

The Functional Rejuvenation Standard

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Abstract (original summary). Molecular target engagement, cellular activity, structural improvement and clinical benefit are different levels of evidence. This paper proposes a functional rejuvenation standard that requires claims to identify which level has actually changed. It prioritizes independent measures of organ performance, durability, patient experience and treatment harms.

A younger marker is not a restored life

The language of rejuvenation is often applied to changes in DNA methylation, plasma proteins, inflammatory markers or cellular appearance. These are important research signals, but patients live through strength, mobility, cognition, organ reserve, independence and freedom from illness. We propose a *functional rejuvenation standard* that requires researchers to specify which form of aging has changed and whether benefits extend beyond the chosen marker.

A layered evaluation

A credible result should separate target engagement, cellular performance, tissue architecture, organ function, clinical outcomes and durability. A treatment may improve one layer without reaching the next. An eye therapy that improves visual function can be valuable without proving whole-body age reversal. A senolytic that decreases inflammatory markers may not reduce falls or cardiovascular events. A new nerve fiber is not necessarily a functioning circuit. These distinctions protect both scientific inference and patient expectations.

The challenge of measuring real improvement

Functional outcomes can be affected by training, placebo effects, concurrent treatments and regression toward the mean. Improved performance may not prove a particular biological mechanism. Durable assessment therefore requires appropriate comparison groups and long follow-up, and often condition-specific outcomes. For older adults, avoiding a hospitalization or retaining independence may matter more than moving an abstract age score by several years.

What it would change

The standard should make clinical and website claims more precise: 'improved a methylation signature in cultured cells,' 'improved axon regrowth in mice,' and 'improved human mobility' are different statements. A technology can be promising at one stage without being dismissed for not yet meeting the last. What should end is the casual collapse of every stage into the word 'rejuvenated.'

A clinical thought experiment

Suppose an intervention decreases a predicted biological age by several years but produces no consistent improvement in everyday activity, clinical disease or recovery after illness. That can be reported as a biomarker response, but not as demonstrated functional rejuvenation. If another intervention improves independence and healing without changing the clock, it has achieved an outcome of genuine value.

What would discriminate among explanations

The standard should require pre-specified clinical outcomes and transparent follow-up. Different diseases justify different endpoints; there is no single functional test appropriate to all organs. Long-term safety can outweigh modest short-term gains. This evidence hierarchy lets early discoveries remain interesting without converting them into premature clinical advertising.

A younger score is not the finish line

Longevity research increasingly measures molecular states that correlate with age. Such measurements can accelerate mechanistic discovery, but they are not substitutes for the outcomes people experience: moving without assistance, maintaining cognition, avoiding serious illness, recovering from injury and living longer with acceptable function. The Functional Rejuvenation Standard is proposed as a conceptual insistence that claims of rejuvenation be linked to sustained, patient-relevant performance and a tolerable safety profile.

This standard must remain distinct from a regulatory framework or validated composite instrument. Different interventions will require different endpoints. A retinal therapy should be judged by meaningful visual function; a muscle intervention by strength, mobility and falls; an immune intervention by appropriately defined infection or immune outcomes. There is no single test that captures all forms of successful biological recovery.

Four levels of evidence

Molecular engagement demonstrates that an intervention changed its intended target. Cellular improvement shows a more meaningful response in the affected population. Tissue and organ measures assess structure and physiology. Patient-centered endpoints determine whether the change translates into durable health benefit. Evidence can be valid at any level, but conclusions must stop where the measurements stop. A change in a methylation clock is evidence of a clock change, not proof that five years of disability risk have disappeared.

A particularly difficult question is whether a treatment can improve performance without reversing aging. The answer is clearly yes: rehabilitation, surgery, sensory aids and effective disease treatment can restore important capabilities without returning tissue to an earlier developmental state. Such interventions may be clinically more valuable than dramatic molecular age estimates. A rejuvenation claim should therefore not be privileged over an ordinary functional improvement if the latter produces better outcomes.

Time and risk belong inside the definition

A treatment could improve a physical-performance measure for six weeks yet cause later organ injury. Another could temporarily increase strength by altering autonomic stimulation without rebuilding tissue. Long-term observation and appropriate comparators are essential. Outcomes should include harms, function under usual living conditions and whether benefits persist after treatment withdrawal.

A claimed improvement must also exceed measurement variability and relevant learning effects. Cognitive tasks improve with familiarity; strength tests vary with motivation and technique; wearables can change output when adherence changes. Trials need prespecified endpoints and adequate controls. Multiple exploratory positive results do not replace a clear primary outcome.

Individualization without abandoning comparability

Patients value different capabilities. For one person, maintaining independence after stroke may be central; for another, reducing frailty-related falls or improving visual navigation matters most. Research can combine

standardized measures with patient-reported outcomes while resisting the temptation to declare success based only on subjective enthusiasm. Any personalized outcome must be defined before the intervention to reduce post hoc selection.

The strongest proposal is conservative in the scientific sense: no molecular marker alone earns the term 'functional rejuvenation.' The term should mean an important, sustained and safe restoration of capacity that would otherwise be expected to decline or remain impaired. This higher bar may slow marketing claims, but it gives the field a more meaningful objective.

Surrogate outcomes need intervention-level validation

A biomarker can predict future illness across untreated populations yet fail to predict the effect of a specific therapy. This is the general problem of surrogate endpoints. If an intervention changes a marker through a pathway unrelated to the processes causing clinical decline, the marker may move while the outcome does not. Therefore, correlations between epigenetic age and disease risk do not automatically validate clock reversal as a trial endpoint for every treatment.

An effective evaluation program would compare intervention-induced biomarker changes against independently measured patient outcomes across different therapies. If a marker consistently tracks clinical benefit in the relevant context, confidence increases. If treatments frequently produce marker improvements without functional gains, its therapeutic interpretation must be narrowed. This is not a reason to abandon mechanistic biomarkers; it is a reason to state precisely what they can verify.

The standard ultimately serves patients by making the meaning of success clearer: improved capacity, reduced disease burden and tolerable long-term risk take precedence over a particularly attractive laboratory number.

Function may change through compensation rather than repair

Suppose a patient walks faster after treatment because pain diminishes or assistive technology improves. The functional gain is genuine, but it may not reflect regeneration of damaged tissue. The Functional Rejuvenation Standard should therefore contain two labels: demonstrated functional benefit and demonstrated biological reconstruction. An intervention can earn the first without claiming the second. This separation avoids devaluing conventional treatment and prevents premature mechanistic conclusions.

For research comparisons, predefined outcome measures and sustained follow-up are essential. A brief performance improvement after coaching or repeat testing is different from a durable return to ordinary life. Medical claims should state what changed, how long it lasted, and whether the mechanism was independently established.

The functional standard should also guard against selective reporting. A trial could show improved walking speed while participants report no greater independence, or it could improve a laboratory measure while raising the rate of adverse events. These divergent findings deserve to be reported together. A composite success label should never conceal an important deterioration in one domain. The ultimate objective is not to establish that all interventions satisfy a single universal metric, but to insist that any claim of rejuvenation specify its functional gain, duration, mechanism and harms.

Selected scientific readings

• Oh HSH et al. (2025). Plasma proteomics links brain and immune system aging with healthspan and longevity. *Nature Medicine*. <https://www.nature.com/articles/s41591-025-03798-1>

• Lu Y et al. (2020). Reprogramming to recover youthful epigenetic information and restore vision. Nature. <https://www.nature.com/articles/s41586-020-2975-4>

• Pyrkov TV et al. (2021). Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit. Nature Communications. <https://www.nature.com/articles/s41467-021-23014-1>

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