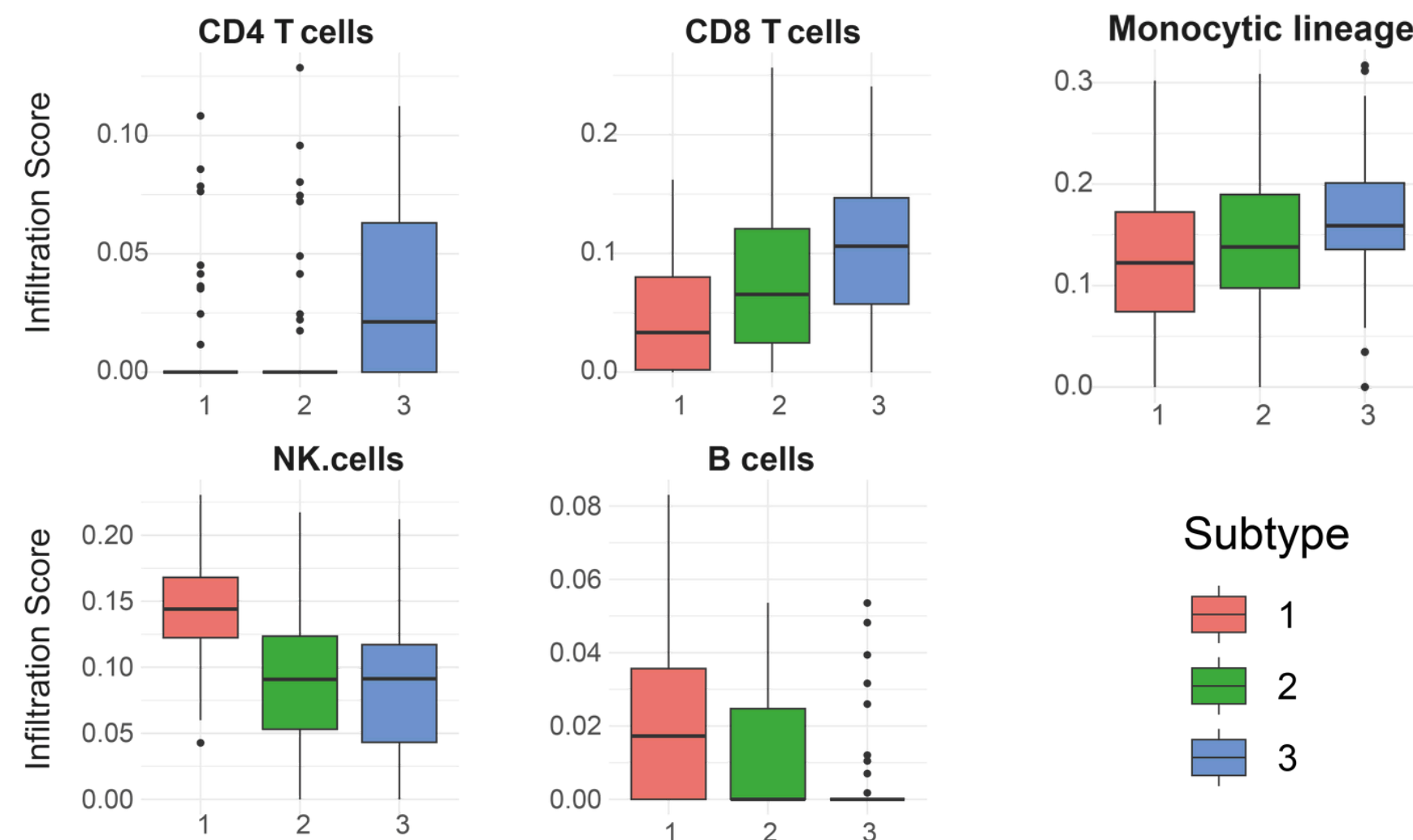
A regression-based approach (DA_505) was evaluated for immune and stromal infiltration inference from bulk gene expression data.



The Tumor Microenvironment of Glioblastoma

In analyses of glioblastoma cohorts, this approach identified subgroups with differing immune infiltration patterns, providing insight into tumor heterogeneity and associations with patient outcomes.

Subtypes Tumor Microenvironment



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AI-driven transcriptomic classification of glioblastoma: Associations with survival and tumor microenvironment.

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Fernandez-Muñoz et al 2025, ASCO Conference

These profiles offer a framework to explore therapeutic hypotheses, including the potential role of immunotherapy in tumors with higher immune cell presence



6. Tumor mutational profile

Understanding the tumor mutational profile

Different types of genomic alterations carry distinct biological and clinical implications

Which alterations drive tumor behavior?

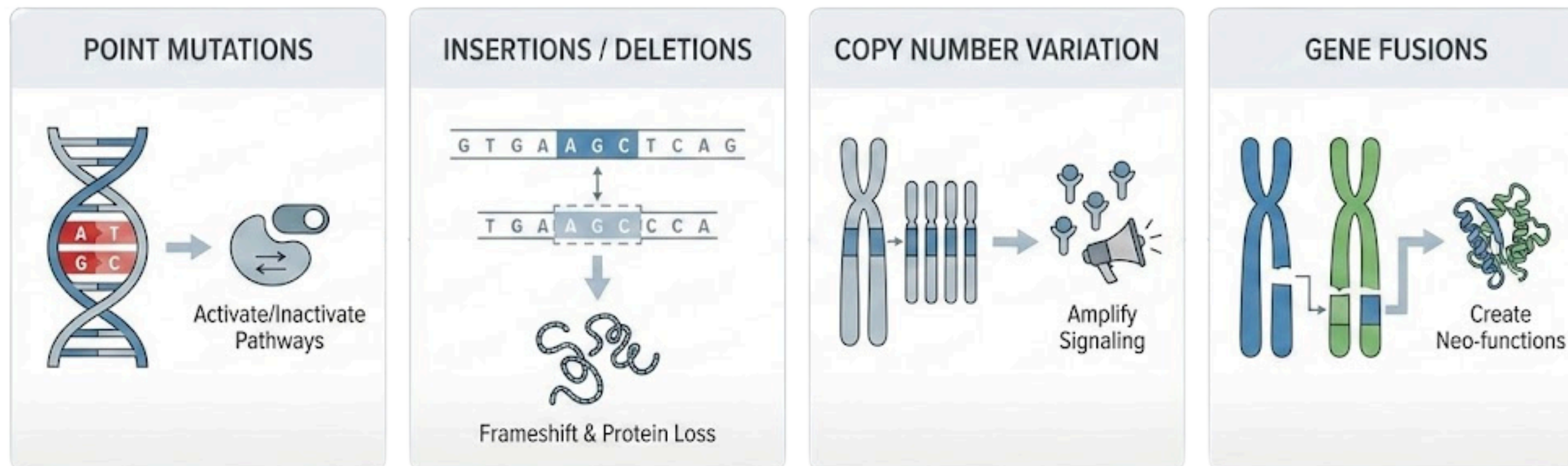
IDH1/2 (glioma), TERT promoter (GBM), BRCA1/2 (HRD)

Which alterations are clinically actionable?

EGFR, HER2, ALK, BRAF, NTRK

Which alterations confer resistance or susceptibility?

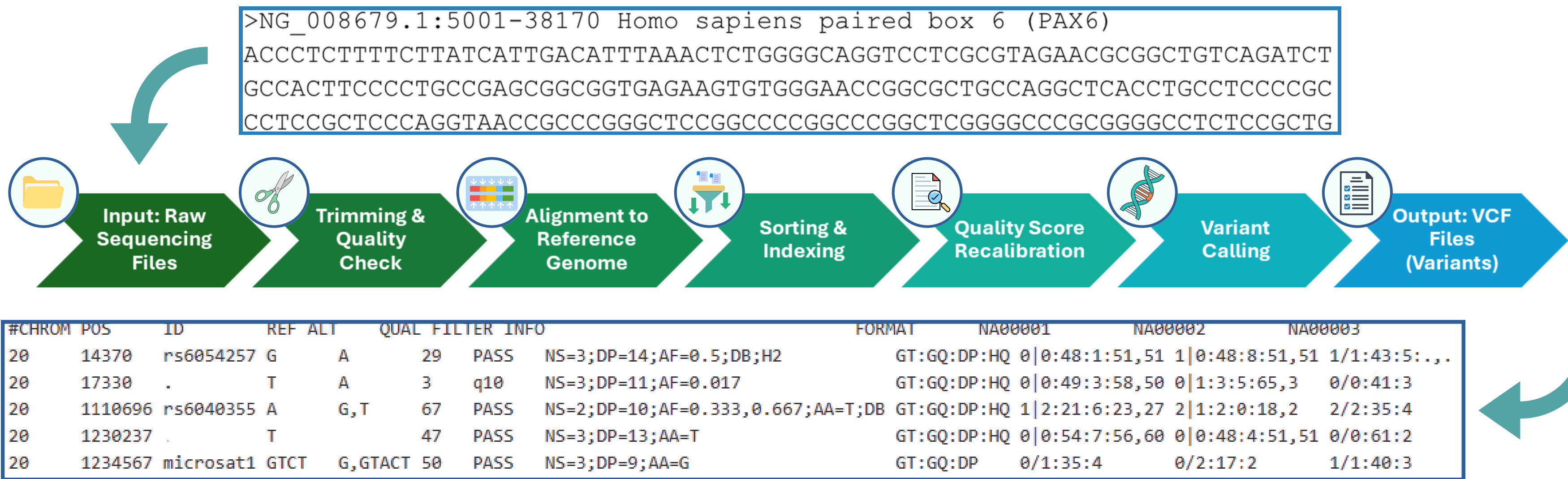
KRAS (anti-EGFR), EGFR T790M (TKI), POLE (ICIs)



Not all genomic alterations carry the same weight—some define phenotype, some create therapeutic opportunities, and others drive resistance

Genome sequencing and mutation detection

High-throughput sequencing generates raw reads that require quality control, alignment, and variant calling to identify genomic alterations. These alterations are then classified by biological impact, clinical actionability, and potential resistance or susceptibility.



The value lies not in detection alone, but in interpretation for **clinical context**

Interpreting detected variants in clinical context

Functional annotation of detected variants helps distinguish biologically relevant, actionable, and resistance-associated alterations

1. MSI	(+)	
2. TMB	69.00 mutations/Mb	
3. somatic variants (IS)	Gene function	Annotation
NF1: pP678fs*10	Tumor suppressor	Pathogenic
TP53: pR273C	Tumor suppressor	Pathogenic
CREBBD: pI1084fs*15	Transcriptional activation	No evidence
MEN1: pR521fs*43	Tumor suppressor	Pathogenic
MSH6: pF1088fs*5	Mismatch repair	No evidence
ARID2: pL97P	DNA binding protein	VUS
CDK4: pN41S	Cell cycle regulation	VUS
ERBB3: pH584N	Growth factor	VUS
ERBB4: pH1118R	Growth factor	No evidence

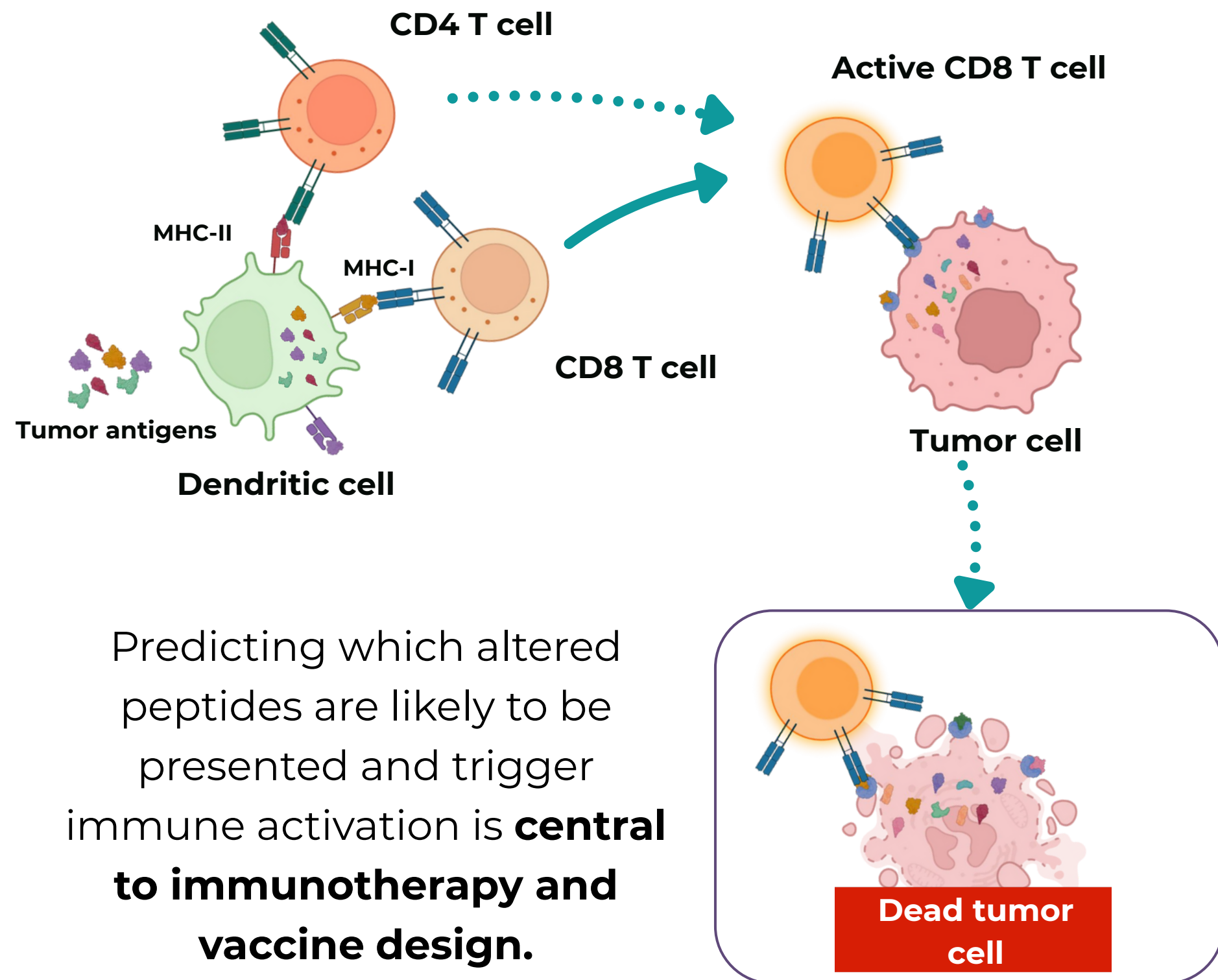
MSI positive + Very high TMB (69/Mb) - Supports **Immune Check Point Inhibitors**
Other detected variants provide biological context but lack current clinical actionability



7. Immunogenicity prediction

Which mutations matter to the immune system?

Only a fraction of tumor mutations result in peptides that are processed, presented by MHC molecules, and recognized by T cells.



Predicting which altered peptides are likely to be presented and trigger immune activation is **central to immunotherapy and vaccine design.**

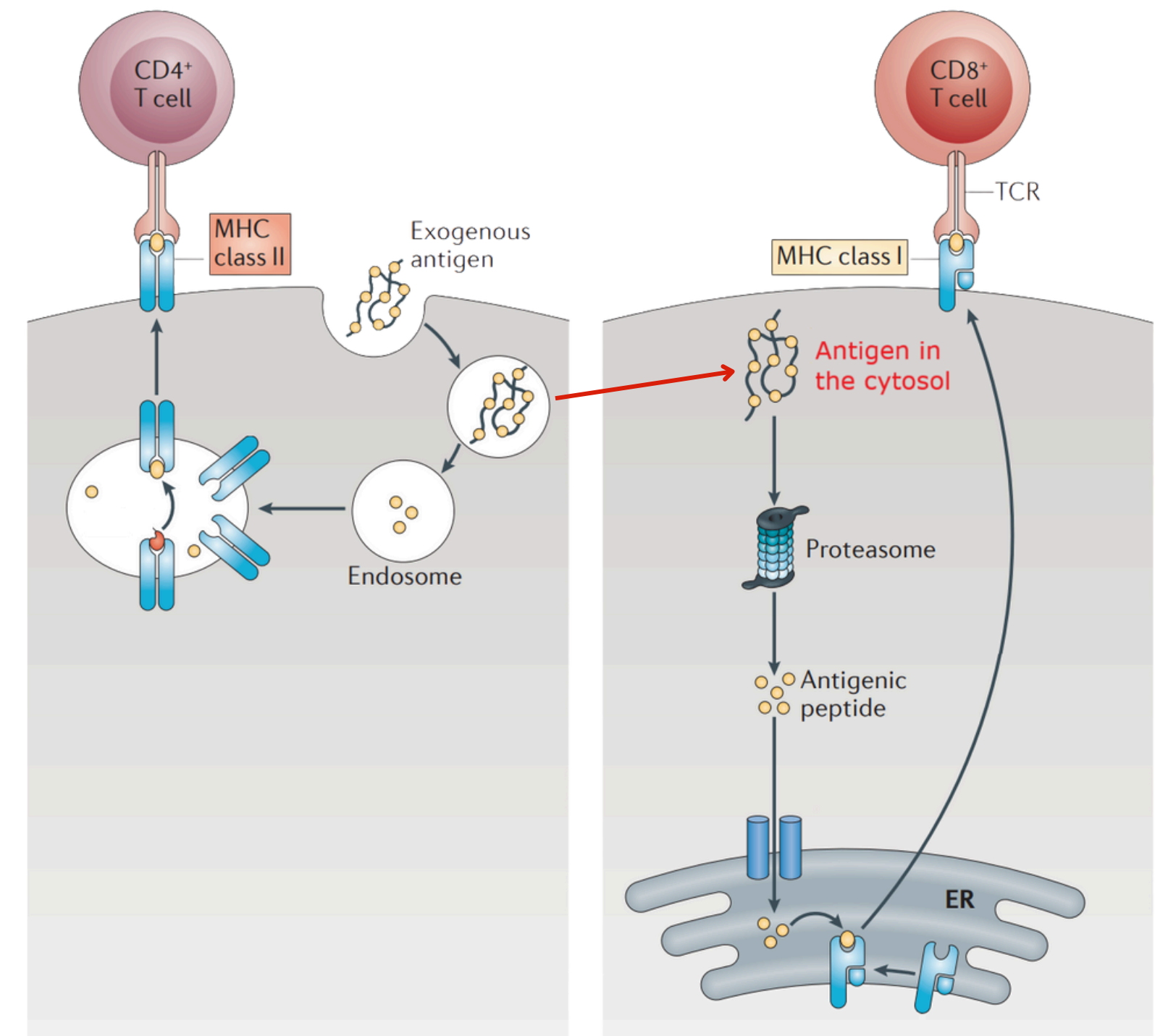
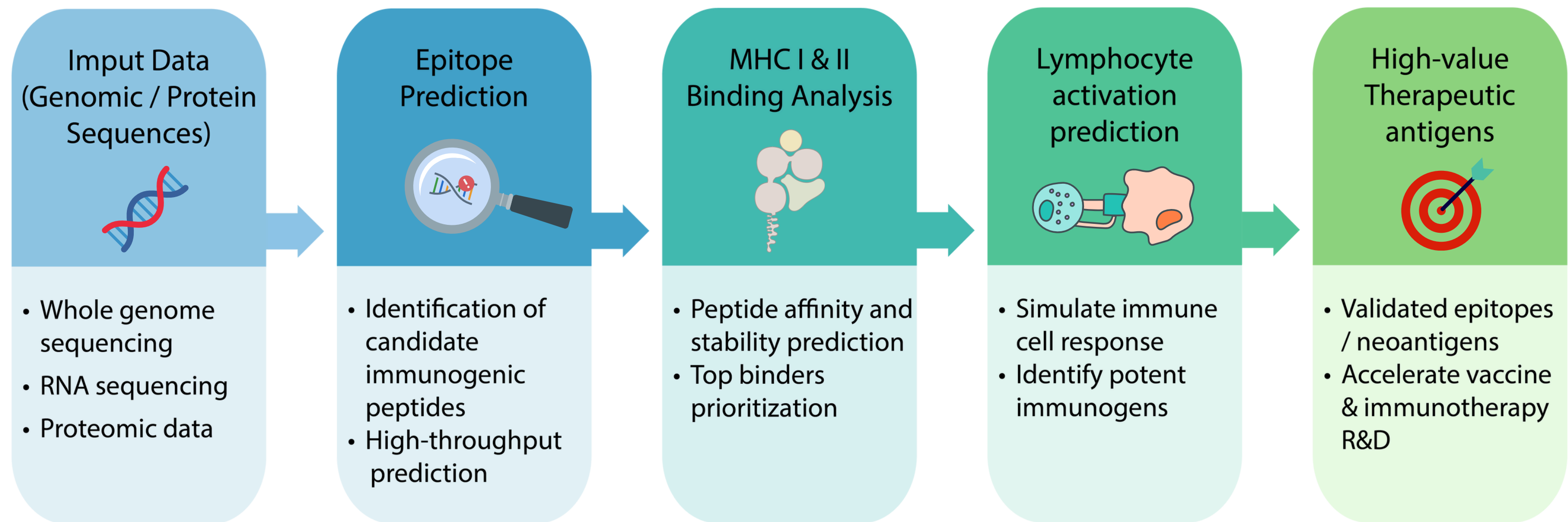


Figure modified from Kobayashi and van den Elsen, Nat Rev 2013

Immunogenicity Prediction

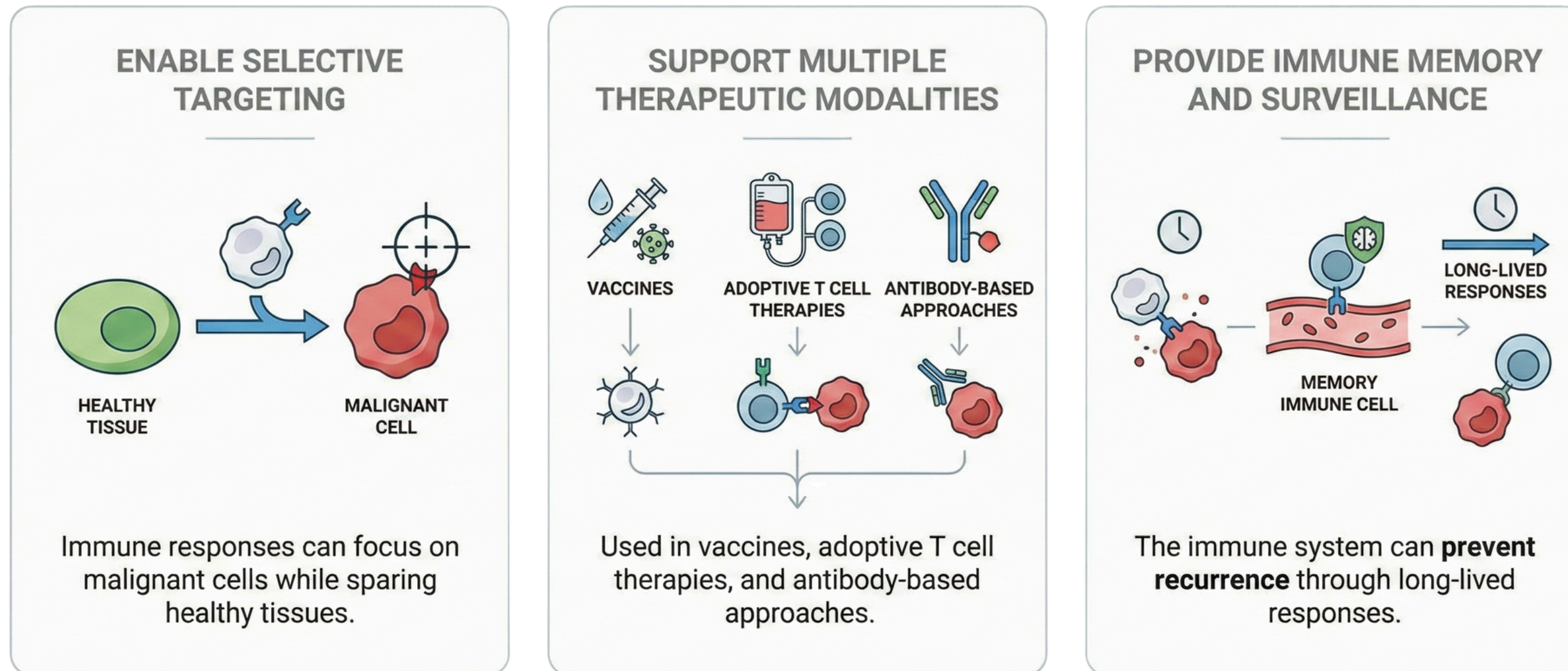
Genomic data can be analyzed to predict candidate neoantigens by modeling peptide processing, MHC binding, and T-cell recognition potential.



These predictions help prioritize which alterations may generate **biologically meaningful immune responses**.

Why tumor antigens matter

Tumor antigens provide the immune system with molecular differences that distinguish cancer cells from normal tissues.



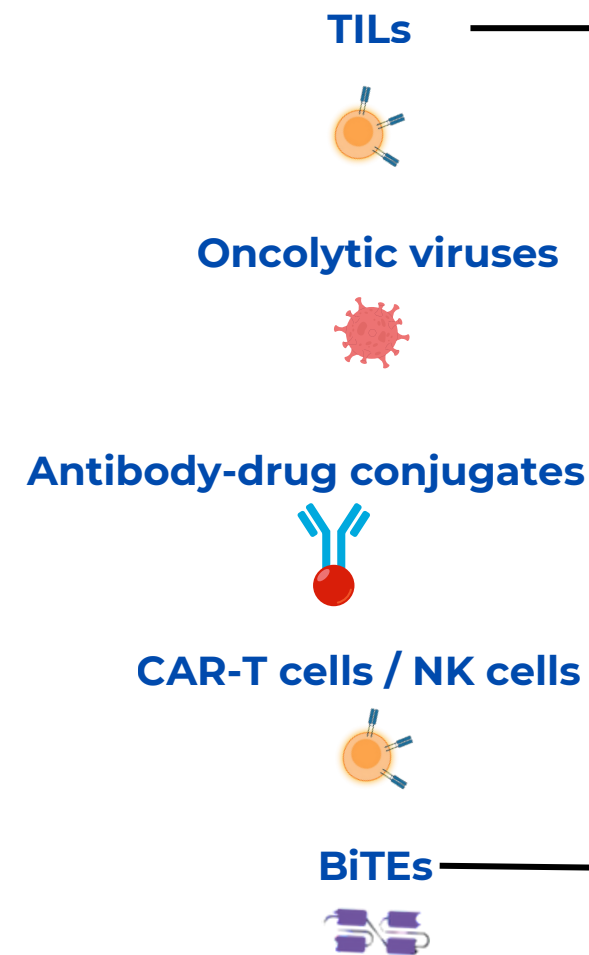
These differences can be leveraged to enable selective and durable **antitumor immune responses**.



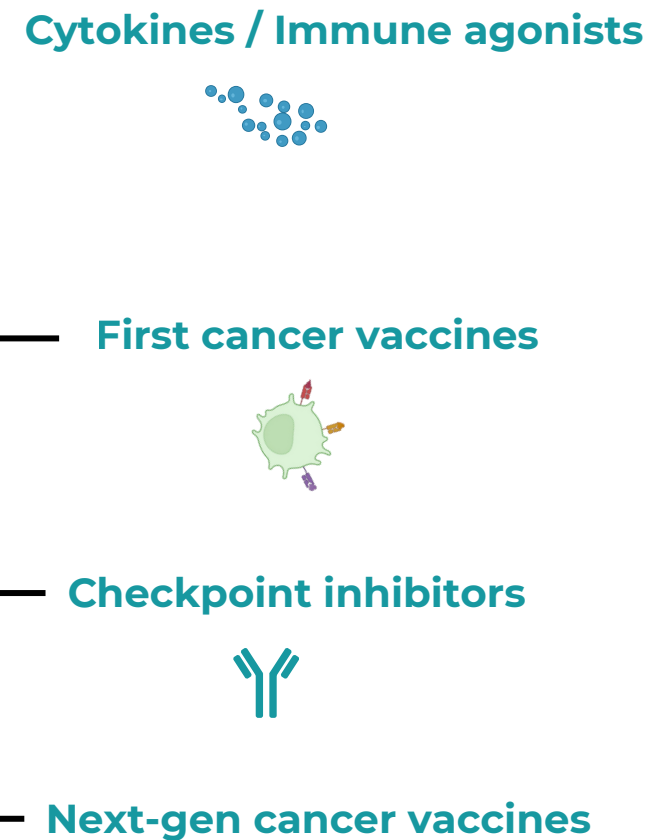
8. Individualized cancer vaccines: A future alternative?

Cancer immunotherapies

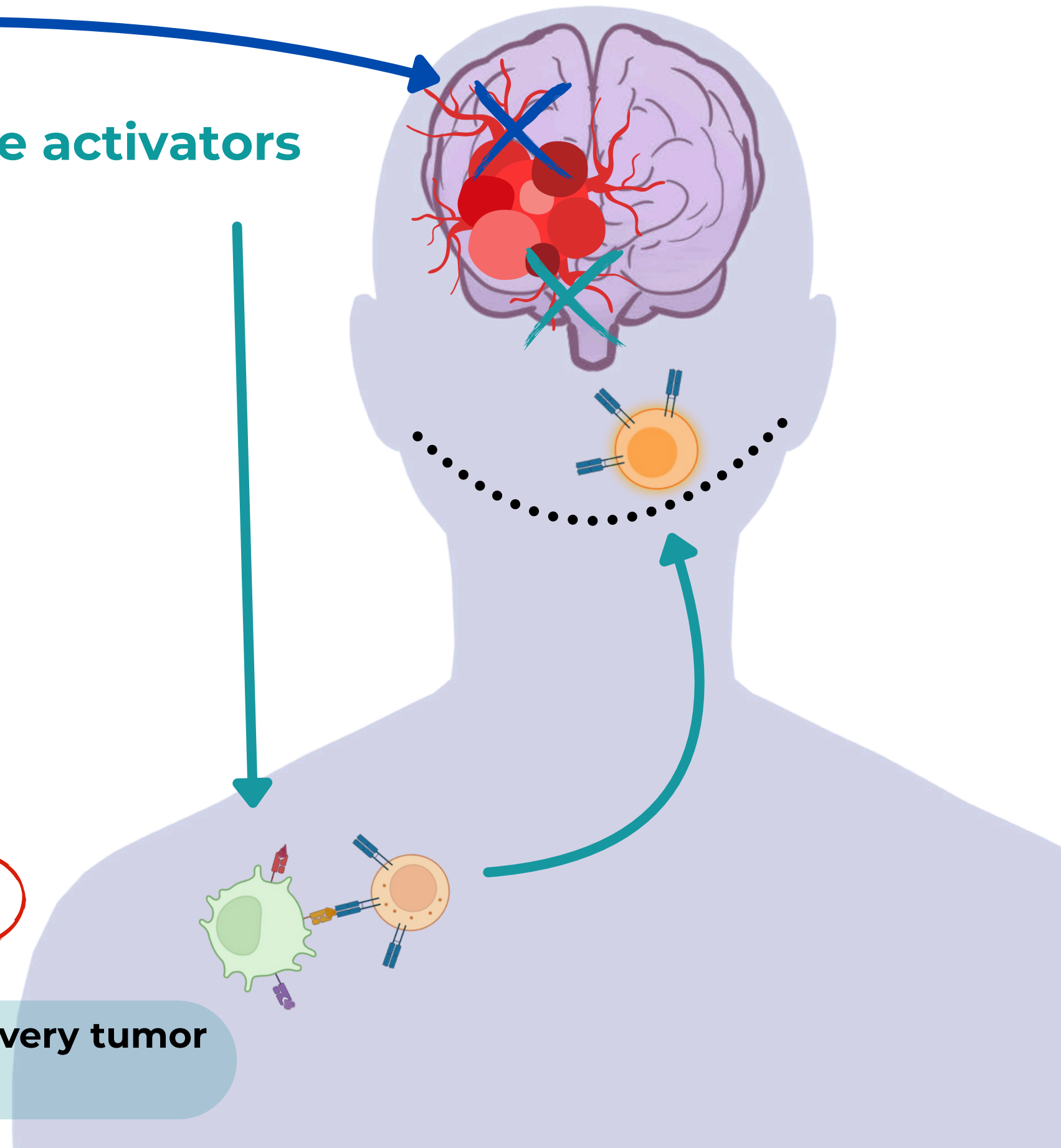
Tumor-targeted therapies



Systemic immune activators



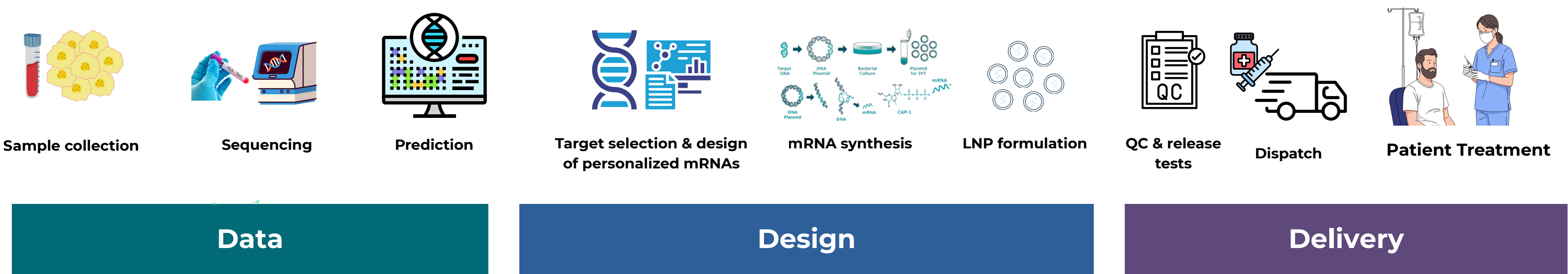
Tumor heterogeneity limits single-target immunotherapies — not every tumor expresses the same target, even within the same patient



Cancer Vaccines: The Individualized Workflow

Each tumor contains its own set of potential immune targets.
Individualized vaccines turn those targets into tailored immunotherapies.

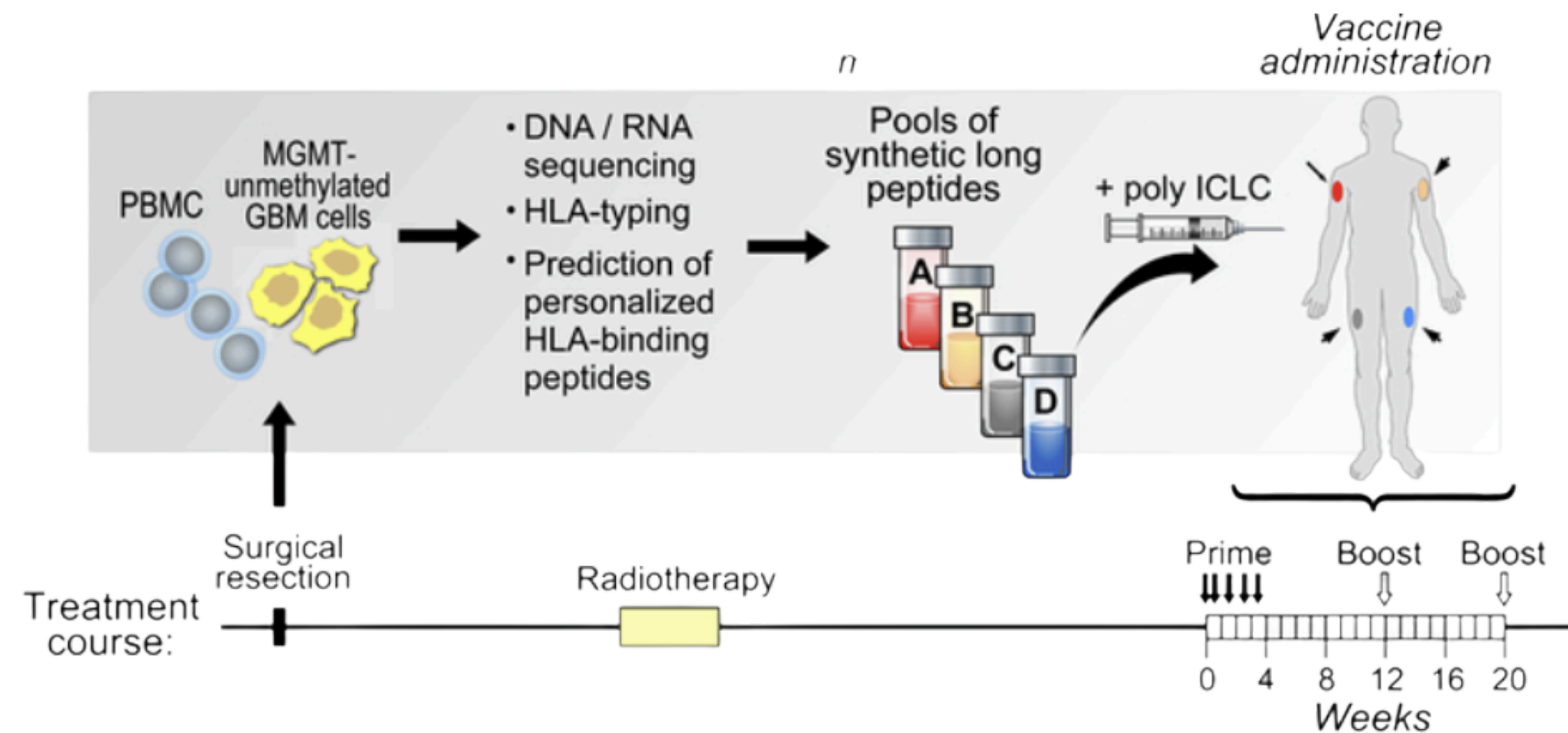
Personalized cancer vaccines manufacturing



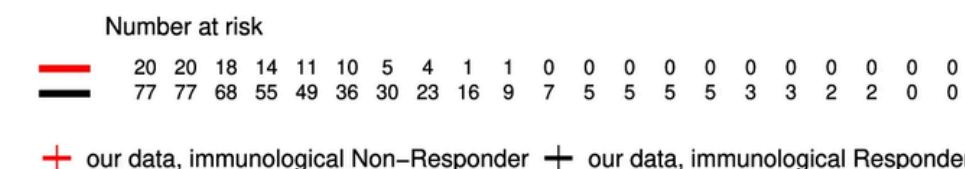
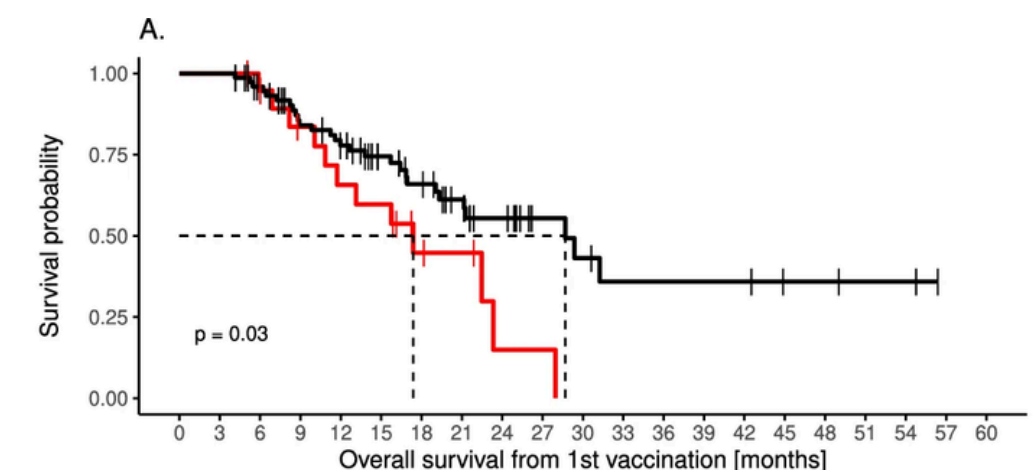
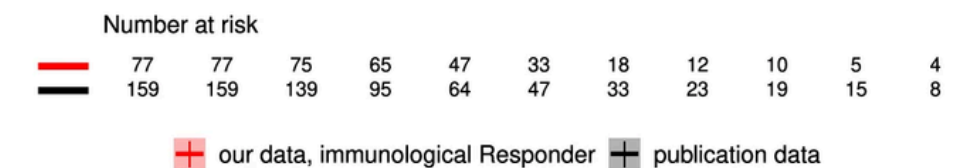
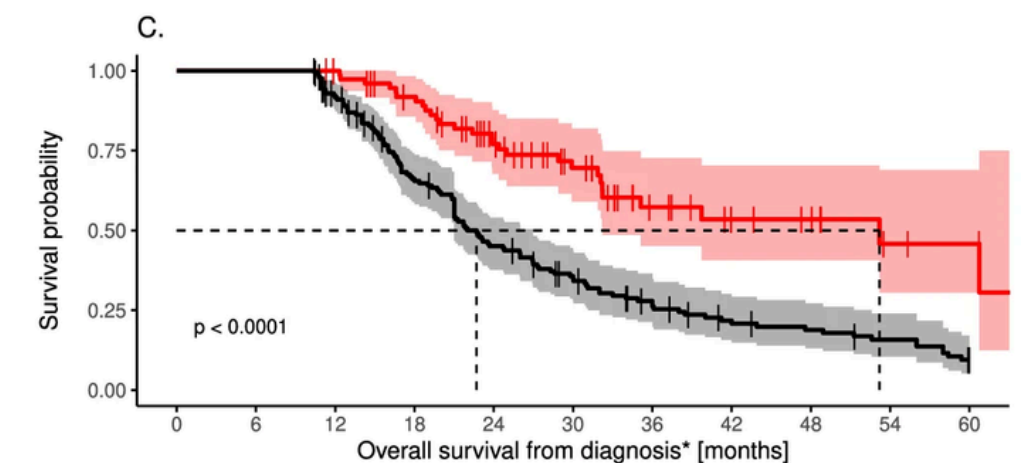
Individualized vaccines aim to convert the tumor's unique mutations into precise immune targets, creating a therapy as unique as the patient.

Personalized cancer vaccines in high-grade glioma

Recent trials demonstrate that patient-specific neoantigen vaccines can elicit CD8+ responses and improve survival in selected glioma patients



Combining vaccines with radiation, checkpoint inhibition, or tumor debulking has shown synergistic potential



Insights from Dr. Reardon Research

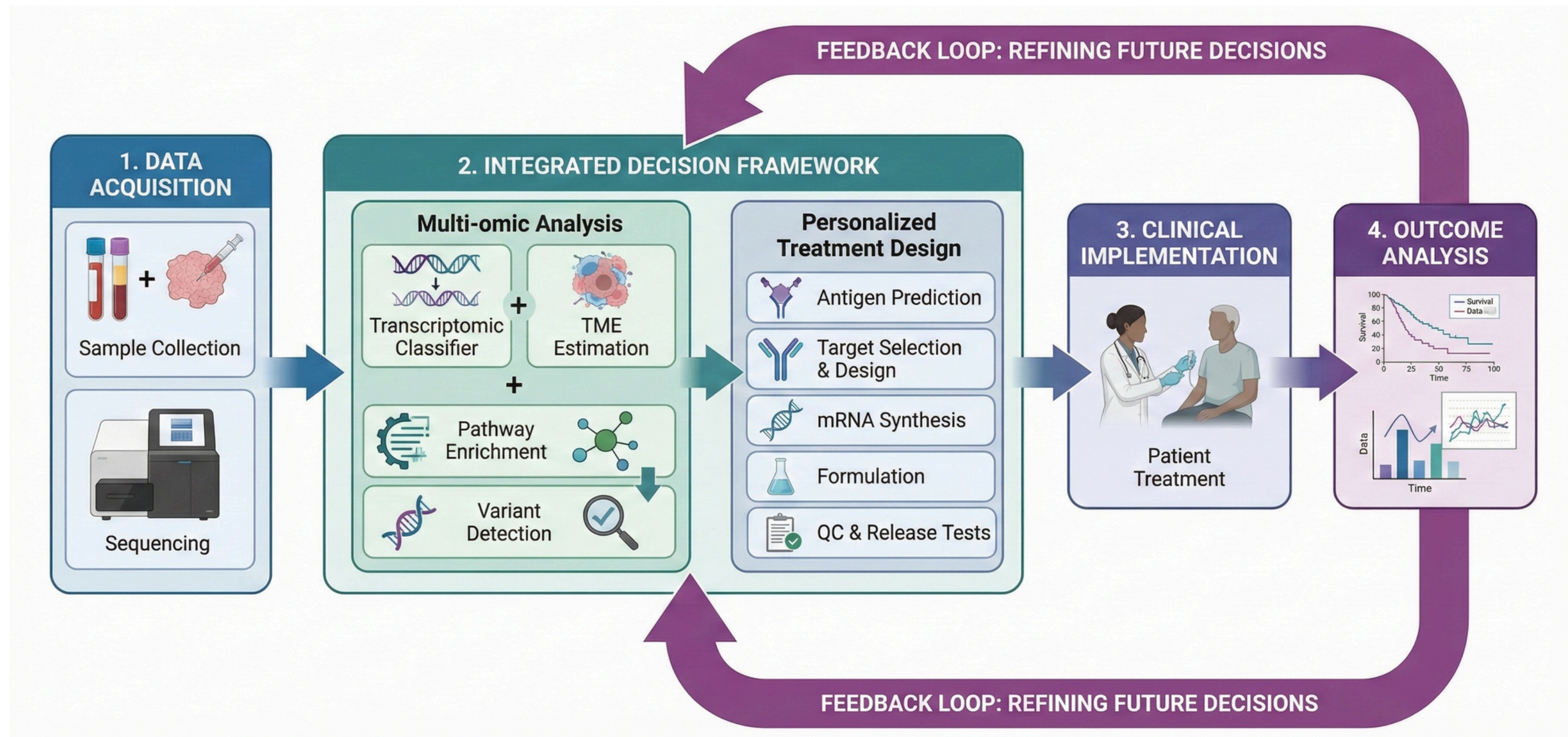
Keskin et al. 2018, Nature
Latzer et al. 2024, Nature Communications



9. An integrated diagnostic and therapeutic approach

A unified model for diagnosis-to-treatment decisions

Modern oncology is moving from parallel diagnostic outputs to **integrated decision frameworks** with clinical outcomes feeding back into the model, refining future diagnoses and treatment decisions.

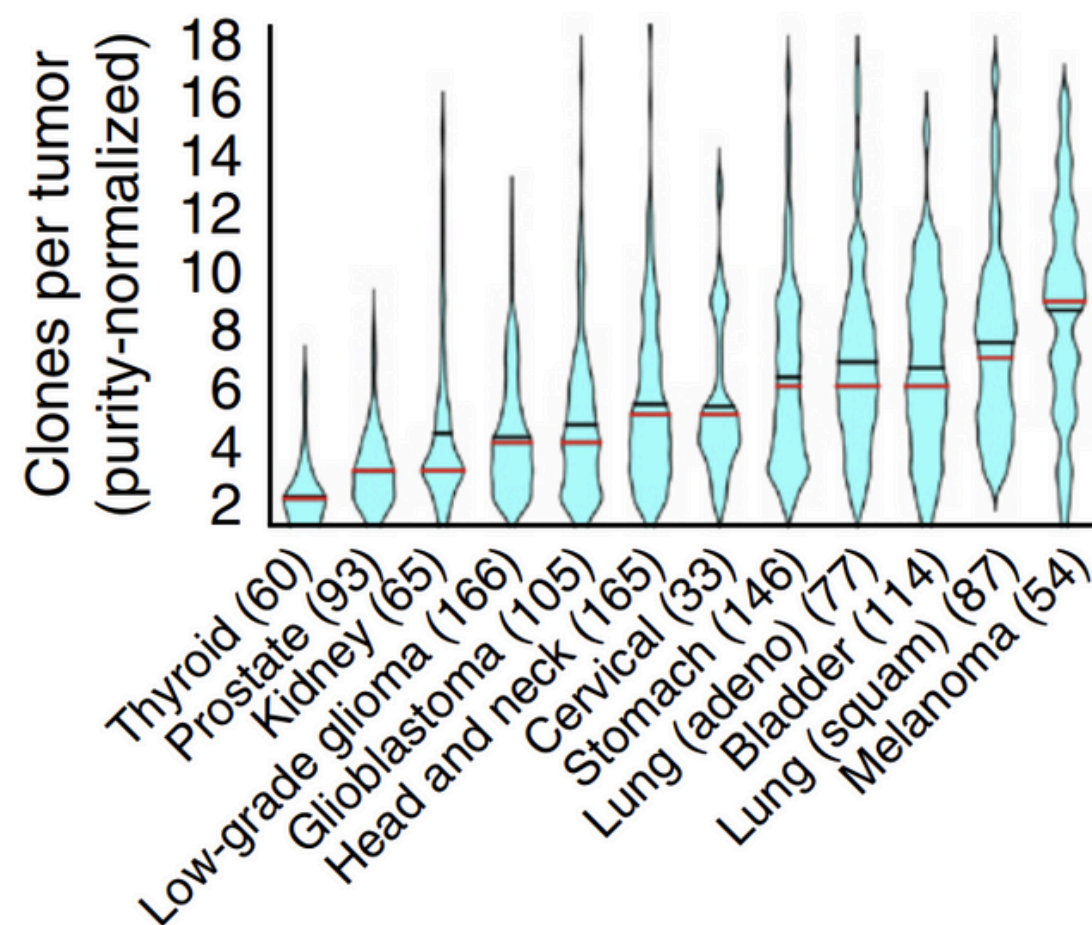




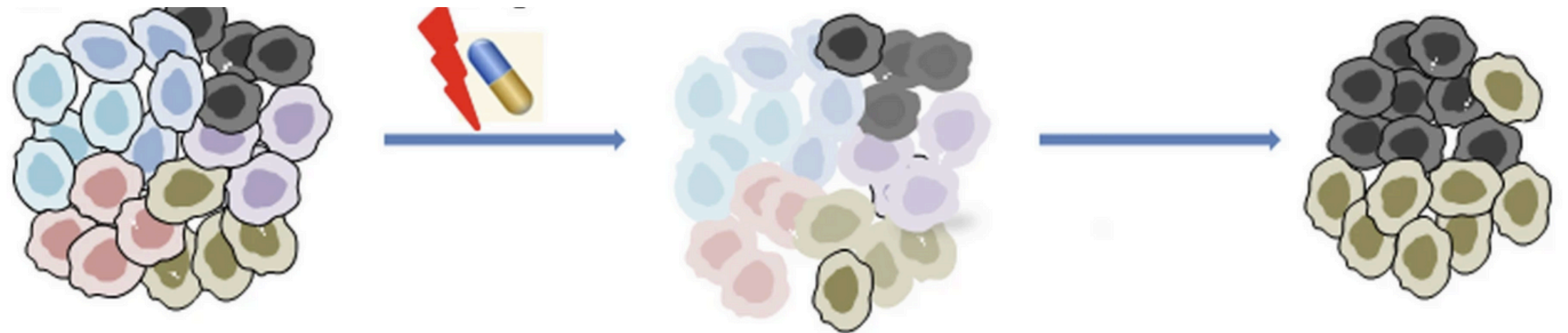
10. Limitations & future perspectives

Intratumoral heterogeneity drives immune escape and relapse

Diverse subclones within a single tumor evolve independently, enabling immune escape and reducing the durability of targeted therapies



Andor et al. 2015, Nature Medicine

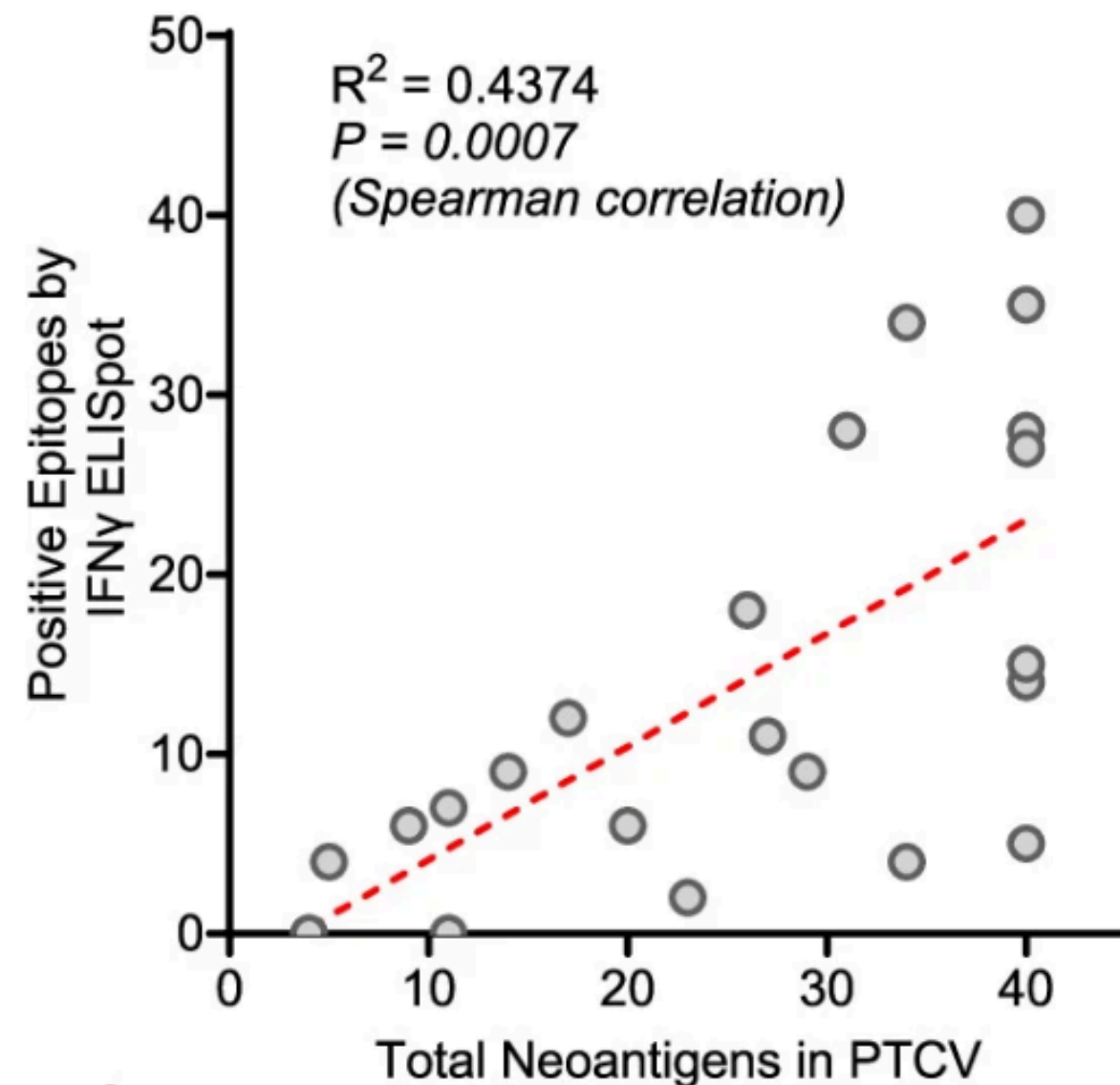


Yue-Chun Fu et al. 2025, Cancer Cell International

A small set of tumor antigens is not sufficient to control advanced, highly heterogeneous tumors

Current vaccine platforms cover only a fraction of tumor antigen diversity

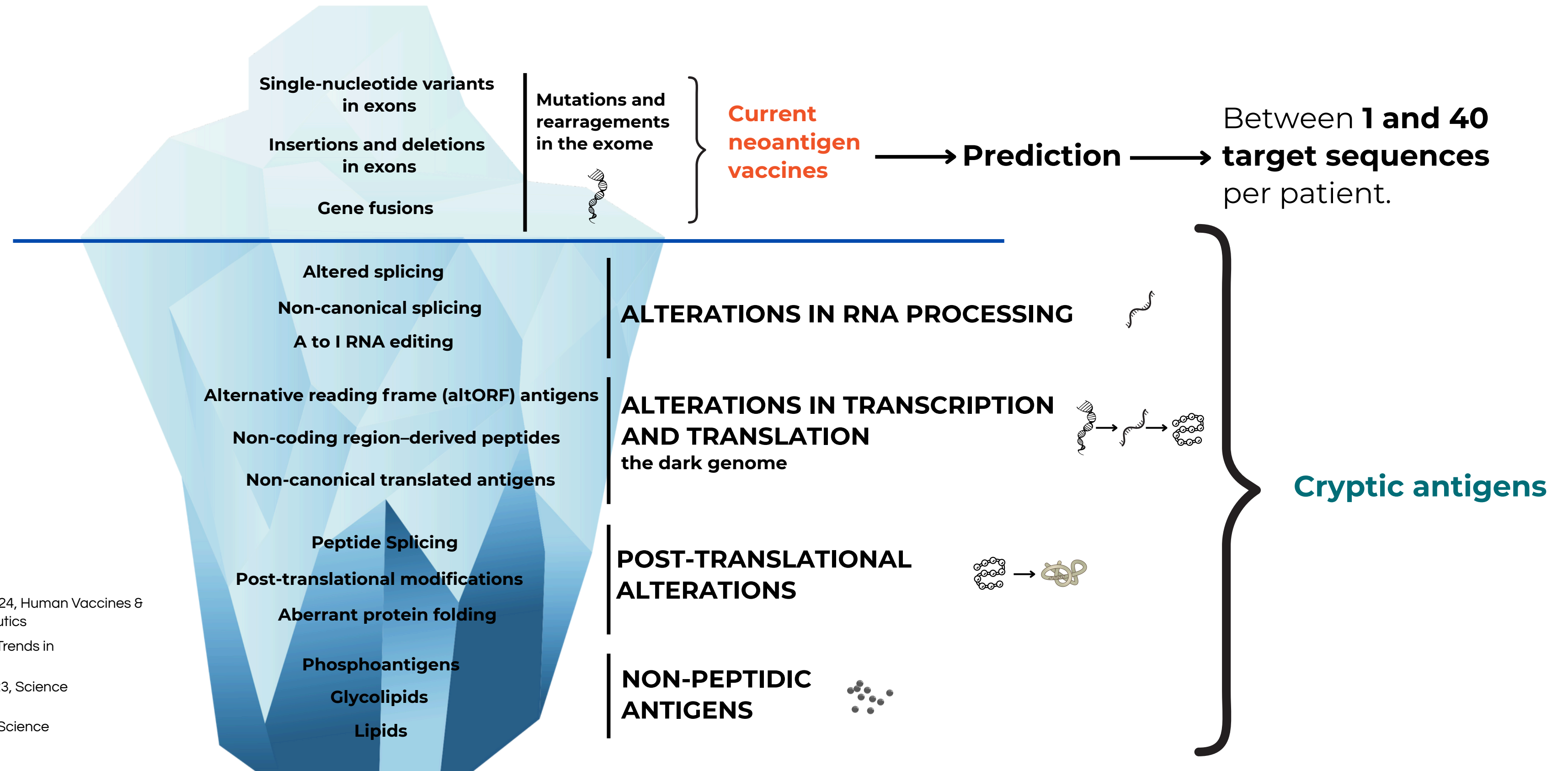
Most personalized vaccines include <40 targets, which may be insufficient in tumors presenting hundreds of heterogeneous neoantigens



More antigens lead to more T-cell clones responding

Current personalized cancer vaccine platforms

Only see the tip of the iceberg of **tumor antigen diversity**



Aparicio et al. 2024, Human Vaccines & Immunotherapeutics

Kina et al. 2025, Trends in Genetics

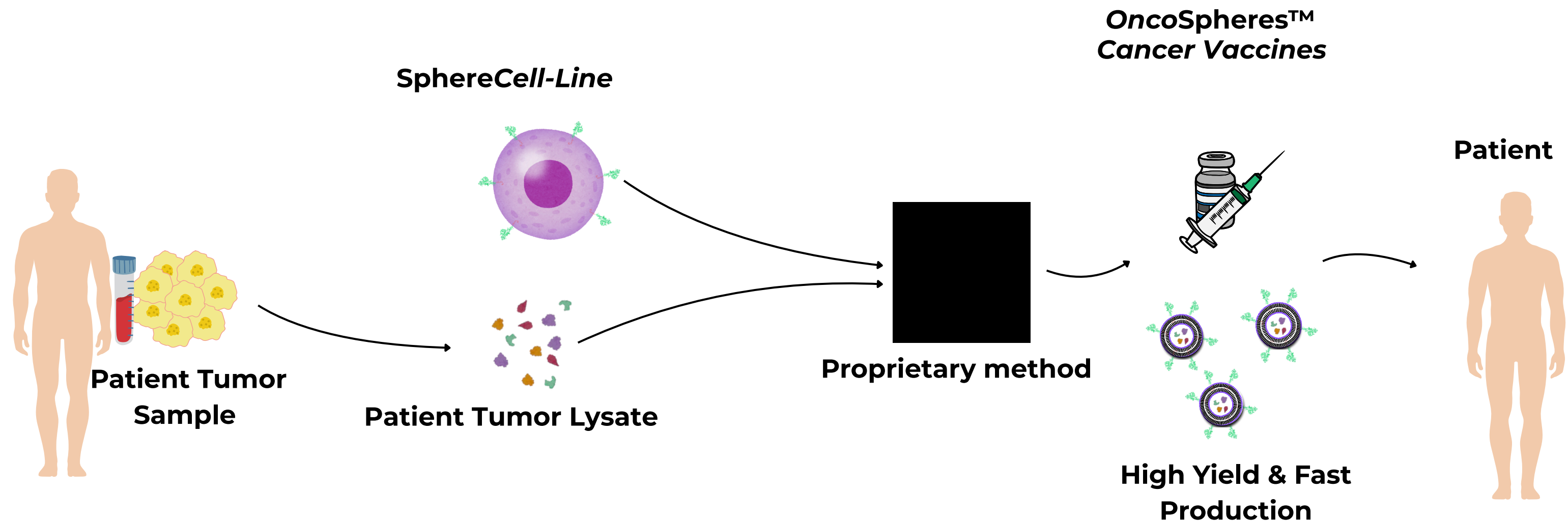
Merlotti et al. 2023, Science Immunology

Raja et al. 2025, Science Advances



OncoSpheres™ — A personalized cancer vaccine derived from the patient's own tumor

A proprietary manufacturing process to generate antigen-rich vesicles that naturally package the full complexity of tumor antigens, including cryptic, patient-specific, and heterogeneous targets, delivered directly to APCs



Full antigenic landscape

Built-in endosomal escape

Rapid manufacturing & scalable



SphereBio

Founders

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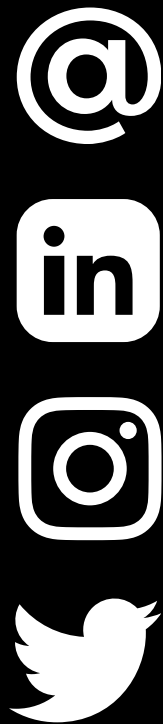
endeavor

FIFARMA

START
GLOBAL



Thank you!



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