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Forum

Aging vs. biological age: Conceptual considerations for age reversal claims

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Whether reversal of biological age and/or aging is possible is among the most actively debated topics in the field of aging. Here, we consider the meaning of biological age reversal and its burden of proof, focusing on foundational issues and the language we use to debate these questions.

Aging vs. biological age

A critical starting point for this discussion, in which molecular and functional approaches can lead to divergent conclusions, is to highlight the difference between "aging" and "biological age" (Box 1). These terms, often conflated, are related yet distinct, and the distinction is important. From a biological perspective, a useful working definition of aging is the time-dependent process of accumulation of negative consequences of life—damage—that results in functional capacity decline, chronic diseases, and ultimately mortality of an organism.[1] In contrast, biological age is a dynamic state defined by the cumulative burden of aging-associated changes that have occurred within a system.

A fundamental consideration when discussing biological age is that it is best understood as a latent variable, a quantity that cannot be directly measured and is observable only through its manifestations. Although aging itself may similarly be considered latent, the challenge is particularly acute for biological age because, unlike chronological age, it lacks a reference standard against which estimates can be compared. The absence of an accepted ground truth means that biological age can only be inferred through modeling approaches that attempt to capture the complex, multidimensional nature of age-related biological changes. Different approaches and models often emphasize distinct aspects of the aging process, leading to potentially divergent estimates of biological age for the same individual. Across individuals, examples of both higher-than-expected biological age estimates early in the chronological age trajectory (childhood disease, progeria) and lower-than-expected biological age estimates at the end of the trajectory (healthy longevity, centenarians, "super agers") exist (Figure 1). Consequently, the field must grapple with the reality that, experimentally, biological age is a construct of our measurement tools rather than an absolute biological property. Under this view, divergence between measures is expected, including divergence across cell types, tissues, and organ systems within the same individual: different approaches represent different projections of a currently undefined and unmeasurable multidimensional phenomenon. Therefore, the methods we use to estimate biological age are critical determinants of the conclusions we draw in aging studies.

Reversing course

With the distinction between aging and biological age in mind, we can consider whether either can be reversed. Reversal is "a change to an opposite direction, position, or course of action" (*New Oxford American Dictionary*). Therefore, we need to ask whether aging and/or biological age can truly be changed in an opposite direction. This is not a purely theoretical discussion, as the aging field has examples of interventions capable of extending lifespan in animals and delaying or preventing aging-associated diseases in humans. There are also many examples of interventions that reverse multiple aspects of aging, for example, rapamycin treatment in laboratory mice and regular exercise in sedentary adult humans. At the same time, new therapeutic classes, such as cellular or chemical reprogramming, as well as replacement and regenerative approaches, may go further by targeting the aging process even more broadly. As these therapies advance to clinical testing, metrics capable of demonstrating reversal of biological age, not merely slowed aging, become urgently needed.

Aging is a complex, lifelong process with genetic, environmental, and stochastic components. Like time, it is unidirectional, and its complete reversal is not achievable due to constraints grounded in physics.[2,3] Although the molecular damage underlying aging accrues

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Box 1. Essential glossary

Aging[†]**.** A progressive process of accumulation of deleterious consequences of life, including molecular and cellular damage, that leads to functional capacity decline, chronic disease, and ultimately mortality. Aging is unidirectional and its complete reversal is not achievable due to thermodynamic constraints, though its rate and route may be modulated by genetic, environmental, and pharmacological factors.

Biological age[†]**.** Conceptually, an individual's biological state defined by the level of aging-associated biological changes, such as accumulation of molecular and cellular damage. In practice, this is often expressed as a number in units of time corresponding to the chronological age at which the average person in a reference population shares the individual's level of aging-associated biological changes. Biological age is best understood as a latent variable: a quantity inferred from measurable indicators rather than directly observed, and a construct of our measurement tools rather than an absolute biological property. Divergence between estimates, including across tissues and organ systems within the same individual, is therefore expected.

Latent variable. A quantity that cannot be directly observed but is inferred from measurable indicators. Biological age is latent because the underlying aging state has no ground truth against which estimates can be validated; different biomarker models represent different projections of this state, and their divergence may reflect this fundamental inaccessibility rather than measurement error per se.

Biological age reversal. A reduction in estimated biological age below a prior baseline, measured using the same parameters, and durable beyond the intervention period. This is distinct from slowing the aging rate, which implies a reduced pace of biological change without necessarily crossing a prior baseline.

Biomarker of aging[†]**.** A quantitative, measurable parameter that, either alone or in a composite, predicts biological age and ideally its changes in response to interventions. Current biomarker models differ in their training objectives and inferential scope: some predict chronological age, others time-to-event outcomes such as disease or death, and others the rate of change. Most are optimized for correlational inference and may not be valid for interventional inference, particularly for states that lie outside their training distribution.

[†]Adapted from consensus definitions proposed by the Biomarkers of Aging Consortium.[1]

irreversibly over the life course, biological age is a dynamic parameter that may be modulated by genetic manipulations, environmental exposures, and pharmaceutical or lifestyle interventions. Biological age reversal is therefore a more realistic prospect. We define it operationally as a reduction in estimated age below a prior baseline, measured using the same parameters, and durable beyond the intervention period. This is distinct from slowing the aging rate, which implies a reduced pace of biological change without necessarily crossing a prior baseline. Importantly, biological age reversal does not require a system to return to the exact prior state; rather, successful reversal may produce a new state that scores younger by available metrics while differing in composition from the system's earlier configuration.

The remaining piece of this puzzle thus becomes: what is the best way to assess biological age? Here, thinking within the field diverges. Age-related changes manifest across all levels of biological organization: molecular damage, phenotypic alterations, and functional capacity decline. While these levels are causally related (molecular changes generally precede phenotypic manifestations, which in turn precede functional decline), they may change somewhat independently. Here, we focus on the two approaches most actively utilized: molecular biomarkers and functional assessments. We also recognize that intermediate phenotypic manifestations, increasingly accessible through approaches such as high-dimensional facial imaging,[4] occupy an important middle ground.

The case for molecular biomarkers of aging

Integrative omic biomarkers of aging have rapidly become a mainstay tool of many aging biologists. Most current molecular biomarkers of aging are built using machine learning approaches, which construct models based on associations of omic features with parameters like chronological age or time-to-event outcomes such as disease or death. Other approaches model longitudinal changes in aging-related features to estimate the pace of biological change over time. These biomarkers may fluctuate, as they compare an individual's molecular profile to a reference population, agnostic (in most cases) to chronological age. This comparative approach forms the basis of biological age estimation using molecular biomarkers of aging. Such biomarkers of aging are increasingly being utilized in clinical trials testing geroprotectors in humans. Although the responsivity of current molecular biomarkers of aging to geroprotective interventions remains to be systematically validated in humans,[5] some recent reports have demonstrated that analogous biomarkers of aging respond to validated lifespan-modulating interventions in mice.[6,7] Proponents thus express confidence in the potential of these tools to serve as surrogate endpoints for future human longevity trials.

A thoroughly validated molecular biomarker provides a straightforward means of demonstrating biological age reversal: a reduced follow-up value compared to the baseline. The beauty of this approach, proponents argue, lies in its high-dimensional, data-driven assessment of molecular profiles. An additional advantage is that multiple data modalities may capture complementary aspects of biological age. Most importantly, molecular biomarkers may be informative early in the aging trajectory, before compensatory mechanisms fail and phenotypic or functional manifestations appear.

Opponents argue that machine learning approaches select features that are associated with aging but not necessarily causal to it. This is true: biomarker models may capture features directly causal to

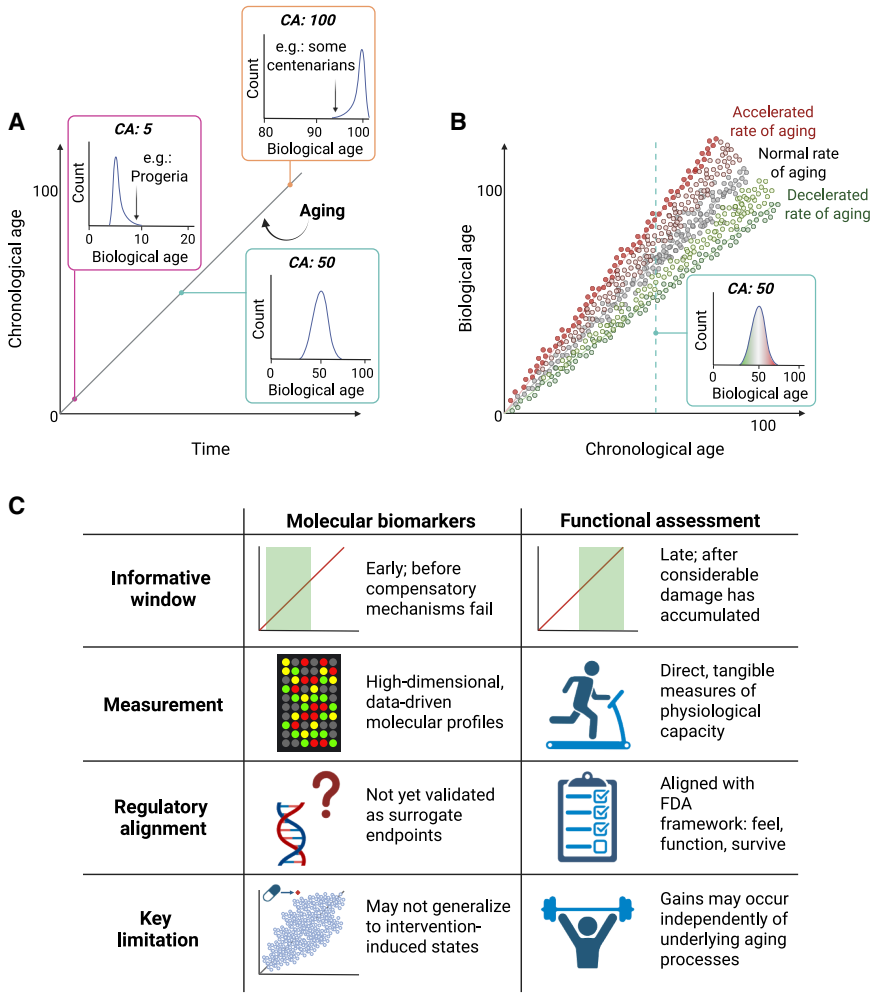

Figure 1. The relationship between chronological age, biological age, and aging

(A) Aging is a process that occurs over the lifespan; biological age is a state that reflects the cumulative burden of aging-associated changes at a given chronological age. Although generally correlated, there is a distribution of biological ages within a population at any given chronological age.

(B) The rate and type of aging determine an individual's position within that distribution. Points represent single individuals within the population distribution, reflecting the stochastic and heterogeneous nature of the aging process. Traced lines represent schematic average trajectories for accelerated, normal, and decelerated aging and are intended as conceptual illustrations. Accelerated and decelerated aging are not discretely separated from the normal distribution but represent the tails of a continuous spectrum.

(C) Comparison of molecular biomarkers and functional assessments across four dimensions relevant to the demonstration of biological age reversal. Informative window refers to the stage of the aging trajectory at which each approach is most sensitive. Regulatory alignment reflects current FDA frameworks for the evaluation of clinical benefit. Key limitation highlights the primary methodological concern for each approach in the context of interventional inference. CA, chronological age.

The figure was created using BioRender.

aging, adaptive responses, or neutral correlates. Some thus argue that biomarkers insufficiently represent aging because they do not reflect direct phenotypic manifestations. From this viewpoint, one might argue that a severe acute illness that transiently perturbs epigenetic clocks does not increase biological age because patients do not develop phenotypes considered attributable to aging, such as hearing loss or hair graying. Whether aging has such exclusive phenotypic signatures—manifestations that can only arise from aging and not from other processes—remains an open question. Additionally, some interventions with well-established health benefits, such as exercise,[8] have not consistently shown the expected changes in biological age estimates using current molecular models. Results can also vary across biomarker models within the same trial: in CALERIE, DunedinPACE responded to caloric restriction whereas GrimAge and PhenoAge did not,[9] raising questions about the sensitivity and specificity of individual biomarkers. Furthermore, models trained on natural aging trajectories may not generalize to intervention-induced states that lie outside their training distribution.

The case for functional assessments of aging

Aging undeniably manifests as a progressive loss of functional capacity over the life course, culminating in morbidity and mortality. Loss of function is the most visible, tangible, and pervasive aspect of

getting older for most individuals. Some researchers thus argue that function is the quintessential metric for assessing biological age. Proponents contend that features linked to functional decline reflect more direct manifestations of aging than the manifold molecular changes that may be captured by omic biomarkers. In this conception, an individual with a molecular profile resembling that of an older person is not biologically older unless they also develop aging-associated functional deficits: for instance, reduced grip strength, hearing loss, or loss of mobility.

From a regulatory perspective, functional assessments align naturally with how therapeutic benefit is evaluated. For the FDA, clinical benefit is defined as a positive effect on how a patient feels (symptom relief), functions (improved daily activity or functional capacity), or survives (increased lifespan). These outcomes are measured through clinical outcome assessments such as patient-reported outcomes, clinician-reported events, or performance tests. Demonstrating a survival benefit in the absence of life-limiting disease is impractical as an endpoint for trials of biological age reversal; likewise, symptom relief in the absence of disease is challenging to assess. Given these constraints, many researchers and regulators argue that function is the most tractable metric for demonstrating clinical benefit in trials of geroprotectors.

From the standpoint of aging-associated loss of functional capacity, the burden of proof for biological age reversal is higher. Functional deficits vary across organ systems, with distinct physiological manifestations; for instance, assessing muscle function and cognitive function requires entirely different tests. Nevertheless, innovative approaches have been proposed. For instance, XPRIZE Healthspan will judge biological age reduction through functional assessments across muscle, cognition, and immune systems. The attraction lies in tangible results meaningful to aging individuals and potentially straightforward integration into medicine, where clinical benefit is described relative to deficits and organized around organ systems.

Opponents point out limitations: because physiological systems age differently and at different rates, assessment of individual organs or systems may not represent a feasible approach to deploying geroprotective interventions at scale. Moreover, functional decline represents a late-stage manifestation occurring after considerable molecular and phenotypic damage has accumulated and compensatory mechanisms have been exhausted; a function-centric view may therefore support only reactive interventions commencing after decline has begun. If geroprotective interventions are most effective when applied before functional decline appears, a function-centric approach may miss the optimal intervention window. Moreover, because many functions may improve with training independent of any change in underlying aging processes, functional gains may lack specificity as indicators of biological age reversal. Greater understanding of the stepwise emergence of aging from molecular to phenotypic to functional levels will likely inform the optimal timing of geroprotective intervention strategies.

Concluding remarks and future perspectives

Both the molecular and functional approaches to the assessment of biological age and its reversal have merit, but ask different questions: How old is the system biologically? versus How well does the system still work? Critically, early trials of geroprotectors will need to rely on both to demonstrate biological age reversal with complementary lines of evidence. Ideally, successful biological age reversal would be characterized by the reversal of both molecular features of aging and functional deficits across multiple organ systems. For now, FDA approval of geroprotectors will hinge on demonstrating how individuals "feel, function, and survive"; thus, functional measures will be essential. Simultaneously, molecular biomarkers assessed as secondary outcomes will be critical for their validation as surrogate endpoints to further accelerate the discovery of novel geroprotectors. It is encouraging to see such data starting to emerge from large clinical trials.[9]

Critical issues remain. For instance, the extent to which reversal at one level (molecular, phenotypic, or functional) propagates to other levels is unknown; demonstrating that reversal of molecular aging biomarkers yields functional improvement, or vice versa, would considerably strengthen reversal claims. The evidentiary threshold for convincingly demonstrating reversal at any level, whether a single biomarker suffices or concordance across multiple modalities is required, also remains to be defined. Robust demonstration of reversal would ideally show effects across biological scales and in multiple organ systems, with durability extending beyond the intervention period. Such criteria would help distinguish true reversal from statistical artifacts, including regression to the mean and batch effects, as well as transient responses, cell composition changes, tissue-specific effects, or normal measurement fluctuation. These challenges underscore a deeper problem: our incomplete understanding of biological age itself impedes our ability to therapeutically target reversal in the most efficacious way.[10] Nevertheless, engaging across divergent viewpoints to address foundational issues, including the plausibility of biological age reversal, is key to advancing the field.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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