

When molecular heterogeneity obscures the underlying biology

A 21-case test of Biology-First Intelligence in undifferentiated sarcoma

In heterogeneous disease, the same molecular feature can arise within different biological architectures. Conversely, biologically related tumors may not share the same observable molecular features.

RESEARCH QUESTION

Can transparent causal reconstruction identify recurrent biological organization that is not apparent from individual molecular features alone - and can that reconstruction generate additional, testable mechanistic information?

The analysis was designed to preserve uncertainty rather than force a single interpretation when the evidence did not support one.

RESULTS AND ANALYSIS

19 / 19

molecularly informative cases supported multi-event structural-genome / copy-number remodeling

18 / 18

claim-informative cases supported a broad viable dosage-imbalanced / aneuploid structural state

The cohort did not converge on one driver, one exact ploidy history, or one universal structural implementation. Instead, the first stable cross-case convergence emerged at the biological process/state level.

RECONSTRUCTED ARCHITECTURE

HETEROGENEOUS CHROMOSOME / SEGMENT EVENTS

STRUCTURAL-GENOME REMODELING

VIALE DOSAGE-IMBALANCED STATE

FOCAL / REGIONAL MOLECULAR MODULES

Shared biological organization did not require identical molecular implementation.

R&D IMPLICATION

Reconstruction generated mechanistic information beyond exact feature matching. In 18 of 19 molecularly informative cases, the frozen reconstructions produced at least one state-level vulnerability hypothesis beyond exact feature matching.

For R&D teams, the practical value is a better-defined biological decision boundary: whether a target, biomarker, or proposed mechanism reflects broader disease organization or only a local molecular feature - and what additional evidence would most change the conclusion.

**The value is not another target list.
It is higher-resolution biological decision-making.**

BIOLOGY-FIRST INTELLIGENCE

BFI is AnnieGuard's proprietary causal reconstruction methodology for determining what complex biological evidence can support, what remains unresolved, and which additional evidence would most change the conclusion.

Reconstruction-derived mechanistic hypotheses

Recurrence within the relevant evidence-informative subset

Proteostasis / dosage-homeostasis 18 / 18

Chromosome-state maintenance / mitotic fidelity 18 / 18

Replication-stress / checkpoint tolerance 16 / 18

Retained-copy / retained-homolog discovery 10 / 19

7 / 19 CDKN2A/CDKN2B deletion
recurred across multiple reconstructed structural contexts

WHAT THIS CAN INFORM

- Target and mechanism evaluation
- Biomarker and patient stratification
- Experimental prioritization
- Translational go / no-go decisions

DISCUSS A RESEARCH PROJECT

Does your current evidence regime support your primary mechanism?

[ANNIEGUARD.COM](https://annieguard.com) →