Researchers find a way to predict which of our organs will fail first

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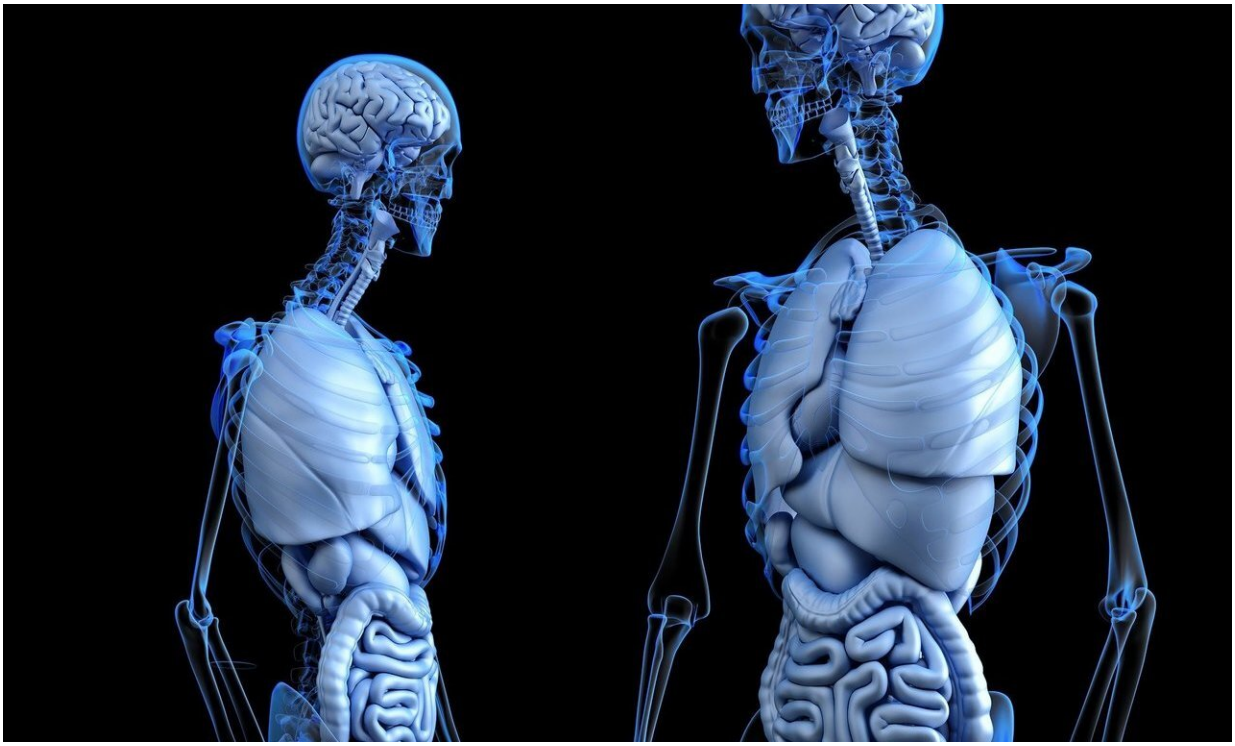

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Like any typical car or house or society, the pace at which parts of our bodies fall apart varies from part to part. A study of 5,678 people, led by Stanford Medicine investigators, has shown that our organs age at different rates—and when an organ's age is especially advanced in comparison with its counterpart in other people of the same age, the

person carrying it is at heightened risk both for diseases associated with that organ and for dying.

According to the study, about one in every five reasonably healthy adults 50 or older is walking around with at least one organ aging at a strongly accelerated rate.

The silver lining: It may be possible that a simple blood test can tell which, if any, organs in a person's body are aging rapidly, guiding therapeutic interventions well before clinical symptoms manifest.

"We can estimate the biological age of an organ in an apparently healthy person," said the study's senior author, Tony Wyss-Coray, Ph.D., a professor of neurology and the D. H. Chen Professor II. "That, in turn, predicts a person's risk for disease related to that organ."

Hamilton Oh and Jarod Rutledge, graduate students in Wyss-Coray's lab, are lead authors of the study, which was published online Dec. 6 in *Nature*.

Biological versus chronological age

"Numerous studies have come up with single numbers representing individuals' biological age—the age implied by a sophisticated array of biomarkers—as opposed to their chronical age, the actual numbers of years that have passed since their birth," said Wyss-Coray, who is also the director of the Phil and Penny Knight Initiative for Brain Resilience.

The new study went a step further, coming up with distinct numbers for each of 11 key organs, organ systems or tissues: heart, fat, lung, immune system, kidney, liver, muscle, pancreas, brain, vasculature and intestine.

"When we compared each of these organs' biological age for each

individual with its counterparts among a large group of people without obvious severe diseases, we found that 18.4% of those age 50 or older had at least one organ aging significantly more rapidly than the average," Wyss-Coray said. "And we found that these individuals are at heightened risk for disease in that particular organ in the next 15 years."

Only about one in 60 people in the study had two organs undergoing aging at that fast clip. But, Wyss-Coray said, "They had 6.5 times the mortality risk of somebody without any pronouncedly-aged organ."

Using commercially available technologies and an algorithm of their own design, the researchers assessed the levels of thousands of proteins in people's blood, determined that nearly 1,000 of those proteins originated within one or another single organ, and tied aberrant levels of those proteins to corresponding organs' accelerated aging and susceptibility to disease and mortality.

They started by checking the levels of nearly 5,000 proteins in the blood of just under 1,400 healthy people ages 20 to 90 but mostly in mid to late stages of life, and flagging all proteins whose genes were four times more highly activated in one organ compared with any other organ. They found nearly 900 such organ-specific proteins, which they whittled down to 858 for purposes of reliability.

To do this, they trained a machine-learning algorithm to guess people's ages based on the levels of those nearly 5,000 proteins. The algorithm tries to pick proteins that best correlate with a trait of interest (in this case, accelerated biological aging in a person or in a particular organ) by asking, one by one, "Does this protein enhance the correlation?"

The scientists verified the algorithm's accuracy by assessing the ages of another 4,000 or so people who were somewhat representative of the U.S. population.

Then they used the proteins they'd identified to zero in on each of the 11 organs they'd selected for analysis, measuring levels of organ-specific proteins within each individual's blood.

While there was some modest aging synchrony among separate organs within any person's body, that person's individual organs largely went their separate ways along the aging path.

Organ age gap

For each of the 11 organs, Wyss-Coray's team came up with an "age gap": the difference between an organ's actual age and its estimated age based on the algorithm's organ-specific-protein-driven calculations. The researchers found that the identified age gaps for 10 of the 11 organs studied (the only exception being intestine) were significantly associated with future risk of death from all causes over 15 years of follow-up.

Having an accelerated-aging organ (defined as having a 1-standard-deviation higher algorithm-scored biological age of the organ than the group average for that organ among people of the same chronological age) carried a 15% to 50% higher mortality risk over the next 15 years, depending on which organ was affected.

People with accelerated heart aging but initially exhibiting no active disease or clinically abnormal biomarkers were at 2.5 times as high a risk of heart failure as people with normally aging hearts, the study showed.

Those with "older" brains were 1.8 times as likely to show cognitive decline over five years as those with "young" brains. Accelerated brain or vasculature aging—either one —predicted risk for Alzheimer's disease progression as well as the best currently used clinical biomarkers do.

There were likewise strong associations between an extreme-aging (more than 2 standard deviations above the norm) kidney score and both hypertension and diabetes, as well as between an extreme-aging heart score and both atrial fibrillation and heart attack.

"If we can reproduce this finding in 50,000 or 100,000 individuals," Wyss-Coray said, "it will mean that by monitoring the health of individual organs in apparently healthy people, we might be able to find organs that are undergoing accelerated aging in people's bodies, and we might be able to treat people before they get sick."

Identifying the organ-specific proteins that best indicate excessive organ aging and, consequently, elevated disease risk could also lead to new drug targets, he said.

Wyss-Coray, Oh and Rutledge have co-founded a company, Teal Omics Inc., to explore the commercialization of their findings. Stanford University's Office of Technology Licensing has filed a patent application related to this work.

Researchers from Washington University; the University of California, San Francisco; the Albert Einstein College of Medicine; and Montefiore Medical Center contributed to the work.

More information: Tony Wyss-Coray, Organ aging signatures in the plasma proteome track health and disease, *Nature* (2023). DOI: 10.1038/s41586-023-06802-1.
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