A105 · Tissue-of-origin aging clocks reveal composite aging states across cancers

Presenter: Payton Bock — Boston University

Authors: Payton Bock, Jackson Smith, Pranav Narnur, Nageen Zahra, Nuzulul Kurniansyah, Stefano Monti

Session: Day 2 · Fri Oct 2, 2026 · 1:15–2:15 PM

Background: Chronological age is a major risk factor for cancer. Efforts to understand the cancer-aging relationship have largely characterized age-associated changes within tumors, leaving unclear whether tumors preserve, reshape, or depart from the aging programs of their tissue of origin. Aging clocks offer a way to quantify such departures and are increasingly applied in disease, including cancer, but their outputs remain biologically ambiguous.

Methods: We mapped age-associated molecular changes across 33 cancer types and six molecular layers in The Cancer Genome Atlas. We then trained transcriptomic aging clocks in matched normal tissues from the Genotype-Tissue Expression (GTEx) and applied them to six cancers, quantifying each tumor's deviation from the molecular aging state expected for normal tissue of the same age. We introduced ClockSHAP, an interpretability method for aging clocks that decomposes each deviation into pathway-level contributions.

Results: Age-associated tumor changes were heterogeneous but structured by tissue of origin. Five of six cancers showed strongly youth-like overall deviations, but these reflected composite states in which youth-like proliferative programs frequently coexisted with older-like damage-response and signaling programs. In breast cancer, a clock trained only on normal breast tissue, applied without retraining, produced reproducible deviations and pathway structure across two independent cohorts (~9,700 tumors), aligned with molecular subtype and TP53 mutation status, and associated with survival.

Conclusions: These findings suggest tumors reshape rather than uniformly advance or reverse tissue-of-origin aging programs. Tissue-referenced aging clocks and ClockSHAP provide a framework for applying and interpreting aging clocks in disease.

Tissue-of-origin aging clocks reveal composite aging states across cancers

Payton Bock*[1], Jackson Smith[1], Pranav Narnur[1], Nageen Zahra[1], Nuzulul Kurniansyah[2], Stefano Monti[1]

[1]Boston University, Department of Medicine, Section of Computational Biomedicine, [2]Boston University, Department of Medicine, Section of Biomedical Genetics

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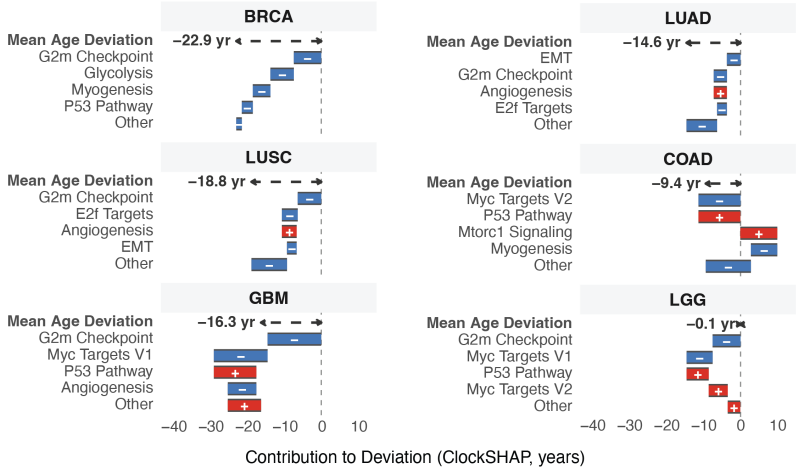

Figure 1. ClockSHAP reveals composite tumor aging states across cancers.
Across six cancers, overall age-matched deviations decompose into coexisting youth-like (blue) and older-like (red) pathway contributions.