

When the Biological Age Clock Lies

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Abstract (original summary).

 Does a lower epigenetic age constitute rejuvenation? This paper distinguishes analytic validity, biological relevance, functional improvement and durable clinical benefit. It explains why cellular composition and regulatory changes can move an age-associated score without repairing scarred tissue or lost circuits, and proposes an evidence hierarchy for interpreting age-reversal claims.

A measurement can improve without a person improving

DNA methylation and plasma-protein clocks can detect regularities associated with age, and some respond to interventions. But statistical predictors do not automatically measure the causal mechanism of disease. A lower clock age could reflect changes in cellular composition, inflammation, medication exposure or expression programs rather than restored structural integrity. Calling every downward movement in a clock 'rejuvenation' confuses a proxy with the outcome it was intended to help study.

Four standards of evidence

We should separate analytic validity, biological validity, functional validity and durable clinical benefit. Analytic validity means the clock reliably measures its chosen features. Biological validity asks whether those features reflect processes relevant to aging. Functional validity demands improvements in strength, cognition, mobility, organ reserve or other concrete capacities. Durable benefit asks whether such gains persist and alter meaningful disease outcomes. An epigenetic reset may pass one standard while failing another. This is especially consequential for reprogramming techniques that aim to change regulatory patterns without turning differentiated cells into pluripotent cells.

Where the mismatch comes from

Cell mixtures in blood can shift after infection or therapy. Tissue-specific clocks may behave differently from blood-derived clocks. A drug could change methylation marks without resolving extracellular fibrosis or somatic mutations. An older patient with an excellent inflammatory profile may nevertheless carry advanced joint degeneration. Conversely, a patient with unfavorable clock results might have outstanding resilience and physical function. None of these possibilities invalidates molecular clocks. They establish that a measurement needs an explicitly defined scope.

A falsifiable editorial standard

Every intervention claiming age reversal should identify the clock, the direction and magnitude of its change, whether the result replicates, and what functional outcome moved with it. Negative evidence would be a large, reproducible clock improvement accompanied by no change in functional recovery or morbidity. The Institute's proposed phrase *functional rejuvenation* should be reserved for the latter class of evidence, not awarded solely because a biomarker becomes numerically younger.

A clinical thought experiment

Consider a hypothetical intervention that lowers an epigenetic age estimate by three years but leaves exercise capacity, wound healing and clinical events unchanged. The honest conclusion is a favorable biomarker change, not a proven extension of healthy life. In contrast, a rehabilitation intervention might improve walking distance and independence without moving a clock at all. It would still have meaningful clinical value.

What would discriminate among explanations

The falsification target is precise: test whether a change in clock age mediates later functional improvement rather than merely accompanying it. If a clock is reproducibly changed by benign transient shifts in blood-cell composition, that component of its interpretation is weakened. If some clocks predict outcome while others disagree, the correct response is comparison and refinement, not choosing whichever score makes the intervention look best.

An accurate predictor can still mislead

Epigenetic and proteomic clocks are frequently evaluated on their statistical agreement with chronological age or future outcomes. These are legitimate research goals, but they are not equivalent to demonstrating that a measured quantity is a manipulable cause of aging. Blood pressure illustrates why prediction and mechanism must be separated: a risk marker can be clinically useful because it predicts outcomes and is itself amenable to causal intervention. An age clock may predict mortality without the clock's constituent features being appropriate therapeutic targets. Changing a surrogate can fail to change the underlying outcome.

Imagine a treatment that alters the proportions of circulating immune-cell subsets. Whole-blood methylation patterns could change, shifting a clock estimate, even if no individual tissue has recovered lost structure. A different intervention might change the transcriptional state of a particular cell type without changing the number or integrity of surviving cells. These scenarios are not demonstrations that all aging clocks are flawed; they show that a composite readout can change for reasons unrelated to the intended interpretation.

The clinical outcome hierarchy

The first level is analytic validity: does the measurement itself reproduce reliably across laboratories, batches and changes in sample handling? The second is predictive validity: does it forecast subsequent outcomes independently of chronological age and established risk factors? The third is biological interpretability: do changes in the score map consistently to relevant tissue states? The fourth is intervention validity: when treatment shifts the score, do patients gain sustained functional benefit or improved hard outcomes? A clock can perform well at the first two and remain uncertain at the last two.

Any anti-aging trial should specify which level its endpoint addresses. If the endpoint is a methylation change, the accurate conclusion is a methylation change. If physical performance, hospitalization or disability improves alongside it, there is stronger evidence of clinical benefit, though causation between clock movement and clinical change may still be unproven. Claiming 'years reversed' from a score alone is a category error unless those years correspond to independently validated biological consequences.

Two competing interpretations of a younger score

The optimistic interpretation is that an intervention has restored a regulatory pattern resembling a younger state, which may eventually improve cellular function. The skeptical interpretation is that it has altered the measured features without correcting the processes that produced the patient's vulnerability. These interpretations need not be mutually exclusive. An intervention could repair part of an age-related mechanism while leaving vascular

scars, clonal mutations, skeletal damage or neuronal loss untouched. The result could be real but partial rejuvenation.

The strongest evaluation would include independently measured functional outcomes, adverse effects, tissue-specific biomarkers and sufficiently long follow-up. A treatment that transiently improves a clock while increasing later malignancy risk could not responsibly be called successful rejuvenation. Conversely, a therapy that reduces falls and improves strength should not be dismissed because its methylation score barely moves.

A useful conceptual counterexample

Consider a patient with progressive hearing loss caused by irreversible destruction of cochlear hair cells. Even a profound shift in systemic blood-based age markers would not demonstrate restoration of hearing. The anatomical loss and the clock readout occupy different causal levels. Similarly, replacing a damaged hip may improve mobility and quality of life without requiring the patient to become molecularly younger. Clinical medicine frequently creates major functional gains by bypassing rather than reversing the biology of aging.

The most valuable future clocks may not pretend to be universal. A measure tied to a specific tissue or biological process, validated against that tissue's function, could give clinicians a narrower but much more useful signal. More modest claims could therefore lead to greater practical value.

A biological clock 'lies' only when its result is asked to answer a question it was not designed or validated to answer. Responsible research should state the clock's domain, its uncertainties, and the kind of benefit its movement actually establishes.

What would invalidate a commercial claim?

Imagine a company reports that its treatment reduced average epigenetic age by five years. Before interpreting the statement, a reader should know whether the assay was blinded, whether the result held in an independent laboratory, whether cell composition changed, and whether the trial included a comparison group. The result might remain scientifically interesting even if those questions are unanswered, but the uncertainty would prohibit a claim of demonstrated clinical rejuvenation. The problem is not marketing enthusiasm in isolation; it is a failure to specify the level of inference.

A stronger design could use an intervention with a well-established functional benefit, then examine whether multiple independent clocks track that benefit. Concordance would support the marker's usefulness but would not automatically establish causality. Discordance could be informative: different clocks may measure different mixtures of aging-associated processes, and some could respond to exposure rather than restoration. The proper conclusion is that these tools require calibration against real outcomes, not that all molecular aging measurements should be discarded.

Selected scientific readings

- López-Otín C et al. (2023). Hallmarks of aging: An expanding universe. *Cell*. <https://doi.org/10.1016/j.cell.2022.11.001>
- Lu Y et al. (2020). Reprogramming to recover youthful epigenetic information and restore vision. *Nature*. <https://www.nature.com/articles/s41586-020-2975-4>
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