Table S1 The characteristics of TLs methods

Methods		Principle	Results	Detection of TL distribution	Accuracy	Sample required	Commercial	Time consumming	Easy operation	Clinical application	Reference
Telo-qPCR		Telomere specific qPCR compared to a reference single copy gene	Relative-quantitative（Ct value）	Average TLs	Large variations between independent labs	gDNA, 10 ng	No	No, 1-2 h	Yes	High-throughput for population-wide studies; not for cancer studies	(Cawthon, 2002)
Modified qPCR	ΩqPCR	Hybridizing and ligating on telomeres to form a circular and do PCR	The number of loops after PCR（Ct value）	Absolute telomere length in kb	High	Single cell DNA	No	No, 2-3 h	Yes	For single cell detection of TL	(Xiong and Frasch, 2021)
	STAR qPCR	Measuring an individual telomere via microfluidic-Digital PCR in nanoliter compartment	The number of TLs after PCR comparing to TLs gradient standard curve	Absolute TL from 0.2 to 320 kb	High	Diluted into single-molecule	No	No, 1-2 h	Yes	High-throughput; apply to polyploid tumors	(Luo et al., 2020)
TRF		Southern-blot detecting telomeric sequences that cannot be digested by restriction enzymes	Mean, median, quartile TLs	Absolute TL values	Gold standard for TL length	gDNA ＞2 μg	Yes	Yes, 2 days	No, only in specialized lab	Limited usage for very large population studies	(Harley et al., 1990)
Modified TRF	STELA	PCR and TRF methods, using G-rich	Detect small subsets of chromosomes	Detect single shortest	Specific for shortest	gDNA, 1 μg	No	Yes 2-3 days	No, only in	Limited usage for very large	(Baird et al., 2003;

Methods		Principle	Results	Detection of TL distribution	Accuracy	Sample required	Commercial	Time consuming	Easy operation	Clinical application	Reference
	U-STELA TeSLA	3’ tail and subtelomere sequence as primers	Detect individual chromosomes	telomere to TL<20 kb	telomere				specialized labs	population studies	Bendix et al., 2010; Lai et al., 2017)
Q-FISH	Interphase FISH	Specific probes binding to telomeres and fluorescence microscopy	Semi-quantitative; Counting the number of telomere signal and fluoresce intensity for average TLs	Longer than 200 bp	Accurate, except wrong estimation of TL distribution when telomeres are aggregated and clustered spatially	Tissues or ＞15-20 cells	No	Yes 2-3 days	Yes	High-throughput Q-FISH to quantify individual TL in interphase cells or tissue biopsies	(Lansdorp et al., 1996)

Methods		Principle	Results	Detection of TL distribution	Accuracy	Sample required	Commercial	Time consuming	Easy operation	Clinical application	Reference
	Metaphase FISH	FISH after blocking cells at metaphase and microscopy the fluorescence number and intensity	TLs and dysfunctional telomere phenotype of individual chromosome end	Longer than 200 bp		Only in active dividing cells		Yes 3-4 days	No, labor demanding	Limited usage in the clinics	
	Flow-FISH	Measuring telomere signal in individual interphase cells by FACS	Fluorescence units value	Average TLs	High false positive	＞105 cells, primarily on lymphocytes	Yes	No 2-3 hours	Yes	Certified as a clinical diagnostic tool for larger scale studies	(Baerlocher et al., 2006)
PHAST		Hybridizing and pulling down telomeric sequence, then measuring by light-sheet	Fluorescence units value	Absolute TLs from 100 bp to 15 kb	Yes	gDNA, 0.1 μg	No	Several hours	Need specialized equipment	No test for clinical samples yet	(Beh et al., 2018)

Methods	Principle	Results	Detection of TL distribution	Accuracy	Sample required	Commercial	Time consuming	Easy operation	Clinical application	Reference
SMRT	Designed telobaits to capture G-rich 3’ tail after enzyme digestion. Dynabeads purify telomere-containing gDNA fragments for PacBio sequencing.	Analysis of sequence data	Absolute TLs nucleotide resolution; sequences	Yes	gDNA, 10 μg for the telobait library	No	Timing on sequencing and bioinformatic analysis	Need specialized equipment	High-throughput; also reveal individual telomeric variant	(Tham et al., 2023)

Table S2 The mitochondrial biomarkers of cellular aging.

Biomarker	Test methods	Cell types	Reference
Increased ROS	DHE staining approach	Monocytes	(Jacinto et al., 2018)
Increased mtDNA mutations	Deep sequence of whole mtDNA	Human colonic crypt stem cells, human colonic epithelium	(Baines et al., 2014; Greaves et al., 2012; Greaves et al., 2006; Taylor et al., 2003)
Low-frequency (less than 0.5%) mtDNA point mutations	Deep sequence of whole mtDNA	Human discarded oocytes	(Yang et al., 2020)
Impaired mitophagy	mt-Keima imaging, anti-TOM20 and anti-LC3B western blotting	Mouse oocytes, mouse cardiac tissue and skeletal myoblasts	(Jin et al., 2022; Stotland and Gottlieb, 2016)
UPR^{mt} decline	Anti-HSP60, anti-ClpP and anti-LONP1 Immunofluorescence or western blotting	Mouse skeletal muscle, rat liver, muscle stem cells	(Bakala et al., 2003; Bota et al., 2002; Yokoyama et al., 2002)
Decreased membrane potential	TMRM, JC-1 staining, rhodamine 123 flow cytometry	Hepatocytes, lymphocytes	(Hagen et al., 1997; Rottenberg and Wu, 1997)

Table S3 Examples of PTM targets involving in the loss of proteostasis in aging or age-related diseases.

PMT	Model	Targets	Amino acid residue(s)	Change in aging or age-related diseases	Reference
Phosphorylation	Mouse	AMPKα	Thr172	decreased	(Salminen et al., 2016)
	Fly	Acinus	Ser 437	decreased	(Nandi and Krämer, 2018)
	Monkey	IRE1α	N.A	increased	(Tan et al., 2020)
	Human, mouse	α-Synuclein	Ser129	increased	(Sandoval-Pistorius et al., 2023)
Ubiquitination	Mouse, cell	Beclin 1	Lys 63	increased	(Xu et al., 2020)
	Worm, fly	INSR	Lys 1057,1079, 1174,1195	increased	(Tawo et al., 2017)
Sumoylation	Worm	CAR-1	Lys185	increased	(Moll et al., 2018)
	Human	LMNA	Lys 262	decreased	(Ghosh et al., 2022)
Acetylation	Human	Tau	Lys 280	increased	(Irwin et al., 2012)
	Mouse	HSF1	N.A	increased	(Jurivich et al., 2020)
S-nitros(yl)ation	Cell	Ero1α	Cys 131,166	increased	(Qiao et al., 2022)
	Mouse	Drp1	Cys 644	increased	(Rizza et al., 2018)
	Mouse	Parkin	Cys 658	increased	(Rizza et al., 2018)
	Mouse	GAPDH	Cys 150,154,245	increased	(Xie et al., 2022)
	Mouse	ATG4B	Cys189,292	increased	(Li et al., 2017)
	Mouse, cell	hmtThrRS	Cys 409	decreased	(Zheng et al., 2020)
S-sulfhydration	Mouse	Hrd1	Cys115	decreased	(Yu et al., 2020)
	Mouse	USP8	N.A	decreased	(Sun et al., 2020)
S-glutathionylation	Cell	(IKK) β	Cys179	increased	(Reynaert et al., 2006; Xu et al., 2022)
S-sulfonylation	Yeast	PKA	Cys 243	decreased	(Roger et al., 2020)

N.A, not available

Table S4 Metabolic biomarkers of aging.

Metabolite	Class	Change with age	Reference
NAD^+	Coenzyme	Down	(Covarrubias et al., 2021; Nacarelli et al., 2019)
α-Ketoglutarate	TCA	Varying[a]	(Chin et al., 2014; Fernandez-Rebollo et al., 2020; Wang et al., 2020b; Wu et al., 2017; Zhang et al., 2021c)
Tryptophan	Amino acid	Down	(Panyard et al., 2022; van der Goot and Nollen, 2013)
Methionine	Amino acid	Varying[b]	(Ding et al., 2021; Houtkooper et al., 2011; Koziel et al., 2014; Parkhitko et al., 2019)
Spermidine	Amino acid derivative	Down	(Ding et al., 2021; Green, 2019; Madeo et al., 2019; Pucciarelli et al., 2012)
Triglycerides	Lipid	Up	(Bucaciuc Mracica et al., 2020; Panyard et al., 2022)
Cholesterol	Lipid	Up	(Bucaciuc Mracica et al., 2020; Panyard et al., 2022)

[a] α-Ketoglutarate may decrease with age in mice and increases in senescent cultured cells.

[b] Methionine decreases in serum but increase in brain of older mice compared to young mice.

Table S5 Typical components and central biomarkers of the SASP.

Subcategory	Component
Chemokines	IL-8, GROα, GROβ, GROγ, MCP1, MCP2, MCP4, CCL1, CCL3, CCL5, CCL11, CCL16, CCL20, CCL25, CCL26
Cytokines	IL-6, IL-7, IL-1α, IL-1b, IL-13, IL-15, IL23a, TNFα
Other inflammatory factors	TGF-β, GM-CSF, M-CSF, G-CSF, IFN-α1, IFN-γ, CCL13, MIF, LIF
Growth factors	AREG, EREG, heregulin, EGF, bFGF, HGF, FGF7, VEGF, ANG, SCF, CXCL12, GDF15, GDNF, IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP6, IGFBP7
Proteases and inhibitors	MMP1, MMP2, MMP3, MMP8, MMP10, MMP12, MMP14, TIMP1, TIMP2, PAI-1, PAI-2, tPA, uPA, cathepsin B, SPINK1, SERPINs
Receptors and ligands	ICAM1, ICAM3, OPG, sTNFRI, sTNFRII, TRAIL-R3, Fas, uPAR, SGP130, EGF-R, WNT16B
Insoluble molecules	Collagens, fibronectin, laminin

Data are derived and processed from cellular senescence- and aging-related literatures (Acosta et al., 2008; Coppe et al., 2008a; Coppe et al., 2010; Coppe et al., 2008b; Gorgoulis et al., 2019; Kuilman et al., 2008; Rodier et al., 2011; Sun et al., 2012).

Table S6 Summary of putative biomarkers of brain aging.

Organ	Level		Biomarker	Test methods	Species[#]	Reference
Brain	Imaging traits	Structural MRI	Brain atrophy: frontal lobe in normal aging; medial temporal lobe in Alzheimer's disease	T1-weighted imaging	Hu	(Fox and Schott, 2004; Scheltens et al., 2021)
			Increased microbleeds	T2*-weighted or susceptibility-weighted imaging (SWI)	Hu	(Ding et al., 2017; Haller et al., 2018)
			Increased white matter lesions	T2-weighted imaging	Hu	(Habes et al., 2018; Jung et al., 2021)
			Impaired white matter integrity	Diffusion tensor imaging (DTI)	Hu	(Kantarci et al., 2014)
		Functional MRI	Decreased cerebral blood flow	Perfusion-weighted MR imaging (PWI), e.g., ASL	Hu	(De Vis et al., 2018; Sun et al., 2021)
			Deceased cerebral metabolic rate of oxygen	Blood oxygen level-dependent functional MRI (fMRI)	Hu	(Lajoie et al., 2017; Lin et al., 2019)
			Decreased functional connectivity between regions of the default mode network	Blood oxygen level-dependent functional MRI (fMRI)	Hu	(Bernard et al., 2015; Wang et al., 2013a)
		PET	Decreased ^{18}F-FDG uptake in the frontal, cingulate, and temporal lobes in normal aging; Posterior cingulate and temporoparietal hypometabolism in Alzheimer's disease	^{18}F-FDG PET	Hu	(Bonte et al., 2017; Frisoni et al., 2017)
			Increased cortical amyloid β deposition	Aβ PET	Hu	(Hanseeuw et al., 2019; Jack et al., 2013)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			Increased tau deposition	Tau PET	Hu	(Berron et al., 2021; Lee et al., 2022b)
	Tissue	Whole brain	Weight loss; Atrophy	Weighed in the fresh state; MRI	Hu	(Dekaban, 1978; Resnick et al., 2003)
		Cortex	Cortical thinning; Gyrification degree decreases	MRI	Hu	(Madan, 2021; Storsve et al., 2014)
		Gray matter	Atrophy	MRI	Hu/Mk	(Good et al., 2001; Resnick et al., 2003)
		White matter	Atrophy; Integrity compromises; Nerve fiber changes; Oligodendrocyte number increases	MRI Diffusion tensor imaging (DTI) Electron Microscope Light microscope	Hu/Mk	(Bennett and Madden, 2014; Peters, 2009; Peters et al., 2008; Resnick et al., 2003)
		Ventricle	Increased volume	MRI	Hu/Mus	(Resnick et al., 2003; Shook et al., 2014)
		Cerebrovascular system	Morphology change; Vascular density reduction	Light microscope	Hu	(Brown and Thore, 2011)
		Neurogenesis	Neurogenesis decline	Fluorescent microscope	Mus	(Ahlenius et al., 2009; Enwere et al., 2004)

#Note: Hu, human; Mk, monkey; Mus, mouse.

Table S7 Summary of putative biomarkers of cardiac aging.

Organ	Level		Biomarker	Test methods	Species	Reference
Heart	Physiology	Vasculature	Large artery fibrosis and stiffness	N.A	Hu	(Komutrattananont et al., 2019)
			Collagen Deposition	N.A	Hu	(Kleefeldt et al., 2019)
			Calcification and thickness of artery walls	N.A	Hu	(Jakovljevic, 2018)
		Atria and ventricle	Fibrosis via myofibroblast	N.A	Hu	(Shirakabe et al., 2016)
			Cardiomyocytes hypertrophy	N.A	Hu	(Shimizu and Minamino, 2016)
			Atria and ventricle stiffness	US	Hu	(Abbasi et al., 2016; Abou et al., 2017)
			Increased LA size	US/MRI	Hu	(Olsen et al., 2021))
			LV concentric hypertrophy	MRI	Hu	(Yoneyama et al., 2017)
			Diastolic dysfunction	N.A	Hu	(Feridooni et al., 2015; Upadhya et al., 2015)
		Valves	Cardiac valves calcification	N.A	Hu	(Coffey et al., 2021; Ukita et al., 2016)
		Pericardium	Pericardium fibrosis	N.A	Mus	(Suffee et al., 2020)
			Deposition of adipose tissue	N.A	Hu	(Bernasochi et al., 2017)
		Conduction system	Reduced number of nodal cells	N.A	Mus	(Choi et al., 2022)
			Reduced heart rate	N.A	Hu	(Pascale and Govoni, 2016)
			Increased incidence of arrhythmia	ECG	Hu	(John and Kumar, 2016)
	Imaging traits	Vascular assessment	Elevated PASP	US	Hu	(Choudhary et al., 2014)
			Increased aortic root diameter	US	Hu	(Wang et al., 2021d)
			Increased carotid-femoral pulse wave velocity	Automatic device for PWV detection	Hu	(Baldo et al., 2018)

Organ	Level		Biomarker	Test methods	Species	Reference
		LA size	Increased LA diameter	US	Hu	(Olsen et al., 2021)
		LA function	Decreased LA expansion index, LA peak systolic strain, LAEF and increased LA stiffness index	MRI	Hu	(Abbasi et al., 2016)
			LA contraction-to-reservoir ratio	MRI	Hu	(Evin et al., 2016)
		LV size	Increased LV wall thickness, LV mass and decreased LV volume	US/MRI	Hu	(Hung et al., 2017; Yoneyama et al., 2017)
		LV function	Decreased EDV and EDV/LDV ratio, increased LDV	US	Hu	(Seo et al., 2020)
			Increased peak LV twist, decreased and delayed LV untwisting	US	Hu	(Hernandez-Suarez and Lopez-Candales, 2017)
			Decreased LV global longitudinal strain, global radial strain, global circular strain, and global area tracking	US	Hu	(Gan et al., 2020)
			Decreased E/A ratio, e' Increased E/e'	US	Hu	(Hung et al., 2017)
			Increased LV isovolumic relaxation time, the time constant of LV isovolumic pressure decay	MRI	Hu	(Peverill, 2019)
			T2 relaxation time	MRI	Mus	(Lee et al., 2022a)
			Decreased the early radial displacement, radial velocity and circumferential strain rate and increased late circumferential strain rate	MRI	Hu	(Lin et al., 2021)
			Reduced and prolonged longitudinal and radial velocities during cardiac diastole	MRI	Hu	(Evin et al., 2016)
		Conduction system	Increased P-wave duration, P-R and Q-T interval; decreased QRS and T-wave voltage; leftward shift of the QRS axis	ECG	Hu	(Steenman and Lande, 2017)

Organ	Level		Biomarker	Test methods	Species	Reference
			Increased PA-TDI	US	Hu	(Abou et al., 2017)
	Cellular alteration	Cardiomyocyte	Increased hypertrophy	Immunoassay	Mus	(Zhang et al., 2022a)
			Increased cell death (apoptosis, pyroptosis, necroptosis, ferroptosis)	FACS Immunoassay	Hu	(Trembinski et al., 2020)
			Increased mitochondrial senescence	Electron microscope	Mus	(Song et al., 2017)
		Fibroblast	Increased activation	Immunoassay, RNA-seq	Hu	(Kalyanasundaram et al., 2021)
			Increased senescence and SASP	Immunoassay	Hu	(Abdelfatah et al., 2019)
		Endothelial cell	Increased EndoMT	Immunoassay	Mus	(Wagner et al., 2018)
			Decreased Angiogenesis	Immunoassay	Mus	(Das et al., 2018)
			Increased senescence and SASP	Immunoassay, RT-PCR	Mus	(Li et al., 2019b)
		Immune cell	Increased infiltration Increased activation	FACS, immunostaining	Mus	(Esfahani et al., 2021)
			Increased SASP	Immunoassay, RT-PCR	Mus	(Martini et al., 2019)
	Molecular changes	Individual molecular pathway	Increased ROS	MitoSOX	Mus	(Dai et al., 2012)
			Increased sSNVs	snRNA-seq	Hu	(Choudhury et al., 2022)
			Increased mTOR phosphorylation	WB	Mus	(Hua et al., 2011)
			Decreased SIRT1, SIRT2, SIRT3	RT-PCR, WB	Mus	(Li et al., 2018; Sakamoto et al., 2004; Tang et al., 2017)
		snRNA-seq/scRNA-seq	Increased IL-7	snRNA-seq	Mk	(Katz et al., 2021)
			Decreased FOXP1, FOXP2	snRNA-seq	Mk	(Katz et al., 2021; Zhang et al., 2022b)
			Increased spectrin repeat containing, nuclear envelope 2 (Syne2)	scRNA-seq	Mus	(Emechebe et al., 2021)

Organ	Level		Biomarker	Test methods	Species	Reference
			Decreased nestin (Nes)	scRNA-seq	Mus	(Emechebe et al., 2021)
	Body fluid	Blood	Increased BNP	Immunoenzymometric assay	Hu	(Yoshida et al., 2019)
			Increased hs-cTnT	Electrochemiluminescence immunoassay	Hu	(de Lemos et al., 2010; Saunders et al., 2011)
			Increased IL-6	ELISA	Hu	(Puzianowska-Kuznicka et al., 2016)
			Increased CRP	Immunoturbidimetry	Hu	(Puzianowska-Kuznicka et al., 2016; Saeed et al., 2018)
			Increased ceramide-phospholipid risk score	LC-MS/MS	Hu	(Hilvo et al., 2020)
		Urine	Increased BNP	Electrochemiluminescence immunoassay	Hu	(Campbell et al., 2020)
			Increased fibrinopeptide A (FPA)	Competitive enzyme-linked immunoassay	Hu	(Sonel et al., 2000)
			Increased CD14	Mass spectrometry, WB	Hu	(Lee et al., 2015)
			Increased alpha-1-antitrypsin (AAT)	Mass spectrometry	Hu	(Delles et al., 2010)

Table S8 Summary of putative biomarkers of vascular aging.

Organ	Level		Biomarker	Test methods	Species	Reference
Blood vessel	Histological features	Vasculature	Increased deposition of collagen fibers, increased and disordered elastic fibers, disorganized arrangement of VSMCs, enlarged lumens, increased intima	H&E/EVG/Masson/IHC/Movat's pentachrome staining/ immunostaining	Hu/Mus/Rat	(Ding et al., 2022; Zhang and Tao, 2018)
	Physiology	Vasculature	Increased blood pressure	N.A	Hu/Mus/Rat	(Poulter et al., 2015)
		Vasculature	Increased carotid-femoral pulse wave velocity (PWV)	PWV	Hu/Mus/Rat	(Townsend et al., 2015; Van Bortel et al., 2012)
		Vasculature	Decreased flow-mediated dilation (FMD)	Ultrasound measuring of FMD	Hu	(Thijssen et al., 2019)
		Finger microvessel	Alterated reactive hyperemia index (RHI)	Ultrasound measuring of peripheral arterial tonometry (PAT)	Hu	(Thijssen et al., 2019)
		Vasculature	Decline in angiogenesis	N.A	Hu/Mus/Rat	(Ungvari et al., 2018)
	Imaging traits	Carotid	Increased cIMT	Vascular ultrasound	Hu	(Homma et al., 2001)
		Vasculature	Increased coronary artery calcium score (CACS)	CT	Hu	(Lanzer et al., 2014)
		Ocular microvasculature	Increased ocular microvascular abnormalities	Fundoscopic examination	Hu	(DellaCroce and Vitale, 2008)
		Abdominal aorta	Increased abdominal aortic aneurysm	Ultrasound/CT	Hu/Mus/Rat	(Bossone and Eagle, 2021)
		Aorta	Occurrence of aortic dissection	CT/MRI/TEE	Hu/Mus/Rat	(Bossone and Eagle, 2021)

Organ	Level		Biomarker	Test methods	Species	Reference
	Cellular alteration	VSMC/VEC	Flattened and enlarged cell shape and size, increased polyploidy, reduced proliferative capacity	SA-β-gal staining/ DAPI staining	Hu/Mus/Rat	(Tian and Li, 2014; Yang et al., 2007)
		VSMC/VEC	Increased SASP	ELISA/CBA	Hu/Mus/Rat	(Tian and Li, 2014; Yang et al., 2007)
		VEC	Decreased NO production and bioavailability	HPLC/DAF-FM DA	Hu/Mus/Rat	(Ding et al., 2022; Sato et al., 1993; Zhang and Gao, 2021)
		VSMC	Decreased sensitivity to vasodilators and vasoconstrictors	Immunostaining/WB/RT-qPCR	Hu/Mus/Rat	(Ding et al., 2022)
		VSMC	Phenotypic switch from contractile to synthetic	Immunostaining/ WB/RT-qPCR	Hu/Mus/Rat	(Gardner et al., 2015)
		VSMC	Increased calcium deposition and the expression of calcification regulatory factors	Von Kossa staining/ Alizarin red staining/ WB/RT-qPCR	Hu/Mus/Rat	(Fakhry et al., 2017; Nakano-Kurimoto et al., 2009; Wang et al., 2019a)
		VSMC	Increased cell plasticity in atherosclerosis	Oil Red staining/H&E staining	Hu/Mus/Rat	(Basatemur et al., 2019)
	Molecular changes	VSMC/VEC	Upregulation of p53/p21 and p16 pathways	WB/immunostaining	Hu/Mus/Rat	(Hernandez-Segura et al., 2018)
		VSMC/VEC	Telomere attrition	Telomere test	Hu/Mus/Rat	(Hernandez-Segura et al., 2018)
		VSMC/VEC	Senescence-associated β-gal activation	β-gal activation staining	Hu/Mus/Rat	(Hernandez-Segura et al., 2018)

Organ	Level		Biomarker	Test methods	Species	Reference
		VSMC/VEC	Genetic determination	High-throughput techniques	Hu/Mus/Rat	(Hernandez-Segura et al., 2018)
		VSMC/VEC	Epigenetic modifications	High-throughput techniques	Hu/Mus/Rat	(Hernandez-Segura et al., 2018)
		VSMC/VEC	Oxidative stress	Fluorescence	Hu/Mus/Rat	(Kurz et al., 2004)
		VSMC/VEC	Mitochondrial dysfunction (PGC-1α, p66Shc, etc.)	WB/immunostaining/ Seahorse assay	Hu/Mus/Rat	(Ding et al., 2022)
		VSMC/VEC	Inflammation (IL-1β, TNFα, IL-6, VCAM-1, ICAM-1, iNOS, etc.)	ELISA/WB/RT-qPCR /CBA	Hu/Mus/Rat	(Wang et al., 2021c)
		VSMC/VEC	Angiotensin II signaling (ACE-1)	WB/immunostaining	Hu/Mus/Rat	(Wang et al., 2003a)
		VSMC/VEC	SIRTs (SIRT1, SIRT3 and SIRT6)	WB/immunostaining	Hu/Mus/Rat	(Grootaert and Bennett, 2022)
		VEC	eNOS and NO	WB/immunostaining/Kit	Hu/Mus/Rat	(Sato et al., 1993)
		VSMC	MMPs	WB/immunostaining	Hu/Mus/Rat	(Gardner et al., 2015)
		VSMC/VEC	Others (HIF-1α, VEGF, Klotho, MFG-E8, etc.)	WB/immunostaining	Hu/Mus/Rat	(Cai et al., 2022; Long et al., 2022; Wang et al., 2021c)
	Body fluid	Blood	Number and senescence of endothelial progenitor cells	Flow cytometry	Hu/Mk/Mus/Rat	(Minamino and Komuro, 2007)
		Serum	Proinflammatory factors: CRP, IL-6, IL-1Ra, ox-LDL	ELISA/CBA	Hu/Mk/Mus/Rat	(Durham et al., 2018; Gopcevic et al., 2021; Ishigaki et al., 2009)

Organ	Level		Biomarker	Test methods	Species	Reference
		Serum	Other circulating proteins, metabolites and biomolecules	ELISA/CBA/ High-throughput techniques	Hu/Mus/Rat	(Hamczyk et al., 2020)
		Blood	Senescence of macrophages, T cells and B cells	Flow cytometry	Hu/ Mk/Mus/Rat	(Ding et al., 2022)
		Blood	DNA methylation age of blood cells	High-throughput techniques	Hu/Mus/Rat	(Hamczyk et al., 2020; Marioni et al., 2015)

#Note: Hu, human; Mk, monkey; Mus, mouse; Rat, Rattus norvegicus. ACE-1, angiotensin-converting enzyme-1; CACS, Coronary artery calcium scores; CBA, cytometric bead array; cIMT, carotid intima-media thickness; CRP, C-reactive protein; CT, computed tomography; DAF-FM DA, Diaminofluorescein-FM diacetate; DAPI, 4,6-diamino-2-phenyl indole; ELISA, Enzyme-linked immunosorbent assay; eNOS, endothelial NO synthase; EVG, elastic-van Gieson; H&E, Hematoxylin & Eosin; HIF-1α, hypoxia-inducible factor-1α; HPLC, High-Performance Liquid Chromatography; IHC, immunohistochemisty; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1β; IL-1Ra, IL-1 receptor antagonist; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; MFG-E8, milk fat globule epidermal growth factor 8; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; NO, nitric oxide; ox-LDL, oxidized low-density lipoprotein; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1α; PWV, pulse wave velocity; RHI, reactive hyperemia index; RT-qPCR, Quantitative real time polymerase chain reaction; SASP, senescence-associated secretory phenotype; SIRT, sirtuin; TEE, transesophageal echocardiography; TNFα, tumor necrosis factor-α; TUNEL, TdT-mediated dUTP nick end labeling; VCAM-1, vascular adhesion molecule-1; VEC, Vascular endothelial cells; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells; WB, Western blot.

Table S9 Summary of putative biomarkers of lung aging.

Organ	Level		Biomarker	Test methods	Species[#]	Reference
Lung	Physiology	N.A	Decreased chest wall compliance	Pulmonary function test	Hu	(Cho and Stout-Delgado, 2020)
			Decreased vital capacity	Pulmonary function test	Hu	(Cho and Stout-Delgado, 2020)(Cho and Stout-Delgado, 2020)
			Decreased maximal inspiratory pressure	Pulmonary function test	Hu	(Cho and Stout-Delgado, 2020)(Cho and Stout-Delgado, 2020)
			Decreased oxygen consumption	Cardiopulmonary Exercise Testing	Hu	(Cho and Stout-Delgado, 2020)(Cho and Stout-Delgado, 2020)
	Imaging traits	N.A	Increased air space size	Computed Tomography	Hu	(Cho and Stout-Delgado, 2020)(Cho and Stout-Delgado, 2020)
	Body fluid	Plasma	Increased CRP	Particle-enhanced immunonephelometry	Hu	(Sanders et al., 2021)
		Plasma	Increased GDF15	ELISA	Hu	(Sanders et al., 2021)
		Bronchoalveolar lavage	Declined number of alveolar macrophage	Flow cytometry	Mus	(Wong et al., 2017)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
	Tissue	Stroma	Increased fibrosis	Masson staining	Hu/Mus	(Conlon et al., 2020)
		Airway	Decrease of mucociliary clearance	Saccharine transit test	Hu	(Proença de Oliveira-Maul et al., 2013)
	Cellular alteration	Macrophage	Upregulated pro-fibrogenic genes: Timp1	Western Blot/ Immunofluorescence	Mus	(Wang et al., 2021a)
		Pulmonary capillary endothelial cell	Upregulated genes: NRP1,HIF2α, Downregulated anti-inflammation genes: EPCR	Immunofluorescence	Mus	(Wang et al., 2021a)
		Fibrobalst	Upregulated Notch pathway	Transgenic reporter mouse	Mus	(Cao et al., 2016)

Table S10 Summary of putative biomarkers in skeletal muscle aging.

Organ	Level		Biomarker	Test methods	Species[#]	Reference
Skeletal muscle	Physiology	Whole body	Unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, low physical activity	Routine medical examination	Hu	(Schaap et al., 2006b)
	Imaging traits	Gastrocnemius Soleus muscle	Increase of intramuscular adipose (IMAT) and connective (IMCT) tissues	Magnetic resonance imaging (MRI)	Hu	(Csapo et al., 2014)
		Erector spinae	Infiltration of intramuscular adipose tissue (IMAT)	Magnetic resonance imaging (MRI)	Hu	(Zoico et al., 2010)
		Whole body	Decreased whole body lean mass	Dual-energy X-ray absorptiometry (DXA)	Hu	(Hull et al., 2009)
		Psoas muscles	Decreased muscle mass	Computed tomography (CT)	Hu	(Lenchik and Boutin, 2018)
		Anterior thigh	Reduction of cross-sectional area (CSA) of muscles	Ultrasound (US)	Hu	(Albano et al., 2020)
	Body fluid	Serum	Decrease in elderly human: sestrin1/sestrin2, VEGF, IGF1, apelin, irisin	Enzyme linked immunosorbent assay (ELISA)	Hu/Mus	(Haden et al., 2000 ; Huh et al., 2014; Miyamoto-Mikami et al., 2015; Quinn et al., 2010; Rai et al., 2018; Rai et al., 2017; Ryan et al., 2006; Yalcin et al., 2018)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Serum	Increase in elderly human: IL6, myostatin	ELISA	Mus	(Haden et al., 2000 ; Hager et al., 1994; Miyamoto-Mikami et al., 2015; Palmeri et al., 2012; Wei et al., 1992; Yarasheski et al., 2002)
		Serum	Increase in old rat: leptin	Radioimmunoassay	Rat	(Mooradian and Chehade, 2000)
		Serum	Decrease in sarcopenia patients: MMP9, irisin, IGF1, and FGF21	ELISA	Hu	(Li et al., 2019a; Naranjo et al., 2017; Suzan et al., 2021; Volpato et al., 2014)
		Serum	Decrease in sarcopenia patients: IL-15, IL-6, CRP, myostatin, IL-10, IL-18, TNF-α	ELISA	Hu	(Li et al., 2019a; Rong et al., 2018; Rossi et al., 2019; Schaap et al., 2006a; Volpato et al., 2014; Yalcin et al., 2018; Yarasheski et al., 2002)
	Tissue	Vastus lateralis muscle	Increased expression of pro-inflammatory genes: IL-6, TNF-α, STAT3, NF-κB	ELISA, IHC, IF, qRT-PCR, Western blot	Hu	(Merritt et al., 2013)
		Tibialis anterior	Elevated FABP3	IF, Western blot, Mass spectrometry (MS) based lipidomic study, Fluorescence recovery after photobleaching (FRAP), qRT-PCR	Mus	(Lee et al., 2020)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Gastrocnemius Quadriceps	PGE2	Liquid chromatography–tandem mass spectrometer (LC-MS/MS)	Mus	(Palla et al., 2021)
		Gastrocnemius, tibialis anterior, quadriceps	Sphingolipids accumulation	Ultra-performance liquid chromatography–mass spectrometry (UPLC-MS), liquid chromatography–tandem mass spectrometer (LC-MS/MS), IHC, IF	Hu/Mus	(Laurila et al., 2022)
		Extracellular matrix (ECM)	Increased Wnt Signaling	Heterochronic parabiosis, Immunostaining, FACS	Mus	(Brack et al., 2007)
	Cellular alteration	MuSC, Muscle fiber	Loss of ciliation and Hedgehog signaling	IF, FACS, MuSC transplantation	Mus	(Palla et al., 2022)
			Decreased FoxO signaling, imposing of $CD34^{high}$ genuine state to $CD34^{low}$ primed state	IF, FACS, RNAscope, ChIP, Bulk RNA-seq, ATAC-seq	Mus	(García-Prat et al., 2020)
			Downregulation of FoxO3	Single-nucleus RNA-seq, RNA fluorescent *in situ* hybridization, Bulk RNA-seq, IHC, IF, Western blot	Hu/Non-human primate	(Jing et al., 2022)
			Elevated THBS1 and $CD47^{high}$ MuSC subset	Bulk RNA-seq, single-cell RNA-seq, qRT-PCR, FACS, IHC, PrimeFlow RNA Assay	Mus	(Porpiglia et al., 2022)
			Reduced NAD^+ level and impaired mitochondrial metabolism	FACS, Mass spectrometry, Alkaline comet assay, Respirometry, IHC, IF, Western blot, qRT-PCR, MuSC transplantation	Mus	(Zhang et al., 2016)
			Impaired autophagy	FACS, Bulk RNA-seq, IHC, IF, Western blot	Hu/Mus	(García-Prat et al., 2016)
			Reduced functional heterogeneity	IHC	Mus	(Tierney et al., 2018)
			Decreased expression of Opa1 and impaired mitochondrial	FACS, IHC, qRT-PCR, ATP assay, MitoSOX staining, Mitochondria quantification	Mus	(Baker et al., 2022; Tezze et al., 2017)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			dynamics			
			Reduced expression of SPRY1 and elevated FGF2-FGFR1 signaling in the niche from myofiber	MuSC transplantation, FACS, IHC, IF, Whole-mount *in situ* hybridization,	Mus	(Chakkalakal et al., 2012)
			Defective in β1-integrin activity and FGF2 signaling	IHC, Western blot, Co-IP, FACS, Bulk RNA-seq	Mus	(Rozo et al., 2016)
			Elevated JAK-STAT3 signaling	Microarray, FACS, IF, Hematoxylin & Eosin staining, qRT-PCR, Western blot	Hu/Mus	(Price et al., 2014; Tierney et al., 2014)
			Reduced NOTCH-1	IHC, FACS, Hematoxylin & Eosin staining	Mus	(Conboy et al., 2003)
			Amyloidosis	IHC, IF, qRT-PCR, Western blot, TMRM/OCR detection, Mitochondrial circularity,	Hu/Mus/ C. elegans	(Romani et al., 2021)
			Decreased $MyoD^+$ MuSC and delayed proliferation	Immunohistochemistry (IF), BrdU incorporation	Mus/Rat	(Sousa-Victor et al., 2014; Zwetsloot et al., 2013)
			Upregulation of CDKN2A accompanied by increased γH2AX, IGFBP5, CDKN2b, IL6 and accumulated SA-β-gal.	Fluorescence-activated cell sorting (FACS), Immunohistochemistry (IF), Immunofluorescence (IHC), qPT-PCR, Western blot, MuSC transplantation	Hu/Mus	(Sousa-Victor et al., 2014)
		Muscle fiber	Increased TGFβ	IHC, IF, qRT-PCR, Western blot	Mus	(Carlson et al., 2008)
		Fibro/adipogenic progenitors (FAP)	Reduced secretion of WISP1	RNA fluorescent *in situ* hybridization, Bulk RNA-seq, slow off-rate modified aptamer assay, Hematoxylin & Eosin staining, FACS, IHC, Western blot, qRT-PCR	Mus	(Lukjanenko et al., 2019)
		Fibro/adipogenic progenitors (FAP)	Reduced expression of IL33	FACS, Hematoxylin & Eosin staining, IHC, Western blot	Mus	(Kuswanto et al., 2016)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Regulatory T cell ($Foxp3^+CD4^+$ Treg)	Increased Smoc2	FACS, IHC, Western blot, mass spectrometry	Mus	(Schüler et al., 2021)
			Reduced accumulation	FACS, Hematoxylin & Eosin staining, IHC, Western blot	Mus	(Kuswanto et al., 2016)
		Myeloid cell	Increased TNFα	IHC, qRT-PCR	Mus	(Wang et al., 2018b)

#Note: Hu, human; Mk, monkey; Mus, mouse.

Table S11 Summary of putative biomarkers of liver aging.

Organ	Level		Biomarker	Test methods	Species[#]	Reference
Liver	Physiology	N.A	Downregulated apparent liver blood flow and perfusion	The plasma clearance of indocyanine green	Hu	(Wynne et al., 1989)
			Reduced liver volume	99mTc- GSA liver scintigraphy	Hu	(Wynne et al., 1989);(Wakabayashi et al., 2002)
			Reduced liver regenerative capacity	Immunostained for Ki67-positive hepatocytes; SA-β-gal staining	Rat/Mus	(Furrer et al., 2011; Liu et al., 2018; Pibiri, 2018)
			Enhanced inflammation and necroptosis	Immunostained for the M2 macrophage marker; ELISA; Flow cytometry;	Hu/Rat/Mus	(Bloomer and Moyer, 2021; Mohammed et al., 2021)
			Increased liver fibrosis	Measuring concentration of OHP; PSR staining	Hu/Mus	(Mohammed et al., 2021; Noureddin et al., 2013)
	Imaging traits	N.A	Decrease in liver weight	CT-LV	Hu	(Meier et al., 2007; Tauchi et al., 1994; Wakabayashi et al., 2002)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			Reduced liver volume	A gray scale B ultrasound scan; CT	Hu	(Wynne et al., 1989);(Wakabayashi et al., 2002)
			Reduced hepatic blood flow	Pulsed echo-Doppler; MRI	Hu	(Wang, 2021)
			Increased liver FDG uptake	FDG PET imaging; MRI	Hu	(Cao et al., 2021; Wang, 2021)
			Increase of liver iron content	MRI T2* imaging	Hu	(Horiguchi et al., 2007; Sheedfar et al., 2013; Zhao et al., 2019)
			Elevated liver fibrosis	Abdominal ultrasound scan	Hu	(Chen et al., 2020; Kuk et al., 2009)
	Tissue	N.A	Mild hepatic injury: cytoplasmic vacuolation, nuclear pyknosis, cytoplasmic hypereosinophilia, diminish of intercellular borders, and increased lipid accumulation	H&E staining	Mus	(Maeso-Díaz et al., 2018)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Sinusoidal endothelium	Pseudocapillarized: reduction in the number and porosity of fenestrations; endothelium thickening; and deposition of perisinusoidal basal lamina and collagen	Transmission electron-microscopic examination; Immunostaining; H&E staining	Hu/Mk/Mus/Rat	(Cogger et al., 2014; Cogger et al., 2003; Ito et al., 2007; Le Couteur et al., 2001; Maeso-Díaz et al., 2018; McLean et al., 2003; Warren et al., 2005)
	Cellular alteration	Hepatocytes	Increased polyploidy;	Feulgen-DNA cytophotometry; Immunostaining; pharmacokinetic analysis; Radioactive or fluorescence dye staining; Biochemical analysis of enzyme activity; RT-qPCR; Western;	Hu	(Kudryavtsev et al., 1993)
			Reduced surface area of endoplasmic reticulum	Pharmacokinetic analysis	Hu	(Schmucker et al., 1990)
			Mega-mitochondria with reduced number and function	Immunostaining; Radioactive or fluorescence dye staining; Biochemical analysis of enzyme activity	Rat/Mus	(Hagen et al., 1997; Navarro and Boveris,

Organ	Level		Biomarker	Test methods	Species[#]	Reference
						2004; Sastre et al., 1996)
			Decreased autophagic activity	Immunostaining; electron microscopy; western blotting	Mus	(Uddin et al., 2012; Xu et al., 2013)(Uddin et al., 2012; Xu et al., 2013)
			Accumulation of lipofuscins	Electron microscopy	Rat/Mus	(Le Couteur et al., 2001; Swanlund et al., 2008; Xu et al., 2013)
			Reduced DNA synthesis rate	[^{3}H]-thymidine incorporation	Mus	(Basso et al., 1998)
			Increased senescence	Immunostaining	Mus	(Basso et al., 1998; Ogrodnik et al., 2017)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Liver sinusoidal endothelial cells (LSECs)	Decreased NO bioavailability	DAF-FM staining	Rat/Mus	(Maeso-Díaz et al., 2018)
			Decreased expression of endothelial NO synthase protein, haem oxygenase-1, and several angiocrine receptors (stabilin-2, CD32b and VEGF-R2)	Immunostaining; RT-qPCR; western blot	Rat/Mus/Hu	(Ito et al., 2007; Maeso-Díaz et al., 2018)
			Increased CD68 positive cells, and secretion of vWF and ICAM-1	Immunostaining; ELISA	Rat/Mus	(Ito et al., 2007; Maeso-Díaz et al., 2018)
			Upregulation of senescent marker p16 and downregulation of SIRT1	RT-qPCR; western blot	Rat/Hu	(Maeso-Díaz et al., 2018)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Hepatic stellate cells (HSCs)	Increased expression of desmin, PDGFRβ	Immunostaining; RT-qPCR; western blot	Mus	(Warren et al., 2011)
			Increased expression of activation markers (α-SMA, collagen1α1, collagen1α2, and p-moesin, TIMP-2 and MMP9)	Immunostaining; RT-qPCR; western blot	Rat	(Maeso-Díaz et al., 2018)
			Increased expression of patatin-like phospholipase domain- containing protein 3 and decreased cellular retinol-binding protein I expression	Immunostaining; RT-qPCR; western blot	Rat	(Maeso-Díaz et al., 2018)
			Increased number and size of intracellular lipid droplets.	Electron microscopy	Mus	(Warren et al., 2011)
			Telomere attrition	Southern blotting	Hu	(Verma et al., 2012a)
		Kupffer cells (KCs)	Increased number	Light microscopy	Rat	(Hilmer et al., 2007)
			Basally activated status	*In vivo* perfusion of fluorescent microspheres	Rat	(Hilmer et al., 2007)
			Reduced phagocytotic activity	*In vivo* perfusion of fluorescent microspheres; *In vitro* incubation with fluorescent particles	Rat/Mus	(Hilmer et al., 2007; Linehan

Organ	Level		Biomarker	Test methods	Species[#]	Reference
						et al., 2014; Partridge et al., 2018)
			Increased cytokine production	Western blotting; ELISA	Rat/Mus	(Hilmer et al., 2007; Linehan et al., 2014; Partridge et al., 2018)
		Other Immune Cell Groups	Redistribution of macrophages to lymphoid collections	Immunostaining	Mus	(Singh et al., 2008)
			Increased pro-inflammatory M1-like macrophages with high CD38 expression	Immunostaining ; flow cytometry	Mus	(Chini et al., 2020; Covarrubias et al., 2020)
			Increased accumulation of neutrophils	Single cell sequencing	Mus	(Mogilenko et al., 2021)
			Reduced abundance of dendritic cells	Single cell sequencing	Mus	(Mogilenko et al., 2021)
			Decreased abundance of naïve $CD8^+$ T cells	Single cell sequencing	Mus	(Mogilenko et al., 2021)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			Age-associated $PD1^{+}TOX^{+}CD8^{+}$ T cell subpopulation	Single cell sequencing	Mus	(Mogilenko et al., 2021)
			Increased accumulation of activated $PD1^{+}CD4^{+}$ T cells	Single cell sequencing	Mus	(Mogilenko et al., 2021)
			Reduced abundance of $CD4^{+}$ T cells	Single cell sequencing	Mus	(Mogilenko et al., 2021)
			Reduced abundance of Natural Killer (NK) cells	Single cell sequencing	Mus	(Mogilenko et al., 2021)
			Reduced abundance of Group1 innate lymphoid cells (ILC1s)	Single cell sequencing	Mus	(Mogilenko et al., 2021)
	Molecular changes	Hepatocytes	Increased expression of HP1β, p21, p16, γ-H2AX and elevated SA-β-gal activity	Immunostaining; Western blotting	Hu/Mus	(Irvine et al., 2014; Wang et al., 2014)
			SASP: IL-6, IL-8	Chemokine protein array	Hu	(Irvine et al., 2014)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			Upregulated chromatin remodeling protein Brm, HDAC1, and the formation of CEBPa-HDAC1-Brm complexes	Western blotting	Rt/Mus	(Iakova et al., 2003; Wang et al., 2008)
			Downregulated SIRT1 expression	qPCR; Western blotting	Mus	(Gong et al., 2014; Ramirez et al., 2017)
			Decreased bivalent H3K9me3; H3K14ac modification	Mass spectrometry; ChIP-Seq	Mus	(Price et al., 2020)
			Lost cyclic protein acetylation	Microarrays analyses; Western blotting	Mus	(Sato et al., 2017)
			Increased expression of RAGE and decreased expression of mitochondrial β-oxidation-related gene: PPARα, CPT1a, CPT1b, and MCAD	Western blotting; qPCR	Mus/Hu	(Wan et al., 2020)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			Decreased expression of MANF	Western blotting	Mus	(Sousa-Victor et al., 2019)
		Hepatic stellate cells	Downregulated SIRT1 expression	Western blotting	Mus	(Ramirez et al., 2017)
			Increased expression of α-SMA, collagen1α1, collagen1α2, PDGFRβ, and p-moesin, desmin, TIMP-2 and MMP9	qPCR; Western blotting; Immunostaining	Rat	(Maeso-Díaz et al., 2018)
			Decreased telomere length	Q-FISH; qPCR	Hu	(Verma et al., 2012b)
		Liver sinusoidal endothelial cells	Downregulation of the eNOS-NO-cGMP vasodilatory pathway, together with reduced angiocrine and antioxidant molecules (Stabilin-2, CD32b, VEGF-R2, HGF, Wnt2, and HO-1)	qPCR; Western blotting	Rat	(Maeso-Díaz et al., 2018)
			Increased PD-L1 expression	Immunostaining	Mus	(Wang et al., 2022)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Kupffer cells	Decreased telomere length	Q-FISH; qPCR	Hu	(Verma et al., 2012b)
			Increased IL-6 level	qPCR	Rat	(Maeso-Díaz et al., 2018)
		Cholangiocytes	Upregulated Twf1 expression	qPCR; Immunohistochemistry	Hu/Mus	(Maroni et al., 2019)
			Increased expression of p16 and γH2A.x, and SASP: IL-6, IL-8, CCL2, PAI-1	FISH; Immunofluorescence	Hu	(Tabibian et al., 2014)
	Body fluid	Serum	Decreased albumin and bilirubin concentrations	N.A	Hu/Rat	(Maeso-Díaz et al., 2018; Verma et al., 2012b)
		Plasma	Increased total cholesterol and LDL cholesterol levels	N.A	Hu/Rat	(Maeso-Díaz et al., 2018; Verma et al., 2012b)
		Serum	Decreased MANF level	ELISA	Hu/Mus	(Sousa-Victor et al., 2019)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Serum	Increased OPN level	ELISA	Hu/Mus	(Gómez-Santos et al., 2020)

#Note: α-SMA: Actin alpha 2, smooth muscle, aorta; CCL2: C-C motif chemokine ligand 2; CD32b: Fc gamma receptor IIb; ChIP-Seq: Chromatin immunoprecipitation-sequence; CPT1a: Carnitine palmitoyltransferase 1A; CPT1b: Carnitine palmitoyltransferase 1B; CT-LV: Computed tomography volumetry; DAF-FM: Diaminofluorescein-FM; ELISA: enzyme-linked immunosorbent assay; FDG: Fluorodeoxyglucose; FISH: Fluorescence in situ hybridization; H3K9me3: Histone 3 Lys-9 trimethylation; H3K14ac: Histone 3 lysine 14 acetylation; H2AX: H2A.X variant histone; HDAC1: Histone deacetylase 1; H&E: Hematoxylin & Eosin; HGF: hepatocyte growth factor; HO-1: Heme oxygenase 1; HP1β: Heterochromatin protein 1β; HSC: Hepatic stellate cells; Hu: Human; ICAM-1: Intercellular adhesion molecule 1; IL-6: Interleukin 6; IL-8: Interleukin 8; ILC1s: Group1 innate lymphoid cells; KCs: Kupffer cells; LDL: Low-density lipoprotein; MANF: Mesencephalic-astrocyte-derived neurotrophic factor; MCAD: Cadherin 15; Mk: Monkey; MMP9: Matrix metallopeptidase 9; Mrc1: Mannose receptor C-type 1; MRI: Magnetic resonance imaging; Mus: Mouse; NK: Natural killer; OHP: Hydroxyproline; OPN: Steopontin; PAI-1: Serpin family E member 1; PD-L1: Programmed cell death ligand 1; PDGFRβ: Platelet derived growth factor receptor beta; PET: Positron emission tomography; PPARα: Peroxisome proliferator activated receptor alpha; PSR: Picrosirius red; Q-FISH: Quantitative fluorescence in situ hybridization; RAGE: Advanced glycation end product receptor; Rat: Rattus; RT-qPCR: Real time quantitative polymerase chain reaction; SA: Galactosyl-human serum albumin; SA-β-gal: Senescence-associated-β-galactosidase; SASP: Senescent-associated secretory phenotype; SIRT1: Sirtuin 1; TIMP-2: TIMP metallopeptidase inhibitor 2; Twf1: Twinfilin-1; VEGF-R2: Kinase insert domain receptor; vWF: von Willebrand factor; Wnt2: Wnt family member 2.

Table S12 Summary of putative biomarkers of kidney aging.

Organ	Level		Biomarker	Test methods	Species	Reference
Kidney	Physiology	N.A	Impaired renal function	Estimate glomerular filtration rate (eGFR)	Hu	(Glassock and Rule, 2012, 2016) (Bolignano et al., 2014; Schmitt and Melk, 2017)
			Nephrosclerosis	Hematoxylin & Eosin staining	Hu	(Denic et al., 2017; Rule et al., 2010)
			Susceptibility to AKI	N.A	Hu/Mus	(Huang et al., 2022b)
			Progression to new CKD	N.A	Hu/Mus	(Nitta et al., 2013)
	Imaging traits	N.A	Increased in kidney surface roughness	Ultrasonography/MRI/CT	Hu	(Hommos et al., 2017)
			Increased in number of cysts	Ultrasonography/MRI/CT	Hu	(Denic et al., 2016)
	Tissue	Nephrosclerosis	Arteriosclerosis/arteriolosclerosis	Hematoxylin & Eosin staining	Hu	(Hommos et al., 2017)
			Global glomerulosclerosis	Hematoxylin & Eosin staining	Hu	
			Interstitial fibrosis	Hematoxylin & Eosin staining	Hu	
			Tubular atrophy	Hematoxylin & Eosin staining	Hu	
	Body fluid	Serum	Creatinine	eGFR	Hu	(Lindeman et al., 1985)
		Serum	Albumin	Albumin to creatinine ratio (ACR)	Hu	(Drüeke and Parfrey, 2012)
		Urine	Exfoliated kidney cells:	mRNA/DNA methylation/scRNA-seq	Hu/Mus	(Wu et al., 2022)
		Plasma	KIM-1	ELISA/Cytokine array	Hu	(Coca et al., 2017; Gutiérrez et al., 2022)
		Urine	KIM-1	ELISA/Cytokine array	Hu	(Malhotra et al., 2020)
		Urine	α1M	ELISA/Cytokine array	Hu	(Wu et al., 2010)

Organ	Level		Biomarker	Test methods	Species	Reference
		Urine	UMOD	ELISA/Cytokine array	Hu	(Puthumana et al., 2021)
		Urine	EGF	ELISA/Cytokine array	Hu	(Ju et al., 2015; Norvik et al., 2021; Torres et al., 2008) (Wu et al., 2020)
		Serum	MMP-7	ELISA/Cytokine array	Hu	(Zhang et al., 2017) (Ihara et al., 2020)
		Urine	MMP-7	ELISA/Cytokine array	Hu	(Zhou et al., 2017)
		Urine	Fibrinogen	ELISA/Cytokine array	Hu	(Wang et al., 2017a)
		Plasma	TNFR-1 and TNFR-2	ELISA/Cytokine array	Hu	(Coca et al., 2017; Gutiérrez et al., 2022; Schrauben et al., 2021; Srivastava et al., 2021)
		Plasma	YKL-40	ELISA/Cytokine array	Hu	(Gutiérrez et al., 2022; Schrauben et al., 2021; Srivastava et al., 2021)
		Urine	YKL-40	ELISA/Cytokine array	Hu	(Malhotra et al., 2020; Puthumana et al., 2021)
		Plasma	MCP-1	ELISA/Cytokine array	Hu	(Gutiérrez et al., 2022; Srivastava et al., 2021)
		Urine	MCP-1	ELISA/Cytokine array	Hu	(Malhotra et al., 2020) (Wu et al., 2010)
		Plasma	suPAR	ELISA/Cytokine array	Hu	(Hayek et al., 2015)

Organ	Level		Biomarker	Test methods	Species	Reference
		Urine	Complement eptides	Proteomic investigation	Hu	(Wendt et al., 2021)
		Serum	Metabolites	Metabolomic quantification	Hu	(Yu et al., 2014)
		Urine	Exosomes and exosomal CCL2 mRNA	Exosome isolation and real-time RT-PCR	Hu	(Feng et al., 2018)
		Urine	Exosomal microRNA	Exosome isolation and real-time RT-PCR	Hu	(Eissa et al., 2016)
		Urine	Exosomal AQP5 and AQP2	Exosome isolation and Western blot	Hu	(Rossi et al., 2017)

#Note: Hu, human; MRI, magnetic resonance imaging; CT, computed tomography; TNFR, tumor necrosis factor receptors; KIM-1, kidney injury marker-1; EGF, epidermal growth factor; suPAR, soluble urokinase-type plasminogen activator receptor; YKL-40, chitinase 3-like 1; UMOD, uromodulin; α1M, α-1 microglobulin; NGAL, neutrophil gelatinase-associated lipocalin; MMP-7, Matrix metalloproteinase-7; WFDC2, WAP four-disulfide core domain 2; CCL2, Chemokine (CC-motif) ligand 2; AQP, water channel aquaporin.

Table S13 Summary of putative biomarkers of skeletal aging

Organ	Level	Biomarker	Test methods	Species	Preference
Skeleton	Minerals	Declined calcium	LCMS/ immunoassay	Hu	(Song, 2017)
		Declined phosphate	LCMS/ immunoassay	Hu	(Song, 2017)
	Extracellular matrix	Declined GAGs	ELISA	Hu	(Gimble et al., 2009)
		Declined collagens	ELISA/ Cytokine array/ qPCR	Hu/Mus	(Gimble et al., 2009)
	Hormones	Declined GHs	ELISA	Hu	(Dixit et al., 2022)
		Declined IGF1in the marrow	ELISA	Hu/Mus	(Bennett et al., 1984; Boonen et al., 1997; Dixit et al., 2022; Tuljapurkar et al., 2011; Young et al., 2021)
		Declined BMP2	ELISA	Hu/Mus	(Yousefzadeh et al., 2021)
		Disturbed and declined ghrelin	Blood test/ ELISA/ Cytokine array	Hu	(Pradhan et al., 2013)
		Declined ACTH	Blood test/ ELISA/ Cytokine array	Hu	(Almeida et al., 2017)
		Elevated glucocorticoids	Cortisol blood test / ELISA	Hu/Mus	(Ajdžanović et al., 2017)
		Elevated leptin	ELISA	Hu/Mus	(Kirk et al., 2020)
		Declined PTH	ELISA/Cytokine array	Hu/Mus	(Yukata et al., 2014)

Organ	Level	Biomarker	Test methods	Species	Preference
		Declined calcitonin	Blood test/ ELISA	Hu/Mus	(Khosla and Hofbauer, 2017)
		Declined Vitamin D	Blood test/ ELISA	Hu/Mus	(Christodoulou et al., 2023)
		Declined androgens	ELISA/Cytokine array	Hu	(Almeida et al., 2017)
		Declined estrogen	ELISA/Cytokine array	Hu	(Almeida et al., 2017)
	Secretory factors	Declined OPG	ELISA	Mus	(Chung et al., 2014)
		Declined P1NP	ELISA	Mus	(Shahnazari et al., 2012)
		Declined OCN	ELISA	Mus	(Shahnazari et al., 2012)
		Elevated M-CSF	Real-time RT-PCR	Hu	(Chung et al., 2014)
		Elevated RANKL	ELISA/ Real-time RT-PCR	Hu/Mus	(Chung et al., 2014; Shahnazari et al., 2012)
		Elevated NTx	ELISA	Hu	(Ryan and Elahi, 1998)
		Elevated CTx	ELISA	Hu	(Takahashi et al., 1999)
		Elevated TRAcP5b	ELISA	Hu	(Kikuchi et al., 2021)
		Elevated DPD	ELISA	Hu	(Tokida et al., 2021)
		Elevated SOST	ELISA	Mus	(Shahnazari et al., 2012)

Organ	Level	Biomarker	Test methods	Species	Preference
		Elevated DKK1	ELISA	Mus	(Shahnazari et al., 2012)
		Elevated CRP	ELISA	Hu	(Koh et al., 2005)
		Elevated IL-1/IL-6	ELISA	Hu	(Zheng et al., 1997)
		Elevated TNF-α	ELISA	Hu	(Zheng et al., 1997)

#Note: GAGs, glycosaminoglycans, long unbranched polysaccharides which are composed of repeating disaccharide units; LCMS, liquid chromatograph mass spectrometer, GHs, growth hormones, secreted from the anterior pituitary; IGF1, insulin-like growth factor 1, polypeptide mainly circulated by liver ; BMP2, bone morphogenetic protein 2, are member of the transforming growth factor beta (TGF-beta) superfamily; secreted from the kidney and spleen; ACTH, adrenocorticotropic hormone, secreted from the anterior pituitary; stimulates cortisol production; PTH, parathyroid hormone, secreted by parathyroid gland, tightly controls calcium and phosphate; OPG, osteoprotegerin; P1NP, Procollagen type I N-terminal propeptide; M-CSF, macrophage-colony stimulating factor; RANKL, receptor activator of NF-kB ligand; NTx, amino-terminal cross-linking telopeptide of type I collagen; CTx, serum cross-linked C-telopeptide of type I collagen; TRAcP5b, tartrate-resistant acid phosphatase 5b; DPD, deoxypyridinoline; SOST, sclerostin; DKK1, dickkopf-related protein 1; CRP, c-reactive protein; IL1/IL6, interleukin-1/ interleukin-6; TNF-α, tumor necrosis factor-α.

Table S14 Summary of putative biomarkers of intestinal aging.

Organ	Level		Biomarker	Test methods	Species[#]	Reference
Intestine	Physiology	N.A	Intestinal digestion and absorption function decreased	qRT-PCR/Western/ Disaccharidase activity	Hu/Mus	(DeJong et al., 2020; Suzuki et al., 2022)
			The microflora structure changed	Altered Schaedler flora (ASF)	Hu/Mus	(An et al., 2018; Ragonnaud and Biragyn, 2021; Thevaranjan et al., 2017)
			Increased intestinal permeability	FITC-dextran oral gavage assay	Hu/Mus	(An et al., 2018; Nagpal et al., 2018; Ragonnaud and Biragyn, 2021)
			Intestinal inflammation	ELISA	Hu/Mus	(Ragonnaud and Biragyn, 2021; Thevaranjan et al., 2017)
	Body fluid	Serum	IL-6, IL-8, CRP, TNF-α, indole and kynurenine	ELISA	Hu/Mus	(Chambers and Akbar, 2020; Espinoza and Walston, 2005; Hohman and Osborne, 2022; Thevaranjan et al., 2017)
		Plasma	LPS, Zonulin and Claudins	N.A	Hu/Mus	(An et al., 2018; DeJong et al., 2020)
	Tissue	Mucus layer	Reduced mucus	PAS/Alcian Blue	Hu/Mus	(Elderman et al., 2017)
		Microbial metabolites	SCFAs: Butyrate	Gas–liquid chromatograph	Hu/Mus	(Nagpal et al., 2018; Sokol et al., 2008)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
		Villi	Increased villous length	Hematoxylin & Eosin staining	Mus	(Nalapareddy et al., 2017; Suzuki et al., 2022)
	Cellular alteration	ISC	Reduced ISC marker Lgr5; Down-regulated signaling pathway: Wnt, Notch and Sirt1/mTORC1; Fatty acid oxidation (FAO) decreased and Cdc42 activity increased	Real-Time PCR/ Fluorescence in situ hybridization, FISH	Hu/Mus	(Igarashi et al., 2019; Mihaylova et al., 2018; Nalapareddy et al., 2021; Nalapareddy et al., 2017; Pentinmikko et al., 2019; VanDussen et al., 2012)
		Crypts	The number of crypts decreased, the regenerative potential decreased after irradiation, the size of intestinal crypts increased	Hematoxylin & Eosin staining /immunostaining	Mus	(Nalapareddy et al., 2017)
		Paneth cells	The number of Paneth cells increased	Lysozyme or MMP7 staining	Mus	(Nalapareddy et al., 2017)
		Goblet cells	The number of goblet cells increased; The secretion of Wnt3 decreased and the signal of Wnt decreased	Alcian blue staining/ Real-Time PCR	Mus	(Nalapareddy et al., 2017; Pentinmikko et al., 2019)

#Note: Hu, human; Mk, monkey; Mus, mouse.

Table S15 Summary of putative biomarkers of pancreatic aging.

Organ	Level		Biomarker	Test methods	Species	Reference
Pancreas	Physiological function	N.A.	Decline in β cell function	Stimulated insulin secretion in OGTT/IVGTT; GSIS in isolated human islets	Hu	(Basu et al., 2003; Chang et al., 2006; Geloneze et al., 2014; Hirose et al., 2016; Iozzo et al., 1999; Lyon et al., 2016; Xiao et al., 2014)
			Pancreatic exocrine insufficiency	FET	Hu	(Herzig et al., 2011)
	Body fluid	Blood	Decline in insulin secretion	ELISA	Hu	(Basu et al., 2003; Chang et al., 2006; Geloneze et al., 2014; Hirose et al., 2016; Iozzo et al., 1999; Lyon et al., 2016; Westacott et al., 2017; Xiao et al., 2014)
			Elevated HbA1c	HbA1c test	Hu	(Arnetz et al., 1982; Yang et al., 1997)
			Increased DNA methylation level of *FHL2* promoter	DNA methylation analysis by pyrosequencing	Hu	(Bacos et al., 2016)
			Increased 8-hydroxyguanine (8-OHG) in diabetic patients	HPLC-ECD	Hu	(Shin et al., 2001)
		Duodenal juice	Decline in secretory volume	SST	Hu	(Ishibashi et al., 1991)
			Decline in bicarbonate secretion	SST	Hu	(Laugier et al., 1991)

Organ	Level		Biomarker	Test methods	Species	Reference
			Decline in chymotrypsin, amylase, phospholipase, and lipase output	SST	Hu	(Ishibashi et al., 1991; Laugier et al., 1991)
			Decrease in secretion frequency	MRCP	Hu	(Torigoe et al., 2014)
		Feces	Increased fecal elastase-1	FET	Hu	(Hedström et al., 2015; Herzig et al., 2011)
	Imaging traits	N.A.	Reduced pancreatic volume	MRI, CT	Hu	(Wang et al., 2021b; Yoon et al., 2020)
			Reduced anteroposterior pancreas diameter	MRI	Hu	(Sato et al., 2012)
			Increased pancreatic hardness	EUS-elastography	Hu	(Chantarojanasiri et al., 2016)
			Pancreatic lobulation	CT, MRI	Hu	(Heuck et al., 1987; Sato et al., 2012; Wang et al., 2021b)
			Increased pancreatic duct diameter	Ultrasonography, ERCP, MRI, MRCP	Hu	(Anand et al., 1989; Glaser and Stienecker, 2000; Wang et al., 2021b)
			Pancreatic steatosis	CT, MRI, Ultrasonography	Hu	(Lesmana et al., 2015; Li et al., 2011; Saisho et al., 2007; Wang et al., 2021b)
			Increased abdominal age	Deep-learning based MRI segmentation	Hu	(Le Goallec et al., 2022)
	Tissue	Pancreas	Increased expression of *CDKN2A*	Single cell RNA sequencing	Hu	(Enge et al., 2017)

Organ	Level		Biomarker	Test methods	Species	Reference
			Accumulated cells harboring DNA sequence rearrangements	Flow cytometry analysis, *in situ* fluorescence imaging	Mus	(Wiktor-Brown et al., 2006)
			Increased 8-hydroxydeoxyguanosine (8-OHdG)	HPLC-ECD	Mus/Rat	(Reiter et al., 1999; Shi et al., 2004)
			Differentially methylated promoters and enhancers, such as increased DNA methylation level of *Hnf1a* promoter and enhancer proximal to *Arid5b*	Reduced representation bisulfite sequencing	Mus	(Chondronasiou et al., 2022)
		Islet	Decline in density and volume	IHC with chromogranin A antibody	Hu	(Mizukami et al., 2014b)
			Islet amyloid deposition	Cango red staining; IHC with IAPP	Hu	(Su et al., 2012)
			Increased fibrosis	IHC with α-SMA antibody, H&E	Hu	(Detlefsen et al., 2005)
			Increased glycolysis	U-^{13}C glucose tracing	Mus	(Murao et al., 2022)
			Decreased expression of *PDX1*, *INS*, *GLUT2*	RT-qPCR; Western blotting	Mus/Rat	(Ihm et al., 2007; Novelli et al., 2000)
			Increased dedifferentiation (chromogranin A (CGA)-positive and hormone-negative cells)	IF	Hu	(Song et al., 2022)
			Decreased transcription of *Hnf4a*	RT-qPCR	Rat	(Sandovici et al., 2011)

Organ	Level		Biomarker	Test methods	Species	Reference
			Increased H3K9me2 and H3K27me3 levels, and decreased H3Ac and H3K4me1 levels at the *Hnf4a* enhancer and its distal P2 promoter	ChIP-qPCR	Rat	(Sandovici et al., 2011)
		Blood vessel	Increased fibrosis of islet vessels; Decline in blood vessel density	IF with PECAM and Laminin antibodys; IF with VCAM-1/CD31 antibody, etc. and 3D imaging	Hu/Mus	(Almaça et al., 2014; Chen et al., 2021; Kehm et al., 2018)
			Advanced glycation end products (AGEs) accumulation: arg-pyrimidine, MG-H1, pentosidine	IHC	Mus	(Kehm et al., 2018)
			Increased amounts of iNOS and 3-nitrotyrosine	IF	Mus	
		Fat	Fatty infiltration and replacement	H&E	Hu	(Matsuda, 2019)
		Acinar	Acinar atrophy; Acinar-to-ductal metaplasia	H&E	Hu	(Matsuda, 2019; Xin et al., 2017)
		Lobule	Patchy lobular fibrosis in the elderly (PLFE); Lobulocentric atrophy	IHC with α-SMA antibody, H&E	Hu	(Detlefsen et al., 2005)
		Duct	Periductal fibrosis; Low-grade pancreatic intraepithelial neoplasia; Duct ectasia	H&E	Hu	(Gupta and Kumar, 2018; Hastier et al., 1998)

Organ	Level		Biomarker	Test methods	Species	Reference
	Cellular alteration	Acinar cell	Decline in mitochondria number; Decreased proliferation	Fluorescence microscopy; BrdU labeling	Mus	(Nagata, 2012; Takahashi et al., 2012)
		α cell	Increased transcriptional noise	Single-cell RNA sequencing	Hu/Mk	(Enge et al., 2017; Li et al., 2021b)
			Increased expression of *TTR*	Single-cell RNA sequencing	Mk	(Li et al., 2021b)
			Compromised basic metabolic function	Single-cell RNA sequencing	Mk	
			Increased expression of cellular senescence marker genes, including *CDKN1A* and *CDKN2A*	Single-cell RNA sequencing	Mk	(Li et al., 2021b)
		β cell	Decline in β cell mass	IHC with insulin antibody	Hu	(Mizukami et al., 2014a; Rahier et al., 2008; Saisho et al., 2013)
			Increase in β cell size	IHC with insulin antibody	Hu	(Mizukami et al., 2014a; Saisho et al., 2013)
			Accumulation of lipofuscin bodies	Electron microscopy	Hu	(Cnop et al., 2010)
			Downregulated expression of cellular identity genes, including *MAFA*, *PDX1*, and *NEUROD1*	RNA-seq; Single-cell RNA sequencing; IHC	Hu/Mus	(Aguayo-Mazzucato et al., 2019; Shrestha et al., 2022)
			Decreased proliferation	IHC with Ki67 antibody	Hu	(Mizukami et al., 2014a; Reers et al., 2009)
			Increased transcriptional noise	Single-cell RNA sequencing	Hu/Mk	(Enge et al., 2017; Li et al., 2021b)

Organ	Level		Biomarker	Test methods	Species	Reference
			Increased expression of cellular senescence marker genes, including *Ldha*, *Igf1r, CDKN2A,* SASP factors	qPCR, Microarray analysis; Immunostaining; Bead-based immunoassay; FACS	Hu/Mus	(Aguayo-Mazzucato et al., 2019; Aguayo-Mazzucato et al., 2017; Helman et al., 2016)
			Decreased PDX1 expression	IHC; RT-qPCR	Hu	(Ihm et al., 2007; Mizukami et al., 2014a; Reers et al., 2009)
			Decreased protein level of PDX1, NKX-6.1, NKX-2.2	Immunostaining	Hu	(Shrestha et al., 2022)
			Increased HSP90B1 expression	Single-cell RNA sequencing; IF	Mk	(Li et al., 2021b)
			Increased expression of autophagy-associated proteins, including LC3A/B, LAMP1, Lamp2	Immunostaining; Western Blot	Hu	(Shrestha et al., 2022; Wang et al., 2013b)
			Increased transcription of mTOR signaling genes, *PS6K*	Immunostaining	Hu/Rat	
			Appearance of autophagosomes	Transmission electron microscopy	Rat	
			Increased transcription of *SORL1*	Single-cell RNA sequencing	Mk	(Li et al., 2021b)
			Decline in mitochondrial DNA copy number	Real-time PCR	Hu	(Cree et al., 2008)
			Decline in stimulus–secretion coupling	Ca^{2+} imaging	Hu	(Westacott et al., 2017)
			Reduced glucose-induced inhibition of KATP channel activity	Patch-clamp technique	Mus	(Tuduri et al., 2022)
			Decreased glucose-induced islet NAD(P)H production	NAD(P)H Imaging		

Organ	Level		Biomarker	Test methods	Species	Reference
			Increased glucose-induced Ca^{2+} signaling and voltage-gated Ca^{2+} current	Ca^{2+} Imaging; Patch-clamp technique		
			Increased protein synthesis, unfolding protein response and ER stress (*HSP90B1, HSPA5, XBP1*)	Aggresome staining; Immunostaining; Single-cell RNA sequencing	Hu/Mk/Mus	(Gonzalez-Teuber et al., 2019; Iwawaki et al., 2004; Kalwat et al., 2021; Lee and Lee, 2022; Li et al., 2021b; Shrestha et al., 2022)
		Endothelial cell	Decreased proliferation	IF with VCAM-1/CD31 antibody, etc. and 3D imaging	Hu/Mus	(Chen et al., 2021)
		Stellate cell	Decreased proliferation	BrdU labeling	Rats	(Fitzner et al., 2012)
			Decreased α-SMA expression	RT-qPCR	Rats	

#Note: N.A., Not applicable; Hu, human; Mk, monkey; Mus, mouse; MRI, Magnetic resonance imaging; EUS-elastography: Endoscopic ultrasound elastography; CT, Computed tomography; MRCP, Magnetic resonance cholangiopancreatography; ERCP, Endoscopic retrograde pancreatography; IF, Immunofluorescence; IHC, Immunohistochemistry; HPLC-ECD, High performance liquid chromatography-electrochemical detection.

Table S16 Summary of putative biomarkers of reproductive system aging.

Organ	Level		Biomarker		Test methods	Species[#]	Reference
Ovary	Physiology	N.A	Subfertility		N.A	Hu/Mk/Mus	(Ahmed et al., 2020)
			Irregular menstrual cycle		N.A	Hu	(Broekmans et al., 2009)
	Imaging traits	N.A	Reduced antral follicle count		Transvaginal ultrasonography	Hu	(Secomandi et al., 2022; Wang et al., 2020a; Yureneva et al., 2021)
			Poor ovarian reserve		Modern stereology techniques	Mk	(Tu et al., 2022).
			Poor response to ovarian stimulation		Transvaginal ultrasonography	Hu	(Ata et al., 2019)
	Body fluid	Serum	Elevated FSH		ELISA	Hu	(Secomandi et al., 2022)
		Serum	Downregulated AMH		ELISA	Hu	(Secomandi et al., 2022)
		Serum	Downregulated inhibin-B		ELISA	Hu	(Secomandi et al., 2022)
		Serum	Downregulated Estradiol		ELISA	Hu	(Secomandi et al., 2022)
		Serum	Elevated GnRH		ELISA	Hu	(Secomandi et al., 2022)
	Tissue	Stroma	Increased fibrosis: Collagen I, Collagen II		Masson staining	Mk	(Lliberos et al., 2021; Wang et al., 2020a)
			Increased inflammatory processes	IL-1α/β, TNF-α, IL-6, and inflammasome genes *ASC* and *NLRP3*	Histological analysis/ELISA	Mus	(Lliberos et al., 2021)
				Increased macrophage-derived multinucleated giant cells		Mus	(Foley et al., 2021; Umehara et al., 2022)
			Increased stiffness: increase in collagen		Histological analysis	Hu/Mus	(Amargant et al., 2020)

Organ	Level		Biomarker		Test methods	Species[#]	Reference
			and decrease in hyaluronan				
		Corpus luteum	Dysfunction in progesterone secretion		ELISA	Hu	(Wang et al., 2003b)
		Follicle	Reduced primordial follicle		Hematoxylin & Eosin staining	Hu/Mk	(Wang et al., 2020a)
			Reduced antral follicle		Hematoxylin & Eosin staining/transvaginal ultrasonography	Hu/Mk	(Secomandi et al., 2022; Wang et al., 2020a)
			Increased atretic follicle		Hematoxylin & Eosin staining	Hu/Mk	(Wang et al., 2020a)
		Follicular fluid	Enrichment of ROS damage products		ELISA	Hu/Mk	(Yan et al., 2022)
			Changes of exosomes and exosomal miRNAs		Transmission electron microscopy/Sequencing	Hu	(Revelli et al., 2009; Zhang et al., 2021a)
	Cellular alteration	Oocyte	Increased chromosome mis-segregation and aneuploidy formation		Biopsies of polar bodies/ Immunostaining	Hu	(Capalbo et al., 2013; Christopikou et al., 2013)
			Spindle instability	Downregulated actin cytoskeleton organization	Polarized light microscopy/ RT-qPCR/Immunostaining	Hu	(Gou et al., 2023)
				Reduction of cohesin proteins: Rec8, SA3, SMC1β		Hu/Mus	(Charalambous et al., 2023; Chiang et al., 2010; Duncan et al., 2012; Jessberger, 2010; Liu and Keefe, 2008; Xu et al., 2005)
			Downregulated antioxidant genes: *GPX1*, *GSR*		RT-qPCR/Immunostaining	Mk	(Wang et al., 2020a)
			Telomere shortening: Tet1		RT-qPCR/Immunostaining	Hu/Mus	(Keefe et al., 2006)
			Elevated DNA damage: FMR1		RT-qPCR/Immunostaining	Hu/Mus	(Ruth et al., 2021)

Organ	Level		Biomarker		Test methods	Species[#]	Reference
			Increased DNA oxidation :8-OHdG		Immunostaining	Hu/Mus/Mk	(Lim and Luderer, 2011; Wang et al., 2020a)
			Mitochondrial dysfunction	Decreased mitochondrial biogenesis: Mitochondria copy number, PGC1a	RT-qPCR	Hu/Mus	(Wang et al., 2017b)
				Accumulation of mtDNA mutations	PCR/RT-qPCR	Hu/Mus	(Barritt et al., 2000; Chan et al., 2005)
				Lower mtDNA copy number	RT-qPCR	Hu/Mus	(Chan et al., 2005)
			Improper epigenetic modifications: reduced H3K9me3 modifications		Immunostaining	Hu/Mus	(Li et al., 2021a)
			Elevated inflammatory response		Histological analysis/ELISA	Hu/Mus	(Lliberos et al., 2021)
			Elevated apoptosis		Histological analysis/RT-qPCR	Hu/Mus	(Li et al., 2022a; Yang et al., 2019)
		Granulosa cell	Downregulated antioxidant genes: *IDH1*, *PRDX4*, *NDUFB10*		RT-qPCR/Immunostaining	Hu/Mk	(Wang et al., 2020a)
			Elevated advanced glycation end products (AGEs)		ELISA	Hu/Mus	(Li et al., 2012b; Pertynska-Marczewska and Diamanti-Kandarakis, 2017; Stensen et al., 2014; Tatone and Amicarelli, 2013; Tatone et al., 2008)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			Elevated DNA damage: γH2AX	Immunostaining	Hu/Mus	(Sun et al., 2018)
			Disordered interaction between oocytes and cumulus cells: decreased BMP15, GDF9, and C-KIT	RT-qPCR/Immunostaining	Hu/Mus	(Park et al., 2020)
Testis	Physiology	N.A	Male hypogonadism	N.A	Hu	(Kaufman et al., 2019; Mularoni et al., 2020)
			Decreased testicular function	N.A	Hu	(Johnson et al., 2015; Matzkin et al., 2021; Salonia et al., 2019; Sharma et al., 2015)
			Birth defects in offspring	N.A	Hu	(Laurentino et al., 2020; Potabattula et al., 2020)
	Imaging traits	N.A	Decreased testicular volume	Ultrasound	Hu	(Mahmoud et al., 2003; Well et al., 2007; Yang et al., 2011).
			Reduced hormone production and spermatogenesis	2-deoxy-2-[^{18}F]fluoro-D-glucose-(FDG)-PET	Hu	(Kitajima et al., 2007; Well et al., 2007; Yang et al., 2011)
			Reduction in testicular spermatogenesis function and testosterone level	MRI	Hu	(Wang et al., 2018a)
	Body fluid	Blood	Decrease of total testosterone and free testosterone	Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)	Hu	(Huhtaniemi et al., 2012; Wu et al., 2008)
			Downregulated INSL3	Specific time-resolved fluorescent immunoassay	Hu	(Ivell et al., 2013; Toppari, 2021)
			Downregulated inhibin B	Immunoassay	Hu	(Chong et al., 2017; Haji et al., 1994)
			Downregulated AMH	Immunoassay	Hu	(Chong et al., 2017; Ramezani

Organ	Level		Biomarker	Test methods	Species[#]	Reference
						Tehrani et al., 2017)
		Semen	Reduced sperm count	Phase contrast microscopy	Hu	(Neaves et al., 1984)
			Decreased semen volume	Graduated conical tubes	Hu	(Begueria et al., 2014; Pino et al., 2020; Veron et al., 2018)
			Reduced sperm motility	Cell eosin Y staining and Makler counting chamber	Hu	(Begueria et al., 2014; Johnson et al., 2015; Pino et al., 2020; Veron et al., 2018)
			Reduced sperm function	Sperm DNA fragmentation index (DFI)	Hu	(Chianese et al., 2014; Deenadayal Mettler et al., 2020; Evenson et al., 2020; Rosiak-Gill et al., 2019)
	Tissue	Seminiferous tubules	Mosaic of seminiferous tubular lesions	Hematoxylin & Eosin staining	Hu	(Perheentupa and Huhtaniemi, 2009)
			Basement membrane and tunica albuginea thickening	Immunostaining	Hu/Mk/Mus	(Dakouane et al., 2005; Gosden et al., 1982; Huang et al., 2022a; Johnson, 1989; Johnson et al., 1984)
			Thinning of the seminiferous epithelium	Hematoxylin & Eosin staining	Hu	(Regadera et al., 1985; Sasano and Ichijo, 1969)
			Narrowing of tubular diameter	Hematoxylin & Eosin staining	Hu	(Perheentupa and Huhtaniemi, 2009)
		Stroma	Interstitial fibrosis	Masson staining	Hu/Mk	(Huang et al., 2022a; Perheentupa and Huhtaniemi, 2009)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
	Cellular alteration	Germ cells	DNA damage and defects in DNA methylation-related molecules: DNMT1 and Np95	RT-qPCR/Immunostaining	Rat	(Selvaratnam et al., 2015; Takada et al., 2021)
		Sertoli cells	Decreased WT1; Reduced expression of junction components proteins: ZO-1, Claudin 11, Jam2, Ocln and Ctnna	RT-qPCR/Immunostaining	Hu/Rat/Mk	(Huang et al., 2022a; Paniagua et al., 1985; Paul and Robaire, 2013)
		Leydig cells	Upregulated inflammatory marker: cyclooxygenase-2 (COX2) and senescence-associated markers: p53, p21	RT-qPCR/Immunostaining	Rat/Mus	(Chen et al., 2007; Wang et al., 2005; Zhang et al., 2020)
			Upregulated ROS production genes: *PRDX6*, *SOD2*, *MT2A*, *MT1X*, *NAMPT*, and *HIF1A*	RT-qPCR/Immunostaining	Hu	(Nie et al., 2022)
			Downregulated capacity of testosterone secretion genes: *Star*, *Cyp17a1*, *Cyp11a1*, *Hsd3b6*, *Hsd17b3*, and LH receptors	RT-qPCR/Immunostaining	Rat/Mus	(Amador et al., 1985; Curley et al., 2019)
			Upregulated suppress cell survival and proliferation suppressors: *PTEN*, *RHOB*, and *ROCK1/2*	RT-qPCR/Immunostaining	Hu	(Nie et al., 2022)
			Upregulated smooth muscle contraction genes: *ACTA2*, *MYH11*, *TPM1/2*, *MYL9*, and *FLNA*	RT-qPCR/Immunostaining	Hu	(Nie et al., 2022)

#Note: Hu, human; Mk, monkey; Mus, mouse.

Table S17 Summary of putative biomarkers of immune system aging.

Organ	Level		Biomarker	Test methods	Species[#]	Reference
Immune	Physiology	N.A	Compromised organismal barriers	N.A	Hu/Mus	(Lian et al., 2020; Rodrigues et al., 2021)
			Excessive inflammatory signaling	N.A	Hu/Mus	
			Degeneration of thymus, exhaustion of adaptive immunity	N.A	Hu/Mus	
	Imaging traits	N.A	Fat cells increase in bone marrow	magnetic resonance imaging (MRI)	Hu	(Blebea et al., 2007)
	Cellular alteration	Macrophages	Decreased Macrophages subset: alveolar macrophages; peritoneal macrophages Increased Macrophages subset: abundance of Fn1+ Ccr2+ interstitial macrophages; CX3CR1+ macrophages in the liver kidney; fetal-derived macrophages in mammary tissue	scRNA-seq; flow cytometry; microscopy	Mus	(Angelidis et al., 2019; Ide et al., 2020; Li et al., 2020; Linehan et al., 2014; McQuattie-Pimentel et al., 2021; Mogilenko et al., 2022; Mogilenko et al., 2021; Wong et al., 2017)
		Neutrophils	Declined migration and phagocytic ability; Susceptibility to the apoptosis process	scRNA-seq; flow cytometry	Hu/Mus	(Brubaker et al., 2013)
		Natural killer (NK) cells	Declined cytotoxicity; Decreased production of cytokines and chemokines; Decreased interaction with DC and macrophages; Downregulated genes: NKp30, NKp46, DNAM-1, NKG2A Upregulated genes: KIR, NKG2C, CD57	scRNA-seq; flow cytometry	Hu/Mus	(Manser and Uhrberg, 2016; Solana et al., 2018; Solana et al., 2012)
		Dendritic cells	Decreased abundance; Decreased production of IFN I and IFN II Increased production of IL-6 and TNF-a,	scRNA-seq; flow cytometry	Hu/Mus	(Agrawal and Gupta, 2011; Gupta, 2014; Jing et al., 2009; Mogilenko et al., 2022; Stervbo

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			lower MHC II molecular expressions in cell surface			et al., 2015),
		T cells	Declined naïve T cell frequency; Increased memory T cell frequency; Declined TCR diversity Downregulated genes: CD27, CD28, Lck, ZAP70, DLG1, Lat, SLP-76, Perforin, GzmB Upregulated genes: P16, P21, P53, CD57, KLRG-1, Tim-3, TIGIT, CD45RA	scRNA-seq; flow cytometry	Hu/Mus	(Rodier et al., 2009; Zhao et al., 2020). (Lian et al., 2020; Mittelbrunn and Kroemer, 2021; Zhang et al., 2021b)
		B cells	Declined naïve B cells frequency; Increased memory B cell frequency; Impaired B cells activation; Impaired ability of forming antibodies; Downregulated genes: CD27, CD40	scRNA-seq; flow cytometry	Hu/Mus	(El-Naseery et al., 2020; Johnson et al., 2002; Pinti et al., 2016)
	Body fluid	Blood	Pro-inflammation factors associated with CLIP (IL6,CRP,TNFα,IL1,IL8,*ect*)	ELISA	Hu	(Chen et al., 2019; Rusanova et al., 2018)
			LncRNA NEAT1 and MALAT1 in exhausted T cells and monocytes associated with aging and frailty	single-cell transcriptome seq	Hu	(Luo et al., 2022)
			LncRNA THBS1-IT1 and THBS1-AS1 in WBC	qPCR	Hu	(Jiang et al., 2021)
			LncRNA NRON in both $CD28^{null}CD8^{+}$ T cells and $CMV_{pp65}CD8^{+}$ T cells	qPCR	Hu	(Wang et al., 2019b)
			LncRNA NONHSAT069381 and NONHSAT140844 in blood sample	qPCR	Hu	(Zhao et al., 2021)
			miR-223 in circulating neutrophils	qPCR	Hu/Mus	(Ruixue Ren et al., 2022)
			miR-34a and miR-9 in PBMC	qPCR	Hu	(Budzinska et al., 2016; Owczarz et al., 2017)

Organ	Level		Biomarker	Test methods	Species[#]	Reference
			miR-96 and miR-145 in PBMC	qPCR	Hu	(Budzinska et al., 2016)
			miR-21, miR-146a, miR-223 and miR-483 in blood sample	qPCR	Hu	(Rusanova et al., 2018)
			miR-181a in T cells	qPCR	Hu	(Kim et al., 2021; Li et al., 2012a; Ye et al., 2018)
			miR-181a-5p in NK cells	qPCR	Hu	(Lu et al., 2021)
			miR-125b in monocytes and naïve CD8 T cells	qPCR	Hu	(Cheng et al., 2015)
		Urine	Urinary C-peptide of insulin	Radioimmunoassay	Mk	(Sacco et al., 2021)
			Thyroid hormones	ELISA	bonobos and chimpanzees	(Behringer et al., 2014)
			Neopterin	HPLC, ELISA	Hu	(Cooper et al., 2022; Svoboda et al., 2008)
			8-hydroxy-2'-deoxyguanosine	HPLC	Hu	(Svoboda et al., 2008)
			SASP factors in EV	Capture sandwich assay	Hu	(Yeh et al., 2021)
			Cell-Free Mitochondrial DNA	qPCR	Hu	(Carrie D Johnston et al., 2021)
		CSF	Lipid transport genes (e.g., APOE, APOC2 and APOBR) in non-classical monocytes	single-cell transcriptome seq	Hu	(Piehl et al., 2022)
			Kynurenine pathway metabolites	LC-MS/MS	Hu	(Solvang et al., 2022)
			TNF-α, IL-10, IP-10 and IL-8	ELISA	Hu	(Hu et al., 2019)
			CCL11	ELISA	Hu/Mus	(Huber et al., 2018)

#Note: Hu, human; Mk, monkey; Mus, mouse.

Table S18 Phenotypic aging clocks.

Types	Sources	Algorithm	Evaluation	Metrics (in years)	Reference
Phenotypes	Eye corner images	DNN	--	MAE = 2.30	(Bobrov et al., 2018)
Phenotypes	3D facial images	SVR (linear kernel) and PLSR	Definition of slow and fast agers supported by levels of health indicators	MAE = 6.1	(Chen et al., 2015)
Phenotypes	3D facial images	CNN	Association with health parameters (n>20) and lifestyles	MAE = 2.8 for age; MAE =2.9 for perceived age	(Xia et al., 2020)
Phenotypes	Brain MRI data	CNN	--	MAE = 4.65	(Cole et al., 2017)
Phenotypes	Brain MRI data	3D CNN	Association with early signs of Alzheimer's disease	MAE = 2.3	(Yin et al., 2023)
Phenotypes	Psycho-social questionnaires	DNN	Predictive of all-cause mortality risk	MAE = 6.70 for age; MAE = 7.32 for perceived age	(Zhavoronkov et al., 2020)

DNN: deep neural network; SVR: support vector regression; PLSR: partial least squares regression; MRI: magnetic resonance imaging; CNN: convolutional neural network;

Table S19 Transcriptomic aging clocks.

Types	Sources	Algorithm	Evaluation	Metrics (in years)	Reference
Transcriptomics	Human peripheral blood	Linear regression	Associations with some biomarkers and risk factors	MAE = 7.80	(Peters et al., 2015)
Transcriptomics	Human dermal fibroblasts	Ensemble ML classifiers	Detecting accelerated ageing in progeria samples	MAE = 4.0	(Fleischer et al., 2018)
Transcriptomics	Human skeletal muscle	Deep feature selection model	--	MAE = 6.19	(Mamoshina et al., 2018)
Transcriptomics	Caenorhabditis Elegans and human fibroblasts	Binarized data with ElasticNet regression	Detecting accelerated ageing in progeria samples	MAE = 6.63	(Meyer and Schumacher, 2021)
Transcriptomics	Human epidermal skin samples	Knowledge-primed artificial neural networks	Model responded in expected ways to known perturbations of biological age in silico	MeAE = 4.71	(Holzscheck et al., 2021)
Transcriptomics	Human $CD8^+$ T cells (single cell)	Mixed-effect ElasticNet	Associations with differentiation and mutation burden	--	(Lu et al., 2022)

Types	Sources	Algorithm	Evaluation	Metrics (in years)	Reference
Transcriptomic	Mouse subventricular zone neurogenic region (single cell)	Lasso and ElasticNet regression	Quantification of transcriptomic rejuvenation	Error = 2.3–4.6 (months)	(Buckley et al., 2023)

Table S20 Summary of metabolic aging clocks.

	Data resource	Clock name	Source	Number	Age range	Resource	Detection approach	Algorithm	Error range (in years)	Reference
1	Metabolomics	Metabolic score	Baltimore cohort	N= 212,157	20-79 years	Urine	^{1}H-NMR	MFP	RMSE = 11.19 for men RMSE = 10.37 for women	(Hertel et al., 2016)
2	Metabolomics	metaboAge	BBMRI-NL	N = 25,253	18-85 years	Blood	^{1}H-NMR	Linear	Median error = 7.3	(van den Akker et al., 2020)
3	Metabolomics	Metabolomic age	The UK Airwave cohort	N = 2,239	19.2-65.2 years	Blood and urine	Multiple platforms	Linear	MAE = 3.96	(Robinson et al., 2020)
4	Metabolomics	Metabolomic age predictor	The KarMe study	N = 301	18-80 years	Blood and urine	Multiple platforms	SVMlinear, glmnet, PLS	RMSE = 8.31-10.98 for men RMSE = 9.02-10.88 for women	(Rist et al., 2017)
5	Metabolomics	Metabolomic Aging Clock	This study	N = 85	20-86 years	CSF	Multiple platforms	Linear	MAE = 6.91-12.85	(Hwangbo et al., 2022)

^{1}H-NMR, proton nuclear magnetic resonance; MFP, multivariable fractional polynomial procedure; RMSE, root mean squared error; MAE, mean absolute error; SVM, support vector machine; PLS, partial least squares; CSF, cerebrospinal fluid.

Table S21 Aging clocks at single-cell resolution.

Data resource	Clock name	Species	Age	Sample Number	Cell Number	Reference
Methylome	scAge	Mouse	1.5 months - 26 months	12	301	(Trapp et al., 2021)
Methylome	PRC2 clock	Mouse	2 months - 22 months	8	95	(Moqri et al., 2022)
Methylome	Tarkhov clock	Mouse	2 months - 24 months	6	275	(Tarkhov et al., 2022)
ATAC-seq	EpiTrace	Human	Cultured hematopoietic stem cells for 20 days	--	800	(Rechsteiner et al., 2022)
Transcriptome	GERAS	Zebrafish	1 mpf - 14 mpf	6	827	(Singh et al., 2018)
Transcriptome	Buckley clock	Mouse	3 months - 29 months	28	21,458	(Buckley et al., 2022)
Transcriptome	Neumann clock	Mouse	3 months - 24 months	19	33,785	(Neumann et al., 2023)
Transcriptome	Lu clock	Human	Newborn - 90 years	24	120,418	(Lu et al., 2022)

Table S22 Characteristics of imaging modalities in aging clocks.

Imaging modality	Stage	Spatial resolution	Invasion	Imaging content	Merits	Demerits	Imaging agents	Applications in aging clocks	Reference
PET/CT	Preclinical and clinical	3 mm	No	Molecular and functional changes; morphological changes	Relatively short scanning time; whole-body view	Radiation; complicated processes of radioprotection; high cost	Radionuclides (e.g., ^{18}F, ^{11}C, ^{68}Ga) labeled ligands	Molecular and functional changes of aging clocks	(Paydary et al., 2021; Prenosil et al., 2022)
PET/MRI	Preclinical and clinical	3 mm	No	Molecular and functional changes; morphological changes	High-resolution of soft tissues	Radiation; complicated processes of radioprotection; high cost	Radionuclides (e.g., ^{18}F, ^{11}C, ^{68}Ga) labeled ligands	Molecular and functional changes of aging clocks	(Yan et al., 2020)
SPECT/CT	Preclinical and clinical	3-5 mm	No	Molecular and functional changes; morphological changes	Easily available imaging agents; economic;	Radiation; relatively low spatial resolution	Radionuclides (e.g., ^{99m}Tc, ^{131}I, ^{111}In, ^{18}F) labeled ligands	Molecular and functional changes of aging clocks	(Ritt, 2022; Zhou et al., 2021)
MRI	Preclinical and clinical	2 mm	No	Functional and morphological changes	High-resolution of soft tissues; non-radiation	Relatively long scanning time; strict contraindications	Gadolinium contrast media	Functional and morphological changes of aging organs	(de Lange et al., 2020)

Imaging modality	Stage	Spatial resolution	Invasion	Imaging content	Merits	Demerits	Imaging agents	Applications in aging clocks	Reference
Ultrasound	Preclinical and clinical	25-50 μm	No	Functional and morphological changes	Convenient; economic; non-radiation	Narrow field of view	Lipid microbubble; nanobubble	Morphological alterations of aging organs	(Brown et al., 2020; Stelwagen et al., 2020)
Photoacoustic imaging	Preclinical and clinical	1–10 μm	Yes	Molecular and functional changes	Super high resolution; high sensitivity	Limited penetration depth	Nanoparticles and organic dyes	Molecular and functional changes of aging related diseases	(Lin and Wang, 2022)
Near-infrared (NIR) fluorescent imaging	Preclinical and clinical	4 μm	No	Molecular and functional changes	Super high resolution; high sensitivity	Limited penetration depth; lack of approved imaging agents	Nanoparticles	Molecular and functional changes of aging related diseases	(Dang and Yan, 2021; Li et al., 2022b)

Table S23 Summary of PET imaging application in aging clocks.

Imaging scale	Hallmarks	Studied aspects	Imaging targets	Direct/Indirect observation	Imaging modality	Imaging agents	Reference
Cell molecular level	Genomic instability	DNA damages	PARP	Direct	PET	^{18}F-FTT, ^{18}F-PARPi, ^{18}F-olaparib	(Pantel et al., 2022; Schöder et al., 2020; Wilson et al., 2019)
			γH2AX	Direct	PET	^{89}Zr-anti-γH2AX-TAT	(Knight et al., 2017)
	Epigenetic alterations	DNA methylation	DAT	Indirect	PET	^{18}F-FP-CIT	(Pak et al., 2021)
			MGMT	Indirect	PET	^{11}C-MET	(Yu et al., 2019)
		Histone modification	HDAC	Direct	PET	^{11}C-MS-275, ^{11}C-Martinostat, ^{18}F-SAHA	(Hendricks et al., 2011; Hooker et al., 2010; Pascoal et al., 2022)
			HDAC	Indirect	PET	^{18}F-FDG	(Schroeder et al., 2013)
	Telomere attrition	Telomerase function	hTERT	Direct	PET	hyperpolarized [U-^{13}C, U-^{2}H]-glucose	(Viswanath et al., 2021)
	Loss of proteostasis	Chaperones	HSP	Direct	PET	^{124}I- labeled monoclonal antibody, ^{11}C-NMS-E973	(Vermeulen et al., 2019; Wick et al., 2014)
		Autophagy	Autophagy induced hypoxia	Direct	PET	^{18}F-EF5, ^{18}F-HX4	(Levy et al., 2017)
Organ level	Misfolded proteins in the brain	Aβ plaques	Aβ	Direct	PET	^{11}C-PiB, ^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben	(Blazhenets et al., 2020; Cho et al., 2020; Vemuri et al., 2019)
				Indirect	PET	^{18}F-FDG	(Doering et al., 2021)
		Tau proteins	Tau	Direct	PET	^{18}F-AV1451	(Ossenkoppele et al., 2021; Schöll et al., 2016)

Imaging scale	Hallmarks	Studied aspects	Imaging targets	Direct/Indirect observation	Imaging modality	Imaging agents	Reference
	Oxidative stress in the heart	Mitochondrial dysfunction	Mitochondrial membrane potential	Direct	PET	^{18}F-TPP^{+}	(Pelletier-Galarneau et al., 2021a; Pelletier-Galarneau et al., 2021b)
			Mitochondria	Direct	Dual-modal imaging (PET and fluorescence imaging)	^{18}F-5MEF	(Zheng et al., 2022)
	Chronic inflammation in the blood vessel	Atherosclerotic plaques	Microcalcification activity	Direct	PET	^{18}F-NaF	(Kaczynski et al., 2022)
			Macrophage density	Indirect	PET	^{18}F-FDG	(Chaker et al., 2019; Tawakol et al., 2006)

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