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Biomarkers of aging and age-related diseases: from linear regression to explainable artificial intelligence

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Motivation and Aim: Discovery of aging biomarkers and development of biological clocks that enable precise estimation of calendar age and sensitive detection of age acceleration, related to the manifestation of age-related diseases remains central to the field. Despite such recent successes as the Horvath and Hannum epigenetic clocks, Phenoage clocks and GrimAge clocks, there is still a keen need to (1) encompassing novel and multi-level biomarkers, (2) elaborating the systems description of aging, (3) developing the age estimators based on advanced Artificial Intelligence tools, including the algorithms that allow for explaining AI based predictions both cohort-wide (population-wide) and individual-wise (personalized).

Methods and Algorithms: We investigate simultaneous DNA methylation (Illumina EPIC) and immunological data (multiplex analysis) from human peripheral blood samples for the control group and patients with end-stage renal disease (ESRD) receiving hemodialysis. We calculate several epigenetic age estimators, build a linear-regression and elastic-net based immunological age-estimator ipAGE, and implement AI-based age-estimators with individual age-acceleration explained by SHAP values.

Results: We demonstrated accelerated aging in terms of the most common epigenetic age estimators in ESRD patients, developed a new clock/predictor of age based on the inflammatory/immunological profile (ipAGE) and identified the differentially expressed inflammatory/immunological biomarkers [1]. IpAGE appeared to be more sensitive than epigenetic clocks in quantifying the accelerated aging phenotype. Moreover, we developed the mixed epigenetic-immunological AI-based age estimators and explain AI models, identifying epigenetic and immunological factors responsible for age acceleration in each single participant.

Conclusion: The obtained results uncover and confirm the deep relation between aging and remodeling of the human immune system, previously conceptualized as the inflammaging theory. The developed immunological clocks allow for a direct inference of immune system aging and shed light on the underlying mechanisms. The most to-date advanced methods of Explainable Artificial Intelligence not only rank the most important populational biomarkers of immunological and epigenetic aging, but allow for the first time to differentially identify specific biomarkers that are responsible for age acceleration of each particular individual.

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References

1. Yusipov I., Kondakova E., Kalyakulina A., Krivonosov M., Lobanova N., Bacalini M.G., Franceschi C., Vedunova M., Ivanchenko M. Accelerated epigenetic aging and inflammatory/immunological profile (ipAGE) in patients with chronic kidney disease. *GeroScience.* 2022;44(2):817-834. doi: 10.1007/s11357-022-00540-4.