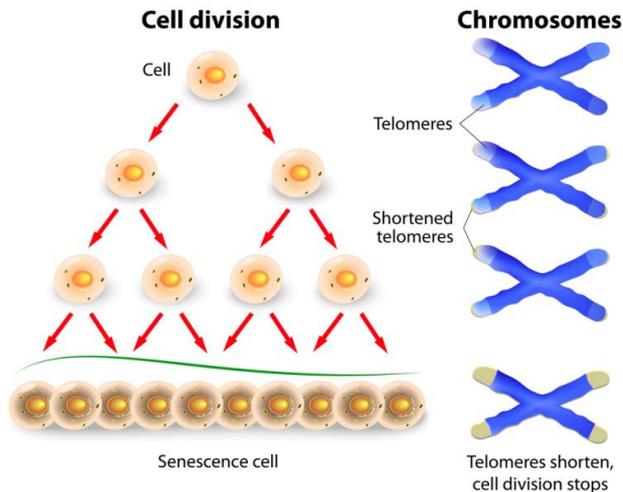# Age and mobility predict death better than one's 'molecular clock'

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Telomeres -- which are protective caps on the ends of our chromosomes -- are DNA sequences that generally shrink with age, acting as a "molecular clock" in human cells. Every time cells divide, telomeres shorten until they become critically short and signal the cell to stop dividing. For these reasons, there has been great interest in the ability of this biomarker to predict mortality. Credit: Woodrow Wilson School

Advances in technology allow scientists to measure intricate details about the human body that greatly enhance understanding of health, disease and aging.

Yet, when it comes to predicting death, more rudimentary measures—like a person's age or a person's ability to climb stairs or walk a short distance—are much more powerful predictors of survival than certain biomarkers, according to a study published in *PLOS ONE* by researchers at Princeton University; Georgetown University; University of Washington; Stanford University; the University of California, Berkeley; and the Universidad de Costa Rica.

Using data from the United States, Costa Rica and Taiwan, the researchers compared a broad set of predictors of death—like age, smoking habits and mobility—with the length of telomeres, DNA sequences that generally shrink with age.

Decades ago, researchers discovered that telomeres—which are protective caps on the ends of our chromosomes—act as a 'molecular clock' in human cells. Every time cells divide, telomeres shorten until they become critically short and signal the cell to stop dividing. Telomere length is typically measured in white blood cells (leukocytes), and shorter leukocyte telomeres have been associated with disease, aging and death. For these reasons, there has been great interest in the ability of this biomarker to predict mortality.

After evaluating data, the research team found that using telomere length to predict a human's death was only marginally better than a "coin toss." Chronological age was, by far, the single best predictor of death in all three countries.

"Scientific evidence on telomere length has been sensationalized and, in some cases, exaggerated by the media and by companies that have capitalized on the research to market products that may promise more than they can deliver," said lead author Dana A. Glei, a senior research investigator at Georgetown University's Center for Population and Health. "This is what fueled our research. We wanted to determine whether telomere length could predict mortality better than other well-established predictors of survival, most of which are less invasive and much less costly to measure."

"We were surprised that most indicators outperformed telomere length, including self-reported measures of health and mobility, an assessment of cognitive function, smoking, exercise, an inflammatory marker and a measure of kidney function," said Noreen Goldman, Hughes-Rogers Professor of Demography and Public

Affairs at Princeton's Woodrow Wilson School of Public and International Affairs and faculty associate at the Office of Population Research.

"We found that the so-called 'molecular clock' was nowhere near as powerful as the pendulum when it came to predicting five-year mortality—at least among older humans," said co-author Maxine Weinstein, distinguished professor at the Center for Population and Health, Georgetown University.

The researchers used data from the U.S. National Health and Nutrition Examination Survey, the Costa Rican Study on Longevity and Healthy Aging and the Taiwan Social Environment and Biomarkers of Aging Study. They analyzed deaths within five years after telomere length was measured in older individuals: age 60 and older for the United States; age 61 and above for Costa Rica; and age 53 and older for Taiwan.

Within each country, the researchers tested telomere length against a broad set of well-established predictors of death. These included basic demographics (age, sex), social factors (marital status, education, and social integration), health behaviors (smoking, exercise), self-reported measures of health (global self-assessed health, physical mobility, limitations with activities of daily living, history of diabetes and cancer, the number of hospital stays in the past year), a cognitive test administered by the survey interviewer and several biomarkers including blood pressure; cholesterol; glycosylated hemoglobin, which is used to monitor diabetes; body mass index; C-reactive protein, which is produced in the liver in response to inflammation; and serum creatinine, which indicates kidney function.

The statistical analysis demonstrated that, while telomere length was associated with survival in all three countries, it ranked lower than many of the other predictors in terms of its ability to distinguish between those who died and those who survived over the five years. Not surprisingly, age was the best prognostic measure in all countries; self-reported mobility was close behind.

Because telomere length is strongly correlated with both age and sex, the researchers next needed to investigate how telomere length fares in predicting mortality after these factors were taken into account. When the researchers controlled for age and sex, they found telomere length ranked near the bottom. It was 15th out of 20 in Costa Rica, and 17th in Taiwan and the U.S. The results show that 13 other indicators could more powerfully predict mortality than telomere length in all three countries.

"To prove its worth, the biomarker 'du jour' should tell us more than we already know based on simpler observables. If mortality prediction is the main goal, telomere length is probably not the best tool," Glei said.

The researchers note some potential limitations of the findings. People who are critically ill might exhibit changes in the distribution of different types of leukocytes that makes their telomeres appear longer. In this study, telomere length is measured in leukocytes, which is common across most research. But some types of leukocytes tend to have longer telomeres than others.

"Telomere length tends to be longer in the type of leukocyte that becomes more dominant when a person is ill. Therefore, a sick person might appear to have 'longer' telomere length, but that is deceptive. In fact, these critically ill individuals may be much more likely to die in the short-term despite the appearance of 'longer' telomeres," Glei said.

It also is plausible that telomere length is a better predictor of long-term mortality, compared to short-term survival, since it reflects the gradual process of cellular aging.

"Alternatively, telomere length might be a predictor of mortality only for certain groups of patients, such as those with cancer," said co-author Rosa Ana Risques, assistant professor of pathology at the University of Washington. "An interesting possibility is that telomere length might not be a good predictor of mortality, but it could be a good predictor of healthy aging. Increasing evidence demonstrates that shorter telomeres are associated with cardiovascular disease, but additional research is needed to clarify the association between telomere length and other diseases of aging such as cancer."

"Another possibility is that change in telomere length might be a more powerful predictor than our measurement, taken at a single time," said Weinstein.

The authors conclude that, while telomere length may eventually help scientists understand aging, it is not as powerful for predicting death over a five-year timespan as other basic, more easily obtained measures—at least among older humans.

"It is much easier and less expensive to ask someone's age than to collect blood, extract DNA and measure telomere length," said Glei.

While these basic measures may not necessarily identify the root causes of disease, the ability to accurately predict mortality can be very valuable to doctors who are advising their patients about the risks and benefits of a potential treatment. For prognostic purposes, doctors often rely on conventional predictors like age, sex and physical function. These findings provide no evidence to suggest that doctors should start testing telomere length in an effort to improve their survival prognoses.

"On the internet, they sell test-your-own-telomere length kits and supplements that are touted to help people maintain their telomeres. We caution buyers to beware," Glei said.

  More information: "Predicting Survival from Telomere Length Versus Conventional Predicators: A Multinational Population-based Cohort Study," dx.plos.org/10.1371/journal.pone.0152486

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