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Retroelement-Based Epigenetic Clock as a Biomarker of Biological Aging

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Background & Unmet Need

- A person's biological age differs from their chronological age as it considers not just the passage of time but also factors such as genetics, lifestyle, nutrition, and comorbidities
- Assessing biological age can serve as a more effective diagnostic tool for age-related diseases and as a prognostic tool for health screening
- Epigenetic clocks are a way to determine biological age based on patterns of DNA methylation at specific regions of the human genome
- However, existing epigenetic clocks face challenges related to accuracy, tissue specificity, biological relevance, and capturing diverse aspects of aging
- Retroelements like HERVs and LINE-1 elements are kept silent by DNA methylation, but have been known to influence gene regulation, genomic stability, and disease upon reactivation with age
- **Unmet Need:** Improved biomarkers of biological aging for assessing age-related risk and disease

Technology Overview

- **The Technology:** Biomarker of biological aging based on the DNA methylation states of HERVs and LINE-1 retroelements
- HERV-Age, LINE-1-Age, and a composite Retroelement-Age clocks were developed using data from >12 K individuals based on the DNA methylation states of HERV and/or LINE-1 elements
- 100% of HERV-Age and 99.9% of LINE-1-Age methylation sites were unique and not part of existing epigenetic clocks*
- **PoC Data:** All three epigenetic clocks were subsequently validated in >2 K samples, with high fidelity to chronological age
- Retroelement-Age was able to measured the impact of therapeutic intervention, demonstrated by (i) a reduction in the biological age of samples from HIV patients undergoing retroviral treatment and (ii) human cortical organoids epigenetically rejuvenated through transient reprogramming

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Patents:
Provisional Filed

Publications:
Ndhlovu et al. *bioRxiv*. 2023 (preprint)

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*Hannum 2013, Lu Telomere 2019, Teschendorff 2020 EpiTOC2, Belsky 2022 DunedInPace, Harvath 2013, Yang 2016 EpiTOC, Horvath2 2018, Levine 2018 PhenoAge, Lue 2019 Grim Age

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Technology Applications

- Predicting the chronological age of humans and pan-mammalian species
- Measure an individual's biological age more accurately to help predict risk of developing age-related diseases
- Tool for monitoring the effectiveness of therapeutic interventions, such as antiretroviral and anti-aging treatments

Technology Advantages

- Predicts chronological age with higher accuracy than existing models
- Elucidates the association between DNA methylation of retroelements and human aging
- Identifies potential biomarkers for anti-aging strategies

Supporting Data / Figures

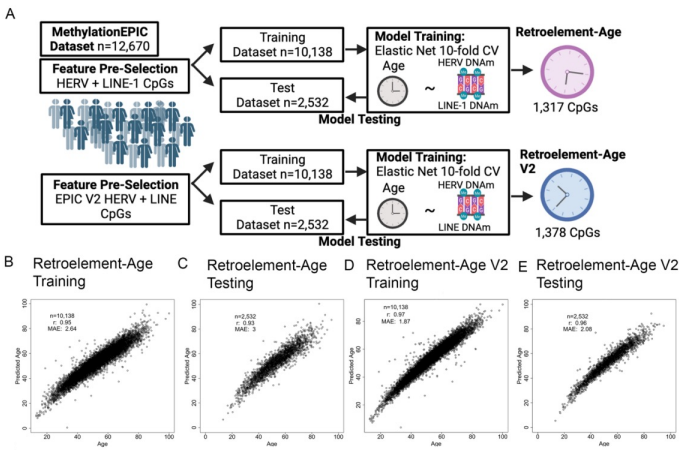

Figure 1. A) Diagram of workflow utilized to construct Retroelement-Age and Retroelement-Age V2. B-E) The age estimates generated by the Retroelement-Age and Retroelement-Age V2 clocks, validated through 10-fold cross-validation on training and test datasets, exhibited strong correlations with chronological age. Panels report the sample size (n), the median absolute error (MAE), and Pearson correlation coefficient (r).

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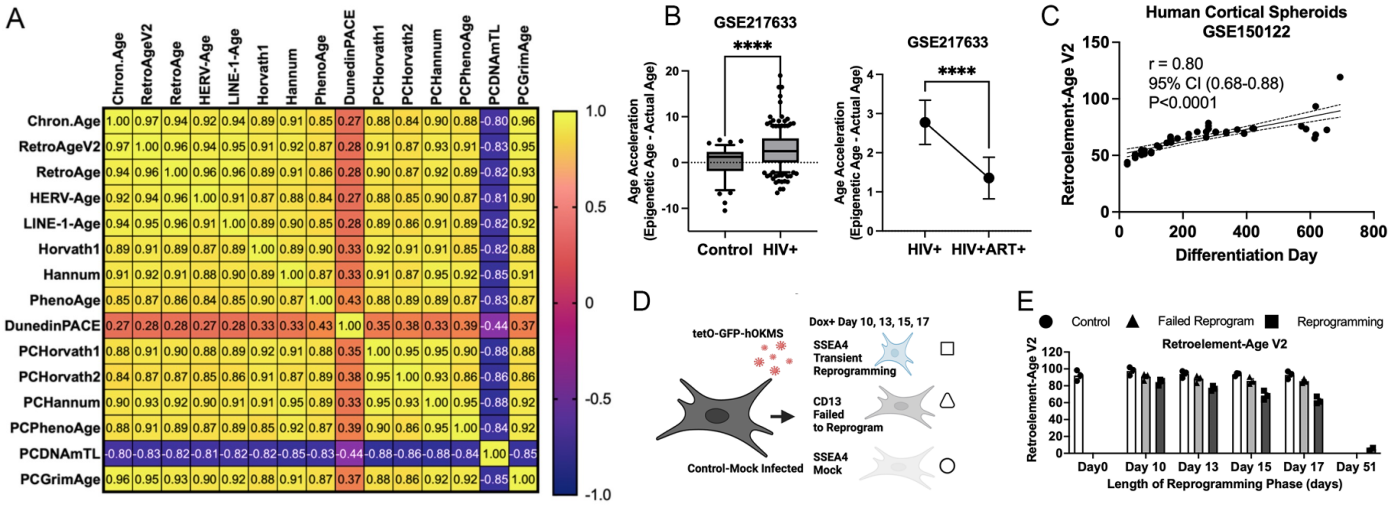

Figure 2. A) A correlogram of chronological age versus various epigenetic clock age estimates of 12,670 individuals. B) Age acceleration detected utilizing Retroelement-Age V2 in external data from people living with HIV compared to healthy controls. Age estimates of people living with HIV before and after 96 weeks of ART. C) Application of Retroelement-Age V2 in tracking human cortical brain organoids culture age. D) Application of retroelement-based epigenetic clocks to transient reprogramming-induced rejuvenation strategies. E) Epigenetic age estimates for Control (circle symbol), failed to program (triangle symbol), and transiently reprogrammed (square symbol) fibroblasts.

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