

One Body, Eleven Biological Ages

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Abstract (original summary). Plasma proteomic methods can estimate relative aging patterns across organs, but an organ-age score is not direct proof of tissue aging. This paper proposes that discordance among organ reserves may matter more than a global average. It examines cross-organ constraints, confounding by protein clearance, and the need to validate predictions against directly measured function.

The problem with the average organism

A body ages as connected organs, not as a perfectly synchronized clock. Large-scale plasma proteomics has been used to estimate relative ages of eleven organ systems and associate those scores with later disease risk. Such models do not directly biopsy each organ or establish that an organ has aged a particular number of years. They show, however, that measured patterns can diverge across systems. That makes a single global biological-age headline potentially misleading, especially when a patient's chief vulnerability resides in an organ whose trajectory differs from the average.

Organ discordance as a systems problem

Suppose cardiovascular function is relatively preserved while renal reserve is limited. A treatment tolerated by the heart may nevertheless destabilize fluid balance and indirectly impair cognition. Similarly, a comparatively healthy musculoskeletal system does not prevent frailty caused by neurological decline. We propose *organ discordance* as the mismatch among functional reserves, not simply as different proteomic scores. Its relevance lies in cross-organ consequences: a failing kidney changes circulating solutes; altered gut absorption affects nutrition; immune dysfunction changes the environment in which wounds heal.

Why proteomic age is not destiny

Plasma proteins can be influenced by medications, inflammation, renal clearance, acute disease and technical differences in measurement. Proteins assigned to one organ may be produced elsewhere or change for reasons unrelated to intrinsic organ aging. Statistical association cannot establish causation. An individual with a high predicted brain-age score is not thereby diagnosed with accelerated neurodegeneration. This is a promising risk-research framework, not a validated comprehensive clinical assessment for general public use.

The innovative question

Could clinicians eventually use organ-specific functional trajectories to choose the bottleneck most likely to undermine recovery? That demands comparisons between proteomic age, imaging, direct physiological testing and patient-centered outcomes. If the proteomic measure fails to add useful information, the concept should be revised. If organ discordance predicts cascading illness beyond conventional measures, it could make longevity medicine less obsessed with lowering a universal age score and more concerned with preserving the weakest critical connection in the system.

A clinical thought experiment

Imagine a patient whose blood proteins suggest accelerated kidney aging but average brain aging, while formal kidney-function testing remains stable. One interpretation is subtle biological change that predicts future risk; another is altered protein clearance or a confounded statistical signal. A responsible article must keep both possibilities open. The patient should not be told that the kidneys have literally aged an extra decade.

What would discriminate among explanations

The real value of organ-specific estimation depends on calibration in different populations, repeatability within an individual and superiority to directly measured organ function. When the signal conflicts with clinical evidence, it should motivate scrutiny rather than overturn an established diagnosis. The Institute's emphasis is on causal relationships among organs, not turning every statistical estimate into a disease label.

The fiction of a single biological age

A liver, a kidney, a vascular network and a skeletal muscle compartment do not experience identical cumulative demands. They differ in turnover rates, cellular architecture, exposure to circulating substances, regenerative capacity and susceptibility to specific injuries. A person with durable muscle function but chronic kidney disease therefore need not have one internally consistent 'biological age.' Organ-specific aging scores attempt to capture such discordance, but these scores are mathematical estimates constructed from selected measurements, not timestamps carried by organs themselves.

The most important feature of discordance is causal direction. A kidney disorder may alter blood pressure, acid–base regulation, erythropoietin production and mineral metabolism, each affecting cardiovascular or skeletal outcomes. A failing heart can reduce renal perfusion. Metabolic liver disease can influence systemic inflammatory and lipid signaling. The observation that an organ-associated proteomic signature looks unusually old does not by itself tell us whether that organ initiated dysfunction in another tissue or merely reflects a shared upstream condition. The difference determines what we can reasonably infer from the score.

Why circulating proteins are difficult witnesses

Blood proteins seem to offer an accessible window into internal organs. Some are enriched in particular tissues, but circulating abundance is influenced by several processes: production, release, distribution, binding, processing and clearance. If a kidney clears a protein more slowly, its plasma concentration may rise without increased expression by the tissue conventionally considered its source. Inflammation can change the proteins released by many organs at once. Plasma volume and sample-handling effects complicate interpretation further. An algorithm may accurately predict chronological age while remaining uncertain about the biological origin of its input signal.

This does not make organ-aging research meaningless. It makes its proper evidentiary question more demanding. An organ-associated signature becomes clinically informative when it forecasts future decline in a corresponding organ, adds information beyond conventional clinical measures, and responds to an intervention in tandem with meaningful functional improvement. Without those steps, 'a 70-year-old liver in a 50-year-old body' remains a striking metaphor rather than a diagnosis.

Organ communication as a possible amplifier

Suppose longstanding renal impairment increases circulating concentrations of selected metabolites and alters hormonal control of calcium and phosphate. Downstream changes in vessels and bone could plausibly follow. The kidney's earlier dysfunction may then accelerate apparent aging elsewhere, but the phrase 'aging spreads'

risks implying a mysterious transmissible state. The mechanistic explanation must instead identify the mediators, their concentrations, responsive tissues and competing causes. Similar caution applies to inflammatory cytokines, extracellular vesicles and endocrine factors proposed to connect different organs.

A useful experiment would compare patients with and without a well-defined organ disorder, matched on major confounders, then follow functional trajectories in other organs. If a candidate circulating mediator rises before downstream impairment, shows a dose-response relationship and changes with targeted treatment, causal plausibility increases. Yet even this can remain confounded; definitive causal claims may require interventions or convincing genetic evidence. A proteomic association is the beginning of investigation, not the end.

A practical clinical interpretation

A person might have preserved aerobic fitness while showing evidence of accelerated vascular stiffness. Another might retain favorable metabolic measurements yet suffer pronounced musculoskeletal frailty. These combinations argue for integrating organ-specific functional tests rather than compressing health into one commercial number. Depending on the clinical context, kidney filtration, albuminuria, measured strength, cardiovascular capacity or cognitive testing may already provide information with more established clinical utility than a proprietary age score.

The Institute's hypothesis would predict that patients with a large, reproducible discordance between particular organ measures have distinctive recovery trajectories or patterns of future disease, above and beyond existing diagnoses. If they do not, the organ-age framework is principally descriptive. Even if a score forecasts risk, it remains necessary to distinguish prediction from a biological mechanism and a reason to treat.

The body ages unevenly because it is not one homogeneous tissue. What remains uncertain is whether current algorithms adequately capture that unevenness and, more importantly, whether their output changes how people should be treated.

A discordance must be reproducible before it is actionable

A patient who is told that their heart is biologically 'older' than their liver needs to know how much variation the test produces upon repeat sampling. Protein concentrations can vary with acute infection, hydration and medication; age models can also differ in their training populations. A large apparent organ-age difference could shrink or reverse when measured by another method. This does not prove the original result was false, but it prevents premature conversion of the estimate into a diagnosis.

A practical evaluation should compare the prediction with established organ-specific measurements and future events. If a cardiac age estimate predicts impaired exercise tolerance beyond known cardiac structure, blood pressure and risk factors, it may be useful. If it merely restates a patient's existing diagnosis, it is descriptive rather than transformative. An organ-age score should clarify what decision it improves and what false-positive burden comes with it.

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>

• López-Otín C et al. (2023). Hallmarks of aging: An expanding universe. *Cell*. <https://doi.org/10.1016/j.cell.2022.11.001>

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Editorial status: substantially revised conceptual article. Evidence-informed, not peer-reviewed, not a systematic review or clinical treatment guidance.