PhenoAge Calculation

PhenoAge is a validated biological age biomarker developed by Levine et al. using data from the third National Health and Nutrition Examination Survey (NHANES III), a nationally-representative sample of 9,926 US adults with >23 years of mortality follow-up.[2] A Cox penalized regression model—where the hazard of mortality was regressed on forty-two clinical markers and chronological age—was used to select variables for inclusion in phenotypic age score. Based on 10-fold cross-validation, nine biomarkers and chronological age were then combined in a phenotypic age estimate (in units of years) as detailed below:

$$PhenoAge = 141.50 + \ln(-0.00553 \times -1.51714 \times e^{xb})^{0.0076927^{0.09165}}$$

where

$$xb = -19.907 - 0.0336 \times albumin + 0.0095 \times creatinine + 0.1953 \times glucose + 0.0954 \times ln(CRP) - 0.0120 \times lymphocyte\ percentage + 0.0268 \times mean\ corpuscular\ volume + 0.3306 \times RDW + 0.00188 \times alkaline\ phosphatase + 0.0554 \times white\ blood\ cell\ count + 0.0804 \times age$$

PhenoAge has been validated using data from NHANES IV (n=6,209), demonstrating excellent correlation with chronological age (r=0.94) and robust associations with mortality outcomes. Specifically, each 1-year increase in PhenoAge was associated with a 9% increased risk of all-cause mortality (HR=1.09, $p=3.8 \times 10^{-49}$), a 9% increased risk of aging-related disease mortality (HR=1.09, $p=4.5 \times 10^{-34}$), and significant increases in cause-specific mortality risks, including a 7% increased risk of cancer mortality (HR=1.07, $p=7.9 \times 10^{-10}$). The biomarker has subsequently been applied in large-scale population studies, including the UK Biobank cohort.[3]

We calculated PhenoAge acceleration (PhenoAgeAccel) as the residual from regressing PhenoAge on chronological age, representing how much older (positive values) or younger (negative values) an individual's biological age is compared to their chronological age. This approach is justified given PhenoAge's demonstrated validity across several large-scale studies and its strong predictive validity for health outcomes in diverse populations.

Reference

1. Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY). 2018;10(4):573-591. doi:10.18632/aging.101414
2. Kuo CL, Pilling LC, Atkins JL, et al. Biological Aging Predicts Vulnerability to COVID-19 Severity in UK Biobank Participants. J Gerontol A Biol Sci Med Sci. 2021;76(8):e133-e141. doi:10.1093/gerona/glab060