PRESS RELEASE

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Clinical ageing clocks: NUS and SGH develop algorithm-powered tests to indicate mortality risk

Singapore, 31 July 2024 – A few tubes of blood, a urine test and a health questionnaire to determine a person's biological age are all that is needed to indicate one's future risk of mortality. A new class of clinical ageing clocks using these tests has emerged – PCAge and LinAge – which outline the healthy and unhealthy ageing trajectories and provide a new way to test ageing intervention strategies.

Clinical ageing clocks are tools or biomarkers that assess various physiological and molecular parameters to estimate a person's biological age, as opposed to his or her chronological age. This new class of clinical ageing clocks – developed by Associate Professor Jan Gruber from the Healthy Longevity Translational Research Programme at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine) and Dr Fong Sheng from the Department of Geriatric Medicine at Singapore General Hospital (SGH) – goes one step further in helping researchers to tailor longevity interventions, bypassing exorbitant longitudinal studies to test the efficacy of longevity drugs or supplements.

As an algorithm that leverages machine learning, PCAge takes advantage of an analytical matrix factorisation technique that can reduce complex high-dimensional data into lower dimensions. This approach generates a more informative representation of a patient's status, providing clues to identify the underlying cause(s) of co-morbidities and can inform the type of interventions that will be most efficacious.

The team used publicly available data from the National Health and Nutrition Examination Survey (NHANES), which is one of the largest health and nutrition study in the United States of America, comprising more than 3,000 participants aged between 40 to 89 years. The researchers constructed their ageing clock (PCAge) using this historical data and went on to test its performance in several separate cohorts of patients. They found that, based on data from a single survey timepoint, often decades before death, PCAge showed significant predictive efficacy over 20 years and across a wide range of ages, illustrating its power in characterising individual future ageing trajectories. Informative predictions could be made in this way well before the onset of any specific pathology.

Furthermore, PCAge outperformed a well-known clinical risk marker, the atherosclerosis cardiovascular disease score, which is a metric used by doctors to predict the 10-year risk of cardiovascular disease or stroke, in predicting survival. Finally, the team generated a streamlined clinical ageing clock, LinAge, based directly on PCAge, that maintains equivalent

predictive power but requires substantially fewer parameters. LinAge can be determined from routine clinical blood tests, a urine test, and health questionnaire.

These results support the insight that a person's chronological or calendar age is less useful in determining how long that person will survive and remain in good health than their actual biological age. It is known that different individuals age differently and the biological age in most people differs from their chronological age. However, a current predicament in the field of healthy longevity is the lack of reliable ways to measure a person's biological age. Said Assoc Prof Gruber, "There are dozens of ageing clocks currently being developed, yet they do not agree on meaningful insights into the status of one's health, including when a person is likely to develop disease or die, which is the crux of healthy ageing."

The streamlined clinical ageing clock, LinAge, has been applied to 40 Singaporeans, aged 65 to 95, in the geriatric clinic at SGH to date. Among these 40 Singaporeans, thus far, several of the patients who participated were found to have previously undiagnosed medical conditions detrimental to their healthy longevity. This enabled the participants to be started on the appropriate medication earlier and led to earlier referrals to the relevant sub-specialties for further clinical management as required.

Regarding future directions, Assoc Prof Gruber who is also from NUS Medicine's Department of Biochemistry said, "The team is looking at repurposing existing prescription drugs to extend lifespan and health span. Using LinAge, we now have a way to measure a person's biological age from their clinical biochemistry. We can now distinguish their ageing trajectories early and customise specific interventions that would improve longevity and lifestyle biomarkers, which differs from one individual to the next."

Dr Fong Sheng from SGH added, "Nevertheless, work is ongoing to validate LinAge in various populations, including in Singapore. Further improvements to LinAge are also currently underway. We hope that our approach to clinical ageing clocks will push the knowledge frontiers of healthy ageing and contribute solutions to add as many healthy years as possible to our rapidly ageing populations."

The paper is published in Nature Aging, titled 'Principal component-based clinical aging clocks identify signatures of healthy aging and targets for clinical intervention'.

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Since the School's founding in 1905, more than 12,000 graduates have passed through our doors. In our pursuit of health for all, our strategic research programmes focus on innovative, cuttingedge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives. The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2024 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2024).

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

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