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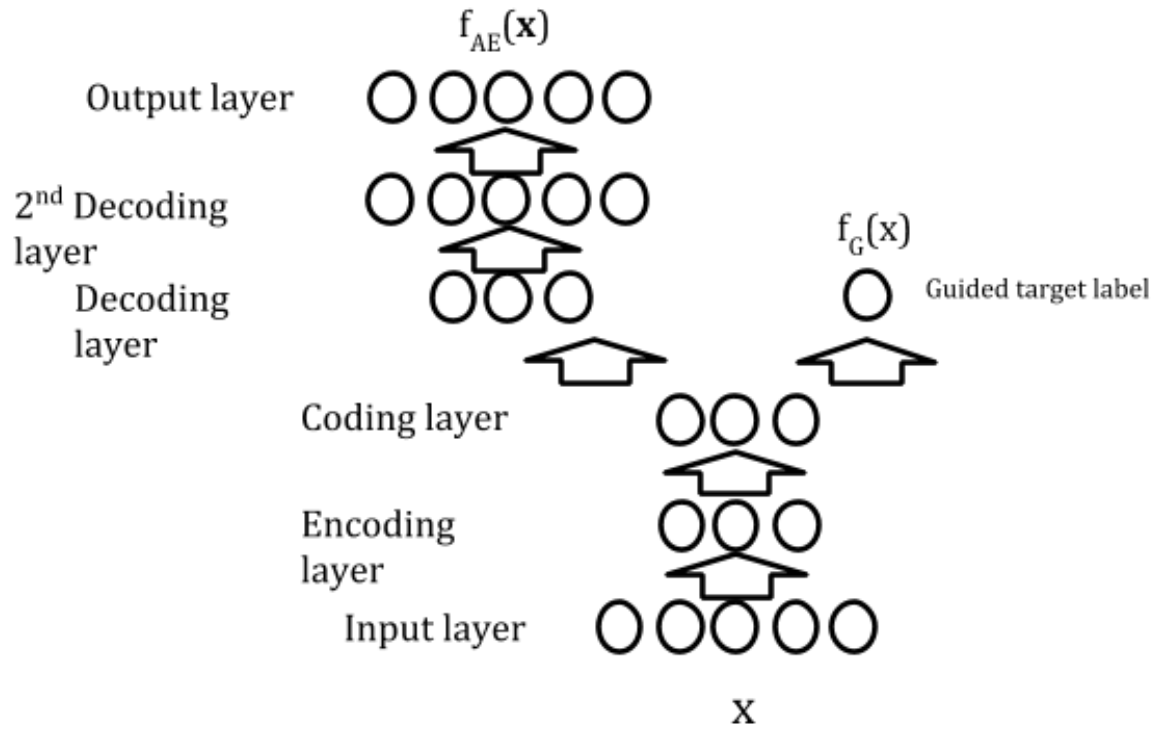
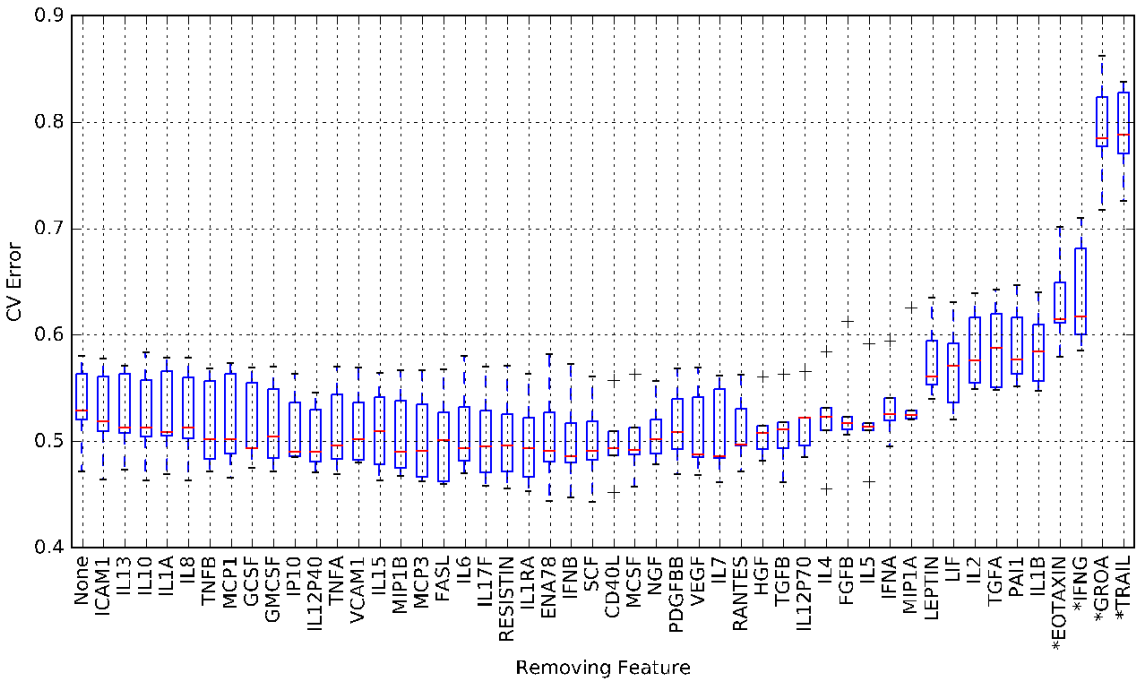
Supplementary information

An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging

In the format provided by the authors and unedited



Supplementary Figure 1. guided-auto-encoder with depth 2 and width 3.



Supplementary Figure 2. Cross-validation feature importance selection for prediction of the inflammatory clock (iAge). We estimated the minimum set of features able to predict iAge. From the left to right, each box represents the 5-fold cross-validation errors for a set of features. The leftmost feature ("None") represents no feature was removed, hence we use all features to predict iAge. Moving from left to right, each box represents the 5-fold cross-validation errors removing one feature at a time (with feature name as shown in the x axis) based on their importance derived from the analysis of the jacobians (low importance feature removed first). With removal of each feature, a p-value (two sample t-test) on the cross-validation errors between current feature set and all-feature-set ("None") is computed. Removal of most features does not significantly affect prediction accuracy. The cross-validation error using only 5 features (EOTAXIN, IFNG, GROA, TRAIL and CXCL9 (which is not removed as it is the last feature)), is not significantly different from the error obtained using all features, indicating that iAge can also be predicted with this reduced set, as accurately as using all 50 features. Boxes represent 25th and 75th percentiles around the median (red line); whiskers, 1.5× interquantile range).

	Group 1 (25 to 44 y)	Group 2 (45 to 59y)	Group 3 (60 to 74 y)	Group 4 (75 to 90 y)	P
N	21	32	25	19	-
Age (mean)	33± 6	53 ± 4	68 ± 4	82 ± 4	<0.001
Female (%)	48	50	72	47	0.25
SBP (mmHg)	117 ± 12	118 ± 12	117 ± 14	123 ± 16	0.36
DBP (mmHg)	71 ± 6	74 ± 9	71 ± 9	69 ± 10	0.35
Heart rate	64 ± 9	58 ± 8	65 ± 12	62 ± 12	0.07
BMI (kg/m^2)	24 ± 3	25 ± 3	24 ± 3	23 ± 3	0.02*
Waist (cm)	83 ± 10	88 ± 9	85 ± 8	89 ± 13	0.23
Glucose (mM)	4.9 ± 0.4	5.1 ± 0.6	5.0 ± 0.5	5.1 ± 0.5	0.20
TC/HDL	3.7 ± 1.4	3.4 ± 1.1	3.2 ± 0.9	3.0 ± 0.7	0.28
Uric Acid	5.6 ± 1.6	5.0 ± 0.97	4.8 ± 1.0	5.7 ± 1.7	0.14
Calcium	9.3 ± 0.3	9.2 ± 0.4	9.3 ± 0.4	9.2 ± 0.3	0.89
TSH	1.60 ± 0.80	1.50 ± 0.60	2.0 ± 0.8	2.0 ± 0.9	0.08
SCr (mg/dL)	0.80 ± 0.12	0.83 ± 0.12	0.80 ± 0.13	0.85 ± 0.18	0.54
Cystatin C	0.80 ± 0.14	0.85 ± 015	0.94 ± 0.16	1.08 ± 0.16	< 0.001
Hs-CRP	1.3 ± 1.3	1.7 ± 2.7	1.5 ± 1.8	1.1 ± 0.8	0.68

Supplementary Table 1. Validation study. Baseline clinical and demographic data.

Supplementary Table 2

	# Features	Sample size
Cell subsets	**25**	**935**
Immune proteins	**50**	**1001**
Gene expression*	**6149**	**394**
Cell stimulations	**84**	**818**
Latent CMV	**1**	**748**
BMI	**1**	**724**
Clinical questionnaire	**57**	**902**
Cardiovascular phenotyping	**37**	**97**

*low variant genes removed

Supplementary Table 2. Available data for the 1000 Immunomes Project.

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65 **Supplementary Table 3**

Predictors	N Subjects	Total Analytes	Outcome	Ref
GWAS, polygenic risk score (lifespan)	1 million	Genome wide genetic variants	validated 7 previously identified loci and 5 novel loci in relations to difference in lifespan. Predicted accuracy of age with MAE of 5 years.	[1]
GWAS (healthspan)	300,447 British individuals	Genome wide genetic variants	12 loci associated with healthspan, or disease-free survival.	[2]
DNA Methylation	656	450,000 CpG markers	predict a person's age with RMSE of 3.88 years and risk of mortality. measured age in many human tissues	[3]
DNA Methylation	8,000	21,369 CpG sites	Final model of 353 CpG sites predict a person's risk of mortality and cancer. Prediction of age has a median absolute error of 3.6 years.	[4, 5]
DNA Methylation (DNAm PhenoAge)	9,926	Phenotypic aging measures + 20,169 CpG sites	risks for an array of diverse outcomes across multiple tissues and cells. Association with all-cause mortality, cancers, healthspan, physical functioning, and Alzheimer's disease	[6]
DNA methylation (GrimAge)	2356	88 plasma proteins + selected subset of CpG sites from 450,000	predictive of time-to-death, time-to-coronary heart disease, time-to-cancer	[7]
Transcriptomics	11,908	whole-blood gene expression	1,497 genes were significant associated with blood pressure, cholesterol levels, fasting glucose, and body mass index. Predicted age with MAE of 7.8 years.	[8]
Transcriptomics	7682	7,682 common genes	High accuracy of actual age bin prediction with MAE of 6.19 years on the test set	[9]

microRNA	5221	whole-blood microRNA expression	127 microRNAs that were differentially expressed by age. The correlation between miRNA predicted age (miRNA age) and chronological age was significant ($r = 0.70$; $P < 1 \times 10^{-320}$).	[10]
Proteomics	677	1,129 SOMAmers	Eleven proteins were associated with chronological age	[11]
Proteomics	240	1,301 Proteins	76 proteins that highly correlated with chronological age, chronic diseases and all-cause mortality	[12]
Proteomics	4,263 young adults	2,925 plasma proteins	non-linear changes in the human plasma proteome with age. differential associations with proteome of age-related diseases and phenotypic traits	[13]
Glycan Age	5,117	24 IgG glycosylation	glycans explained variance in age considerably more than other biomarkers of age like telomere lengths. Correlation between age and predicted age is .76.	[14]
Metabolomics	44,168	226 metabolic biomarkers	14 biomarkers independently associating with all-cause mortality. C-statistic = 0.772 and 0.790 when looking at 5- or 10-year mortality, respectively.	[15]
Immunological cell subsets (IMM-Age)	135	73 immune-cell subsets	Low and high IMM-Age have different all-cause mortality that is statistically significant (p = 0.018).	[16]
PhotoAgeClock	8,414	High resolution pictures. visual photographic biomarkers	achieve a mean absolute error of 2.3 years in chronological age prediction	[17]

Supplementary Table 3. Notable aging clocks. Extracting signatures of aging has becoming increasingly popular. Monitoring the aging process in different modalities from cellular to tissue level have produced aging clocks with varying ability to correlate the different aspects of chronological aging and healthy aging. Some of the notable aging clocks are depicted, ranging from those using a wide array of biological modalities to facial features. The current standard efforts have mostly been exploring each modality in isolation. Future attention would benefit from combining modalities to provide a more wholistic resolution on the aging process.

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