Data driven interventions in aging

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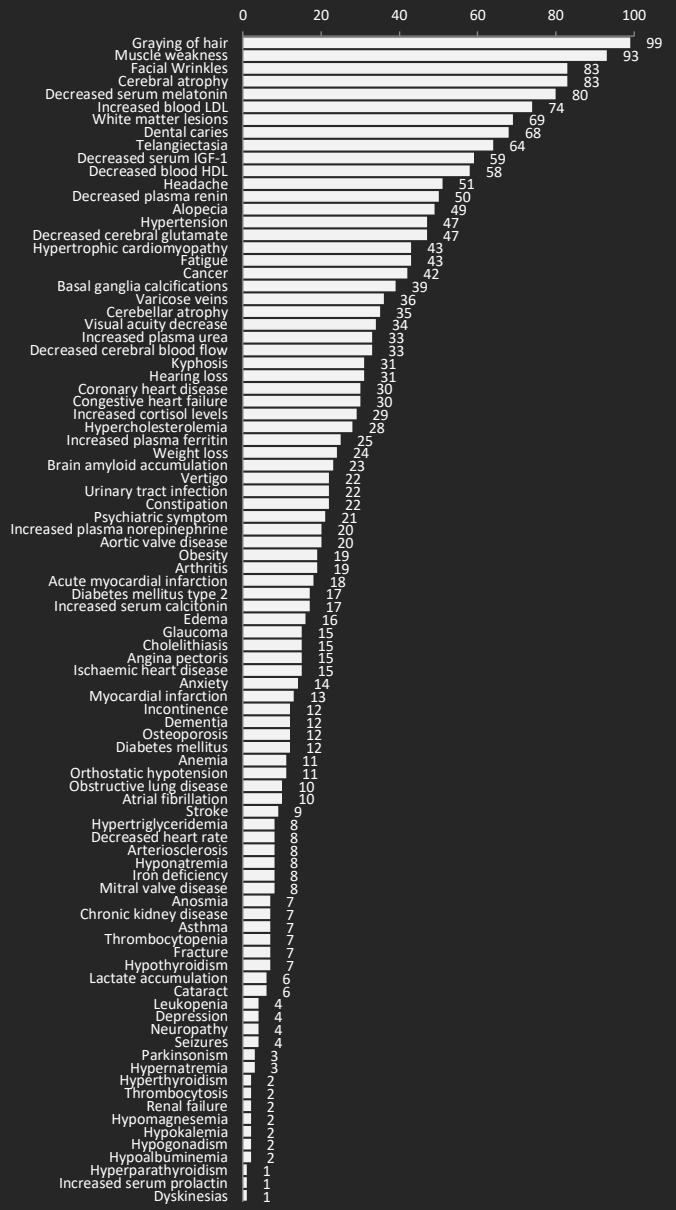
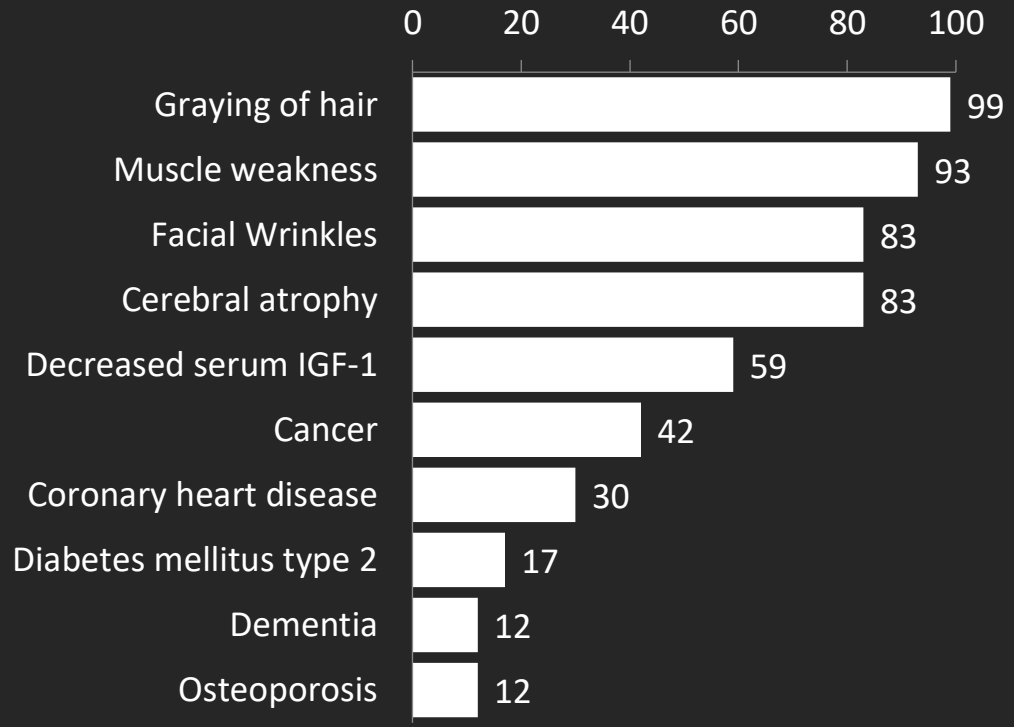
Disclaimer:
MSK is the founder of Forsoegsperson.dk, Soosys.com and Tracked.bio and consults for the Healthy Longevity Clinic, Longevity Vision Fund, Deep Longevity and Novo Nordisk





Andreassen, Ben Ezra, Scheibye-Knudsen, Aging, 2019

Phenotypes from healthcare records

Can we find patterns of aging in 33 million pathology reports?

Hospital Name
Address

Surgical Pathology Report

Patient: Last Name, First Name
MRN: Medical Record Number
DOB: Date of Birth (Age: #)
Gender: M/F

Accession Number: **Specimen Identification**
Procedure: Date
Attending: Doctor's Name

Clinical History: Large Gastric Mass

Specimen: Gastric Mucosa

Diagnosis

Stomach, Partial Gastrectomy:

- Malignant Epithelioid Gastrointestinal Stromal Tumor
- Tumor Size 10 x 9 x 8 cm
- Cell Type: Epithelioid and Spindled
- High cellularity; present
- Mucosal Invasion: Focally present adjacent to ulceration
- Mucosal ulceration present
- Mitotic Count: 10/50 HPF
- Myxoid background: Focally present
- Foci of necrosis present
- CD117, vimentin, and CD34: uniformly positive

Gross Description

The specimen consists of an approximately 5 x 7 cm portion of gastric mucosa that is surrounded and underlying by a lobulated mass which is 10 x 9 x 8 cm. The central portion of the mass appears to have an approximately 1.5-cm ulcer. The mucosa away from the area of ulceration is partially removed from the underlying tumor. The underlying mass appears encapsulated and lobular. Gross sections show the lesion to consist of several different patterns. A single area has a gray to gray-tan pattern with an area of central necrosis showing a fairly uniform appearance whereas; other regions of the tumor are gray white- and somewhat lobular in appearance. Areas of yellow necrosis are scattered through the tumor. Representative portions submitted.

Microscopic Description

Sections through the neoplasm show it to be primarily a high cellular neoplasm. The cells are in part arranged in fascicles and clusters with enlarged elongate nuclei having relatively find nucleoli. In some areas, the fascicles have an interwoven appearance. Mitotic figure up to 10:50 HPF. A few areas show foci of necrosis with the cells appearing to be surrounded by somewhat myxoid stroma. Foci of displayed necrosis are present. The lesions appear circumscribed, although not specifically encapsulated. It focally involved the mucosa and shows full thickness ulceration. The tumor immediately beneath the mucosal area of ulceration has a nearly lobular somewhat spindled growth pattern. Some areas of the

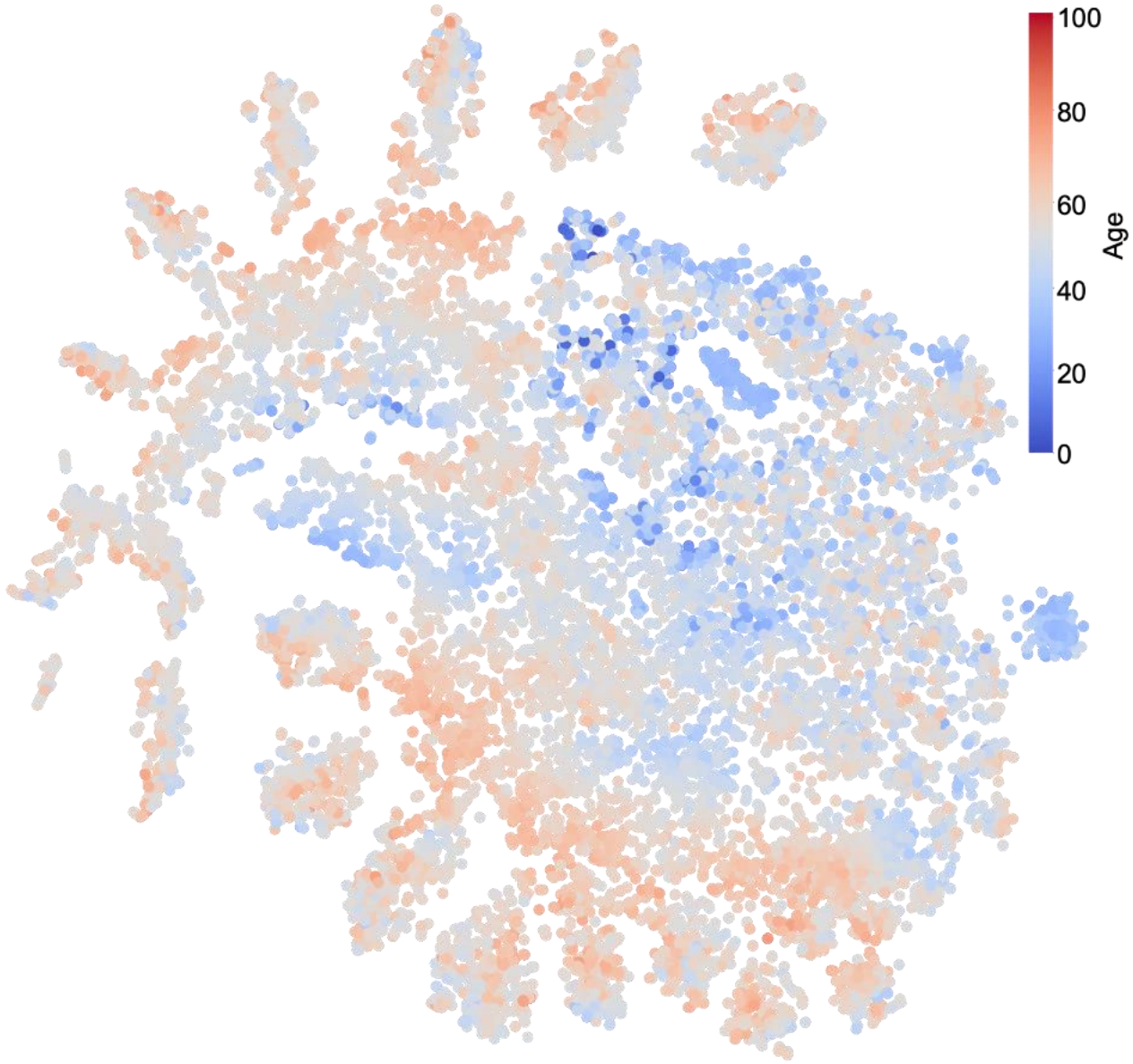
Clinical feature matrix

~10K features (words)

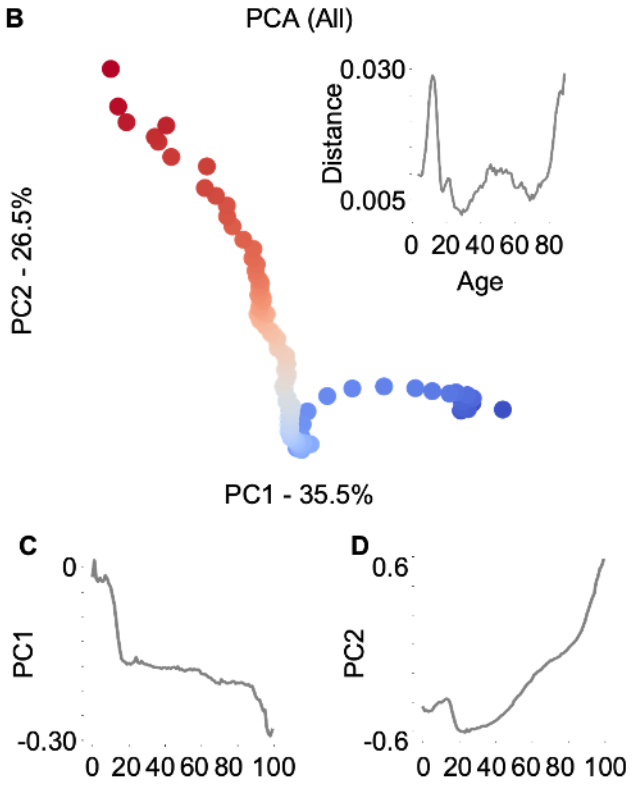
33,3M reports

	Neoplasia	Granuloma	Macrophage	Lymphocyte	Osteoclast	Fat necrosis	Giant cell	...
Report 1	1	1	1	1	1	1	1	...
Report 2	0	0	0	0	0	0	0	...
Report 3	0	0	0	0	0	0	0	...
Report 4	0	0	0	1	0	0	0	...
Report 5	0	0	0	0	1	0	0	...
Report 6	0	0	0	0	0	0	0	...
Report 7	0	0	0	0	0	0	1	...
...	...	...	...	...	...	...	...	...

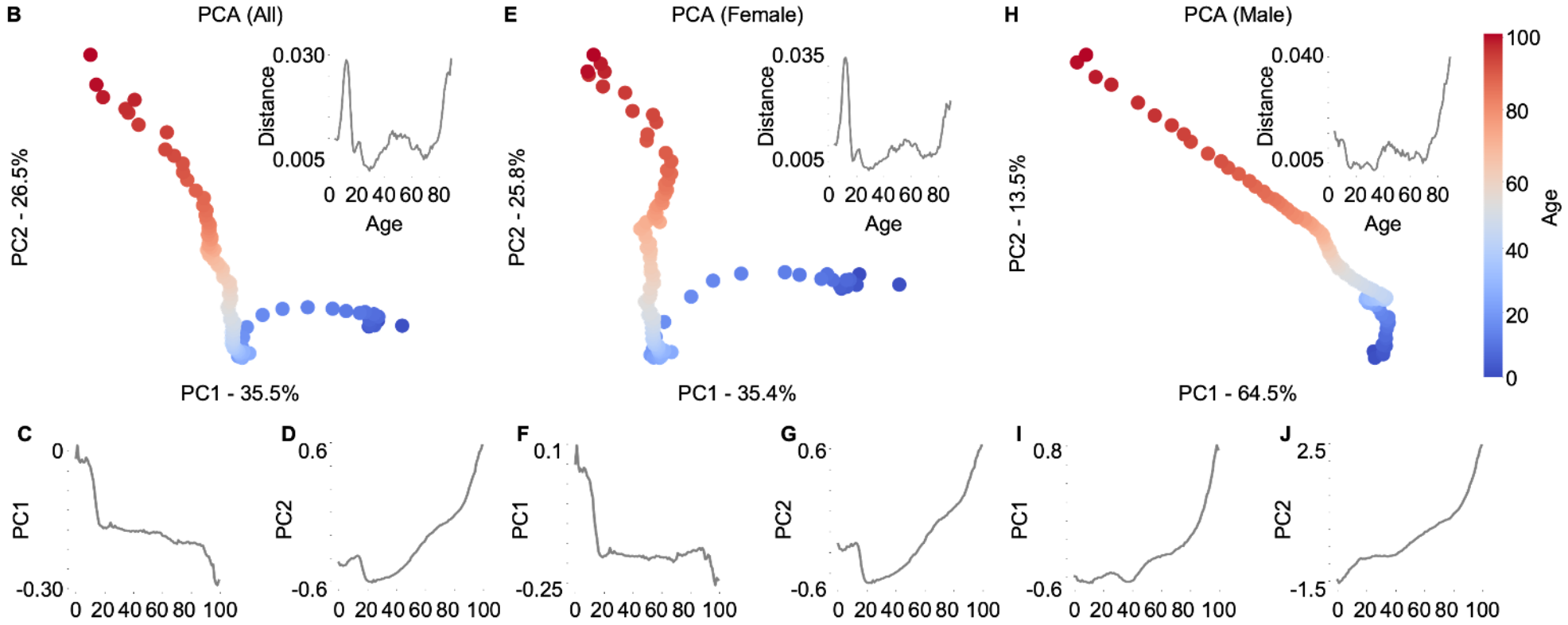
The chaotic nature of aging



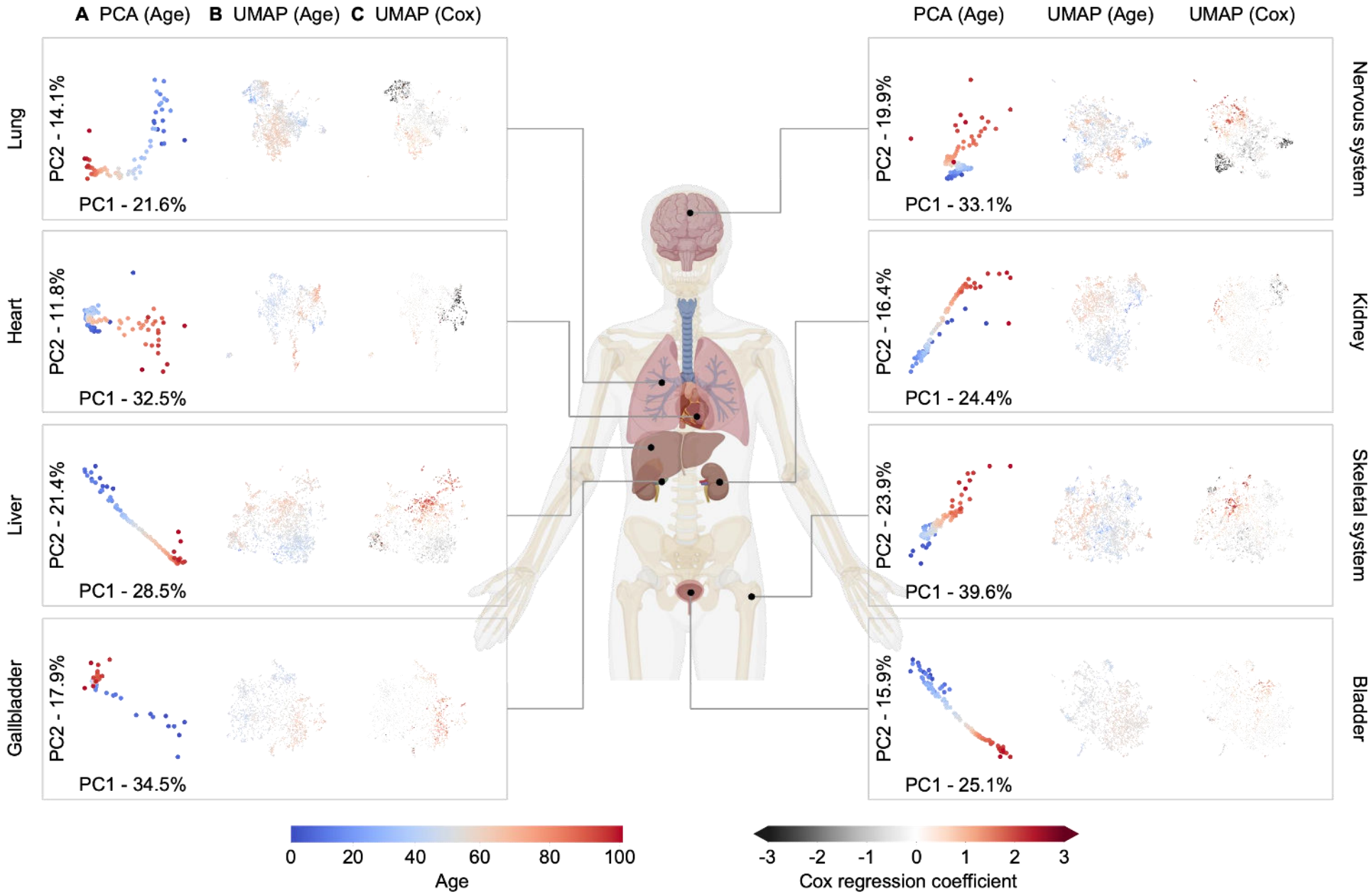
Records strongly correlate with age



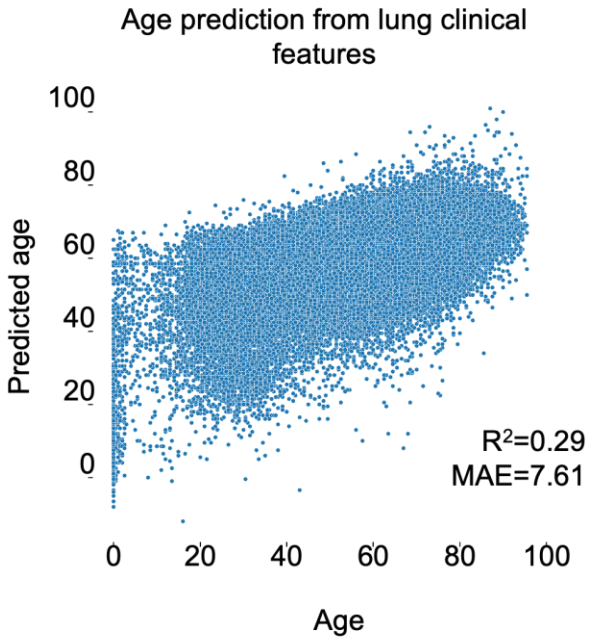
Males age faster but later and females earlier but slower



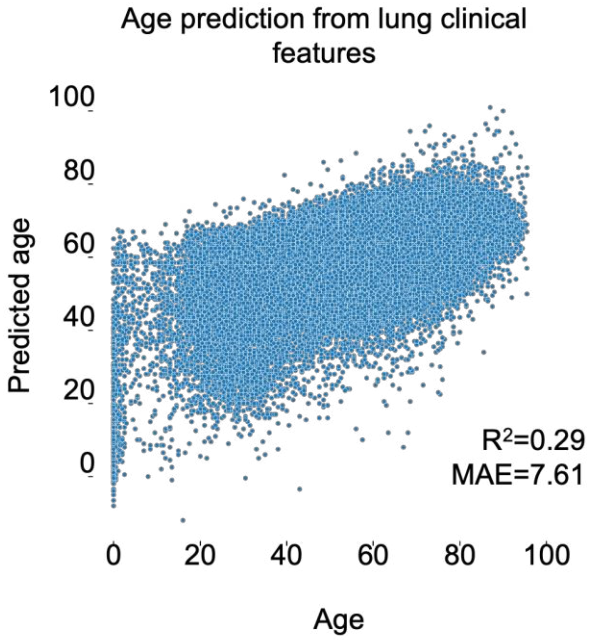
Tissue specific aging trajectories

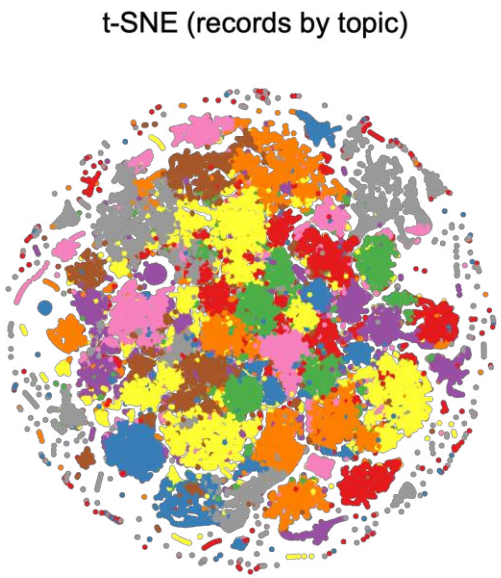


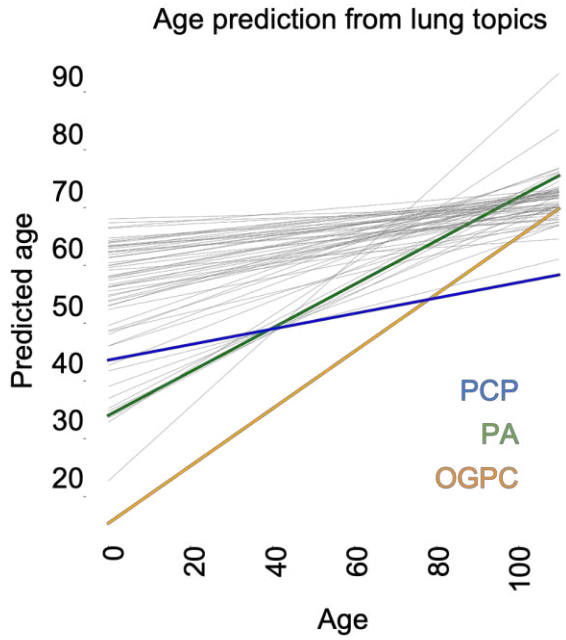
Predicting age from terms

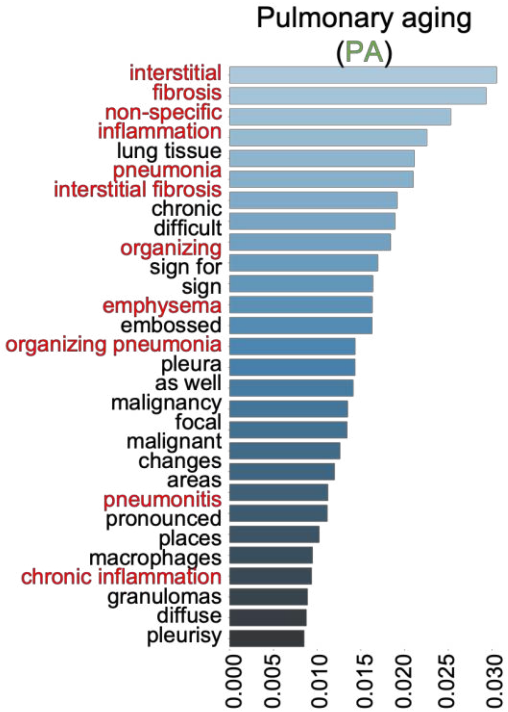


Predicting age from topics

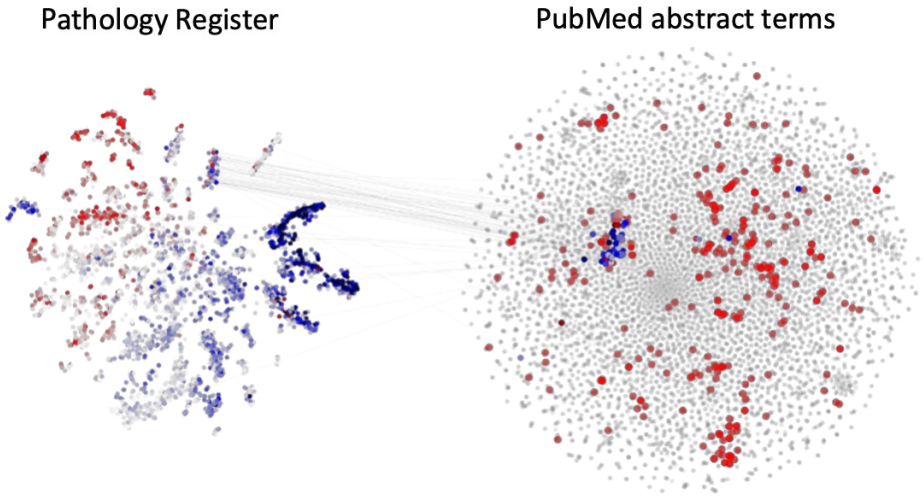








Identifying compounds targeting aging



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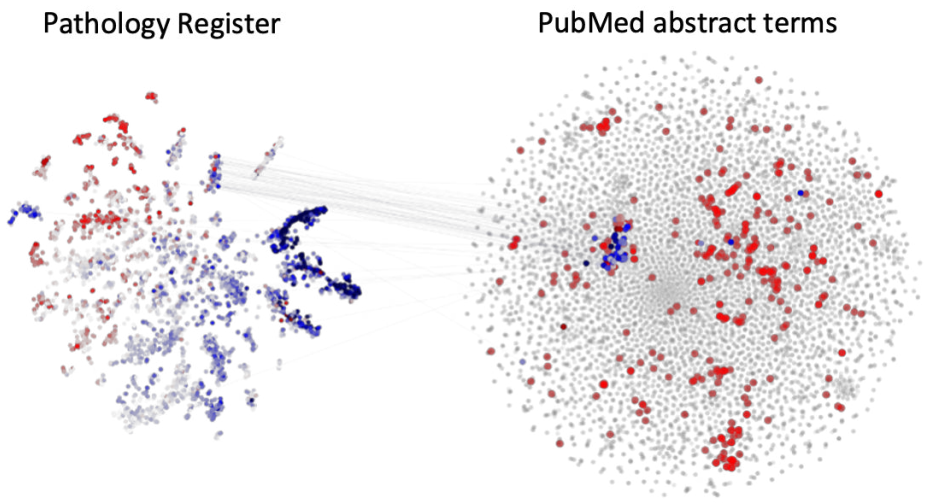
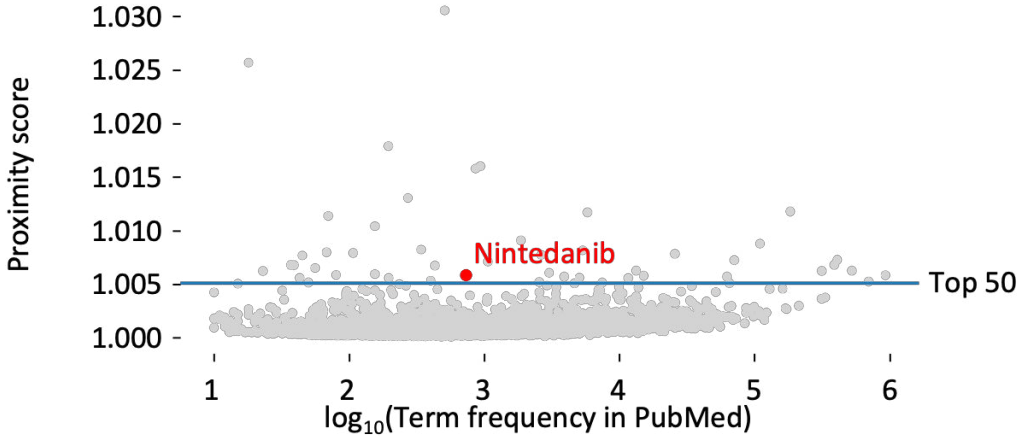
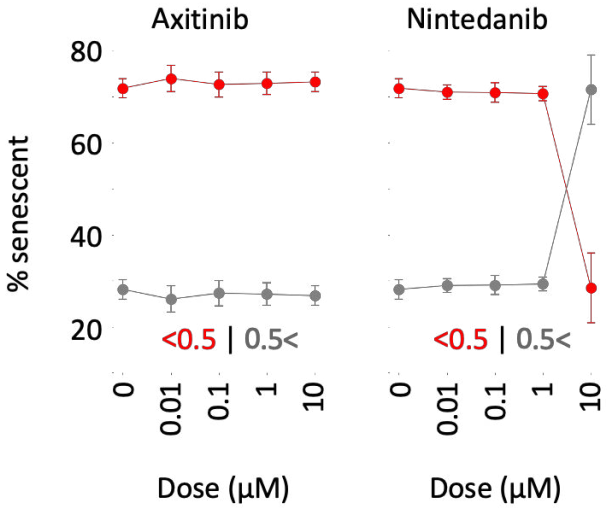
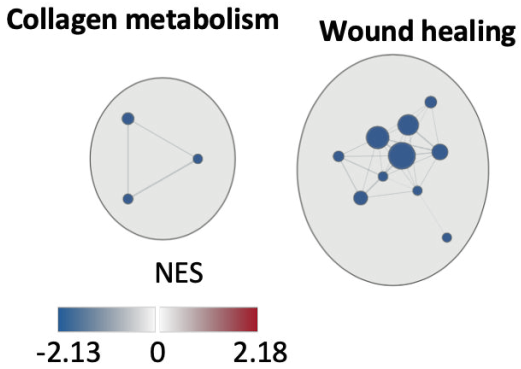
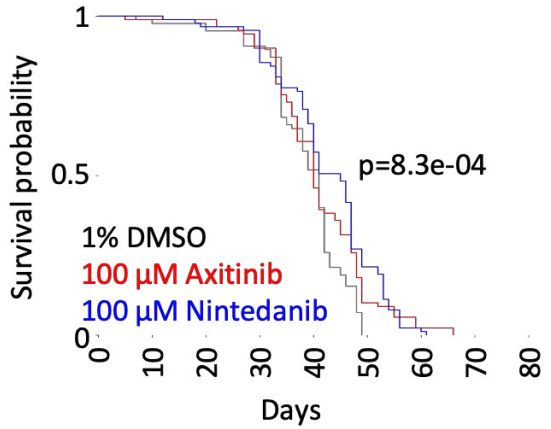




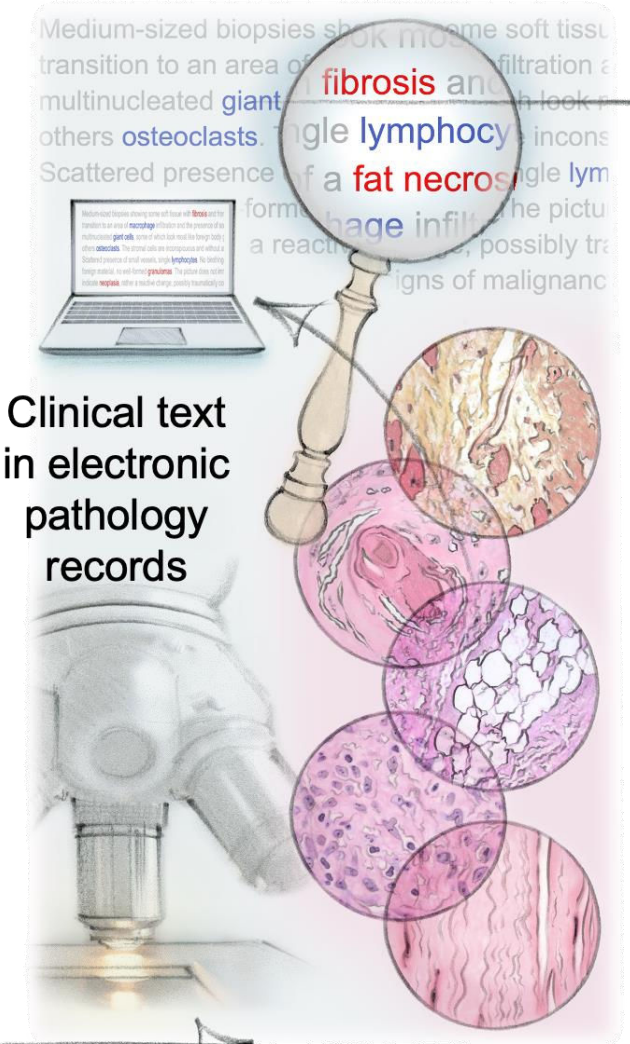




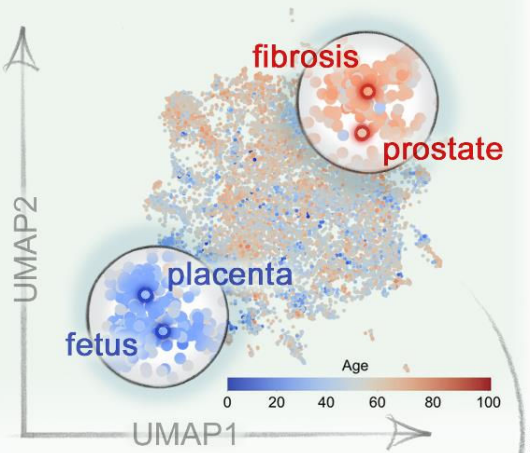


33 million histological samples

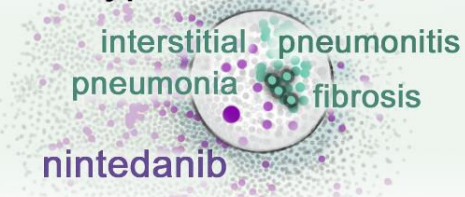
Clinical text in electronic pathology records



The human pathome

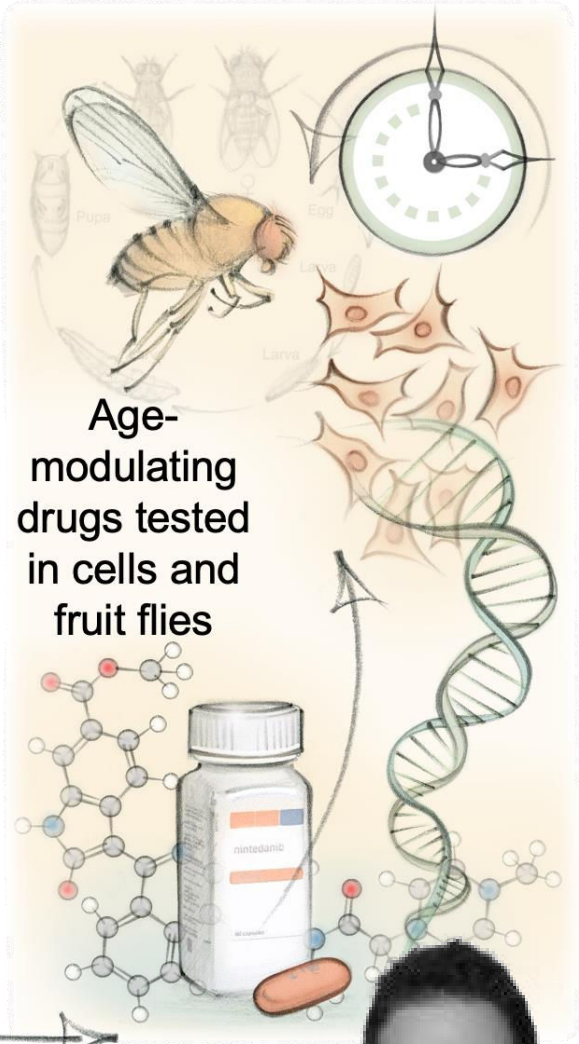


Thousands of age and mortality associated phenotypes



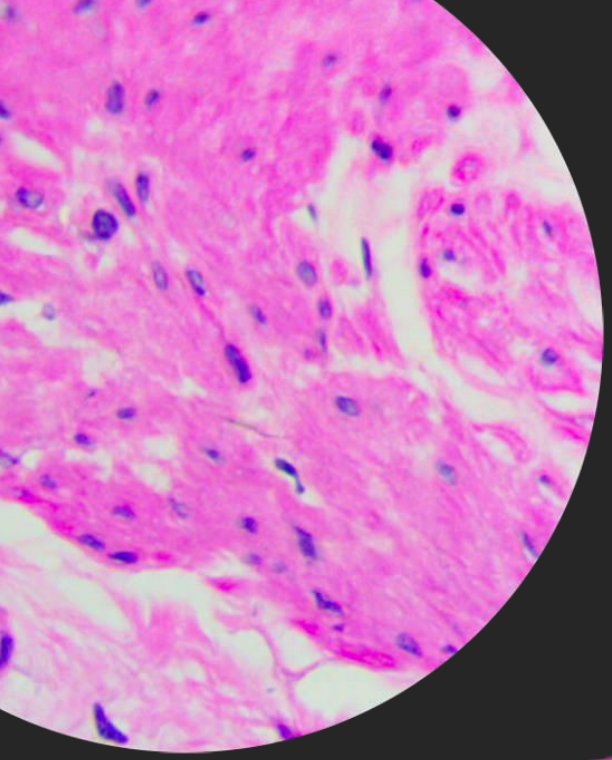
Cross-referencing in PubMed for aging interventions

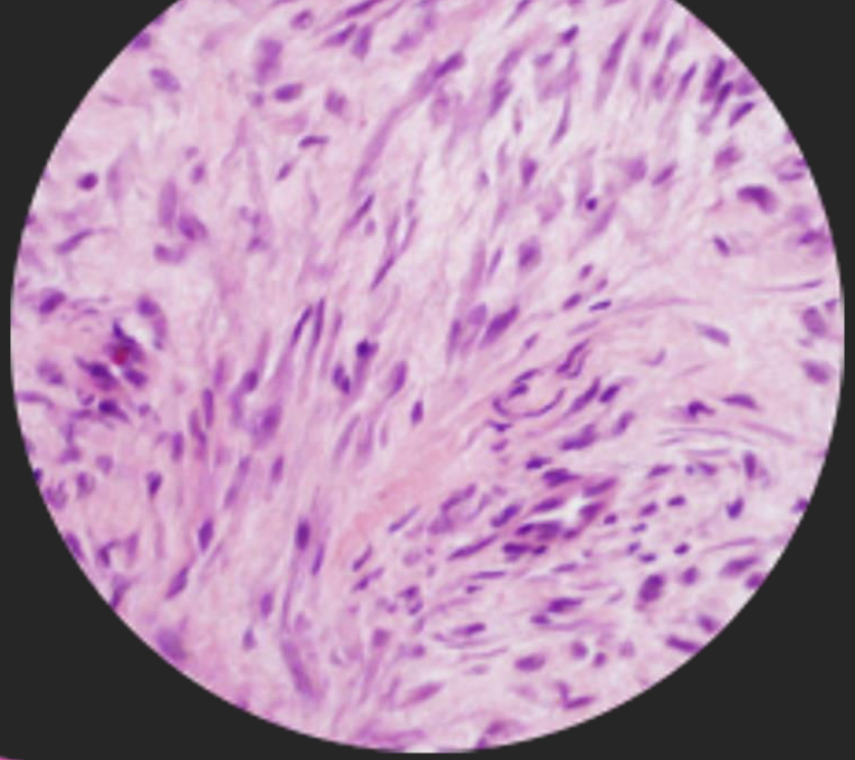
Age-modulating drugs tested in cells and fruit flies

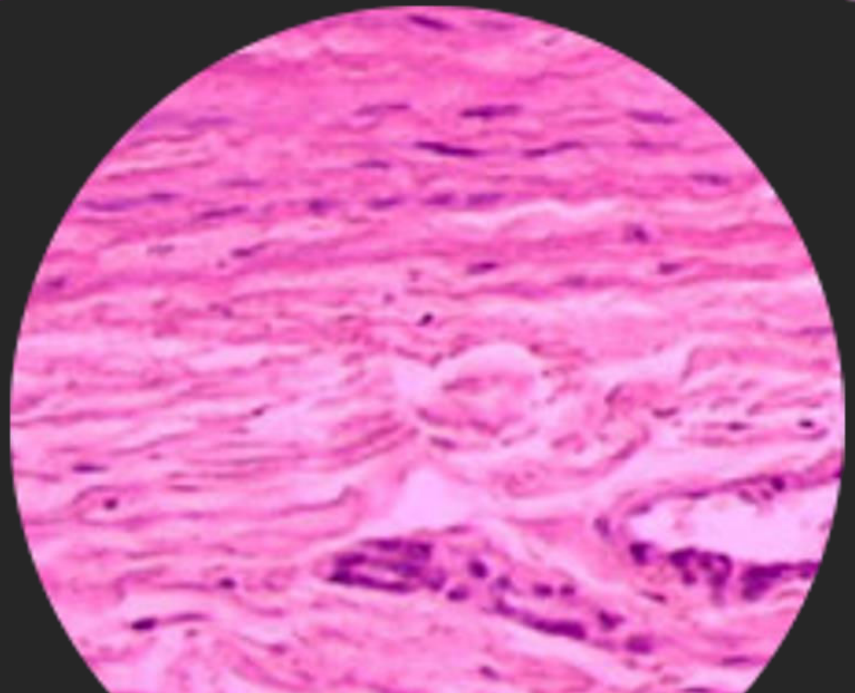


www.pathoage.com

Michael Ben Ezra



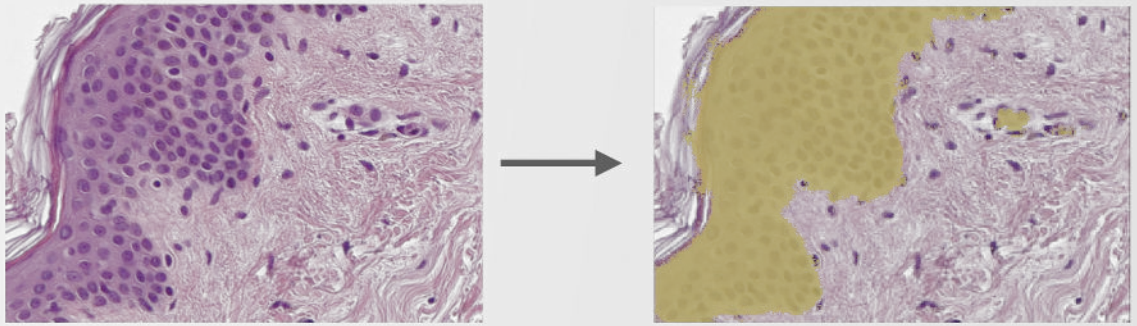




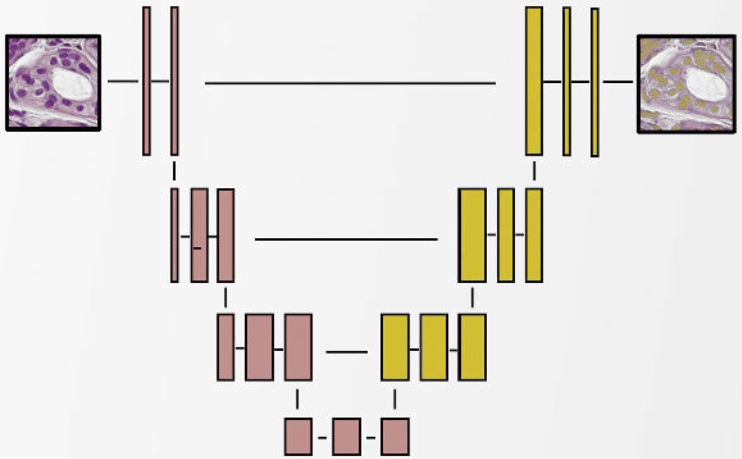
Can we predict age from tissues?

Detection and Segmentation

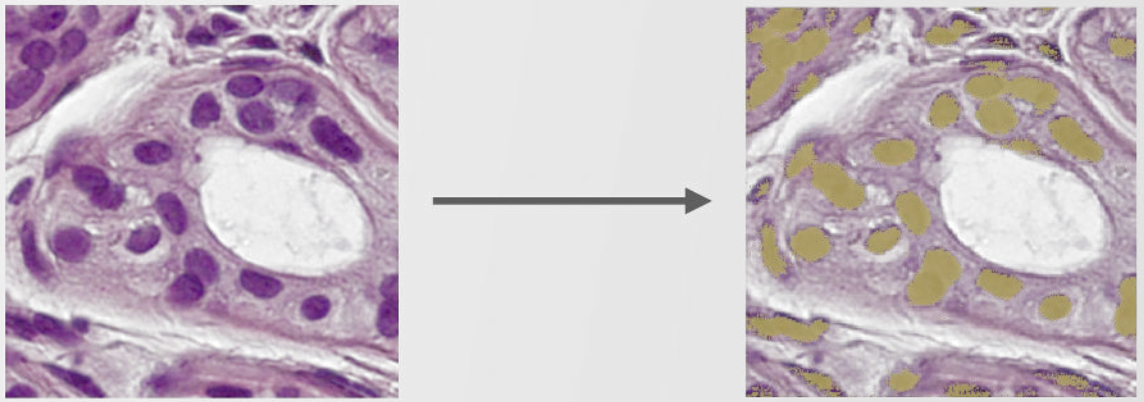
A fully-convolutional neural network (U-net) was trained to recognize tissue types and other sub-cellar features, such as nuclei. Detected regions can be further analyzed.



Detection of the epidermis



U-Net architecture

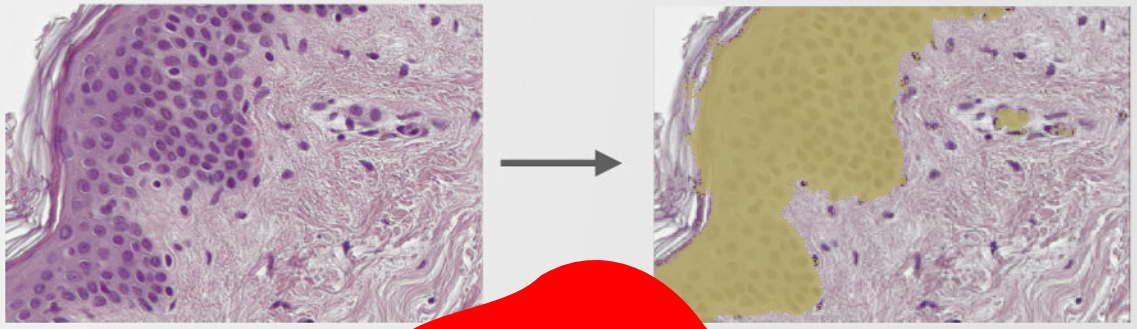


Detection of nuclei

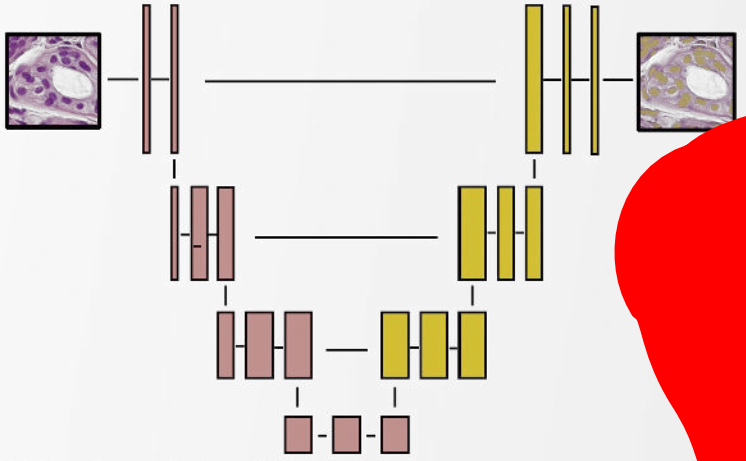
200 skin samples -> 80% training set, 20% test-set

Detection and Segmentation

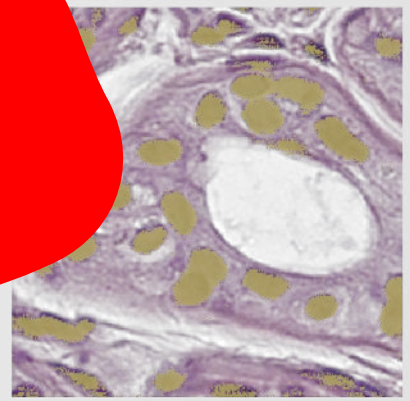
A fully-convolutional neural network (U-net) was trained to recognize tissue types and other sub-cellar features, such as nuclei. Detected regions can be further analyzed.



Detection of the epi



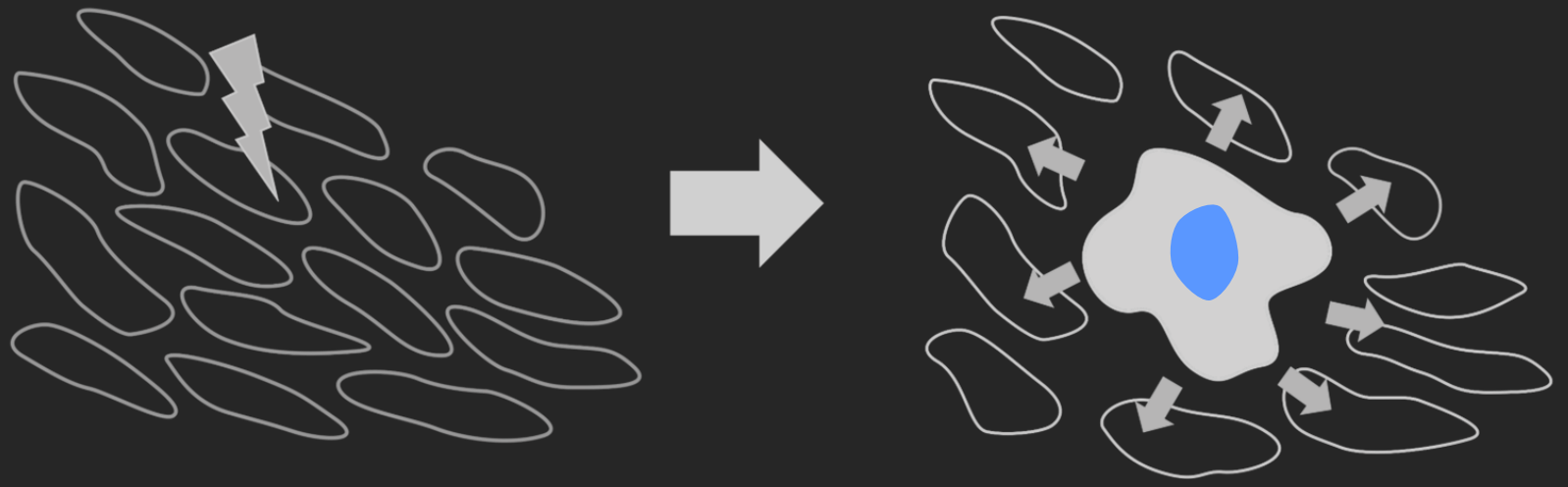
U-Net architecture



Failed

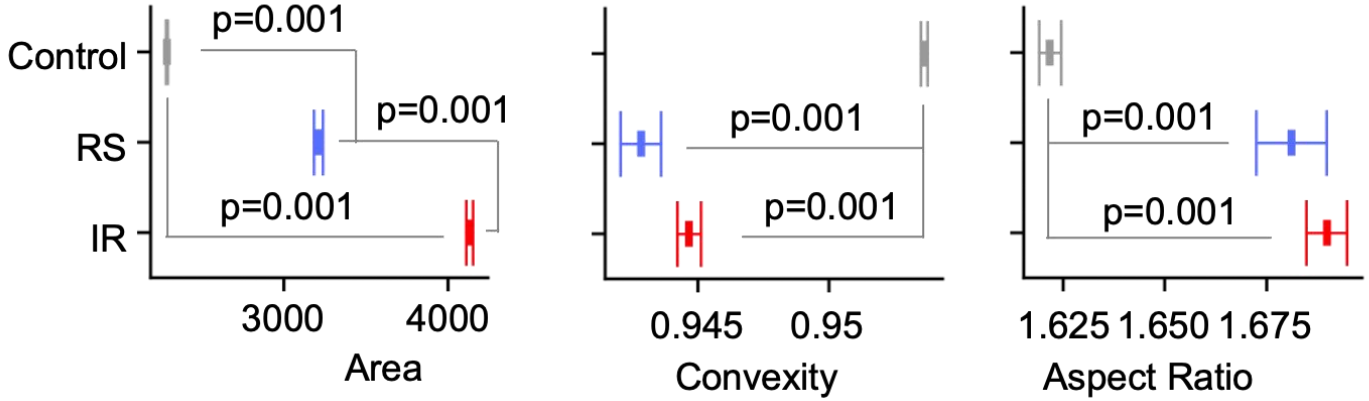
200 skin samples -> 80% train test-set

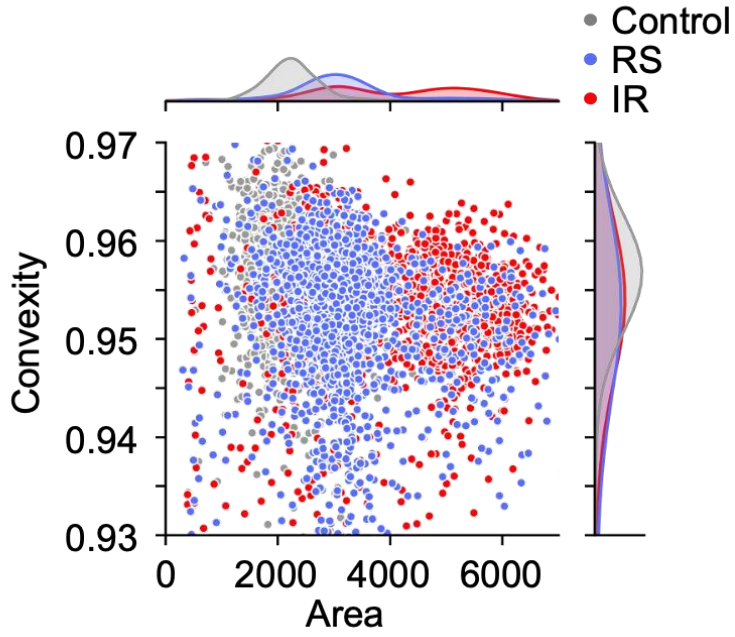
Nuclear morphology in aging

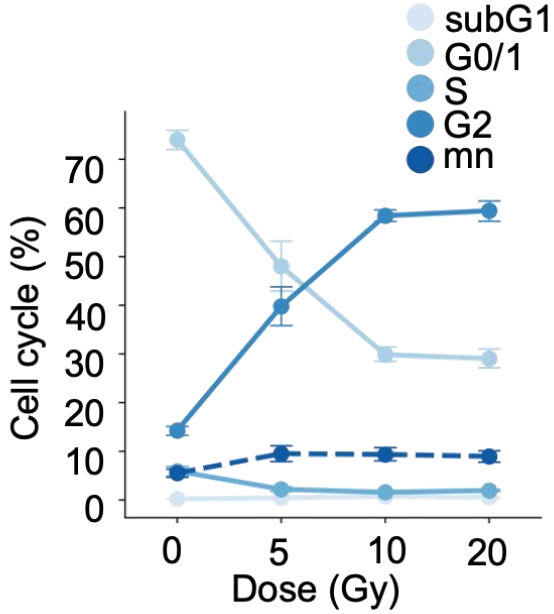


Perhaps we can use nuclear morphology to identify senescent cells?

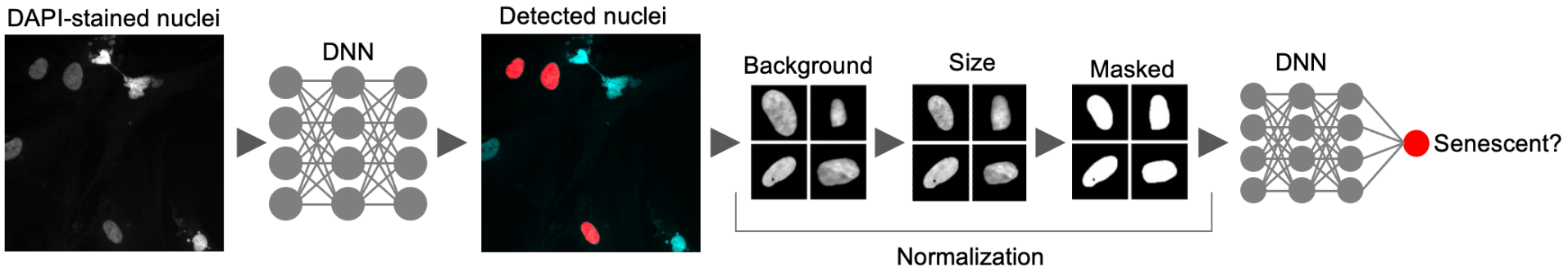
Nuclear morphology changes with senescence

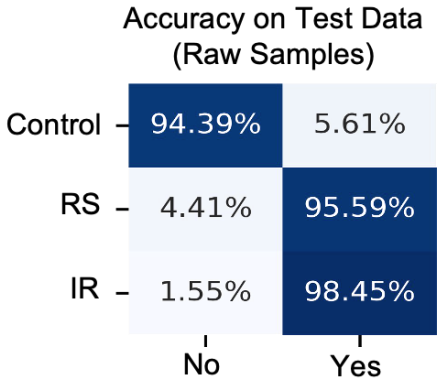


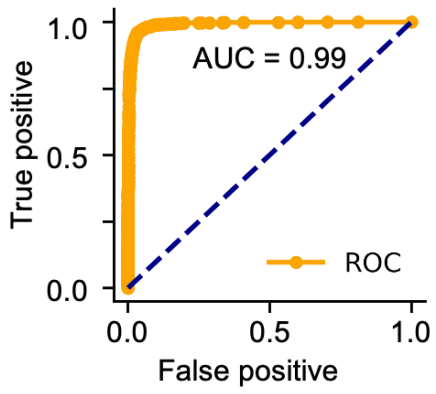


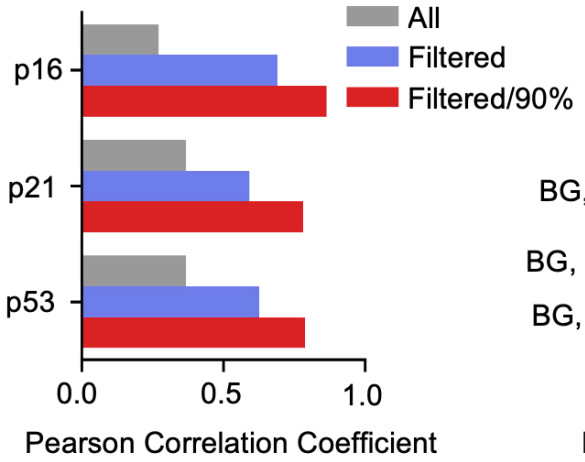


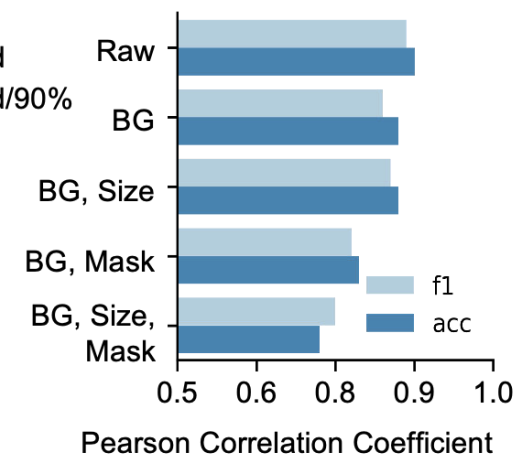
Deep neural network predicts senescence



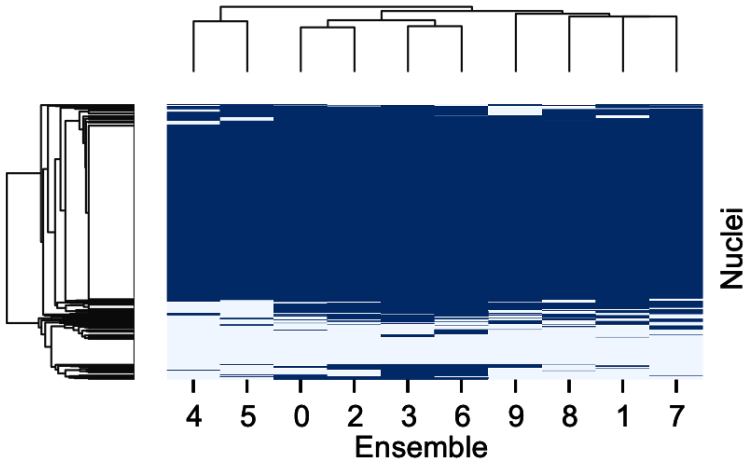


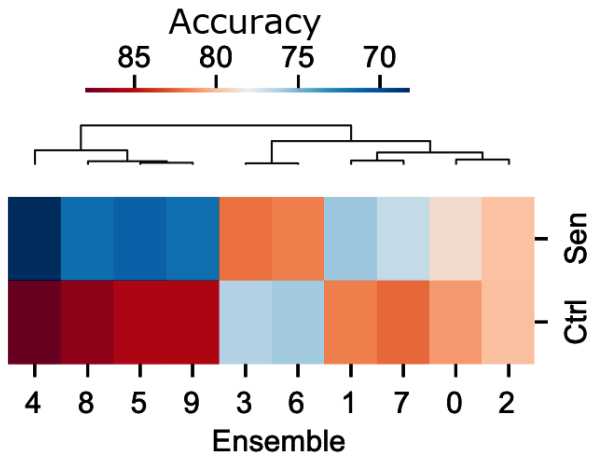


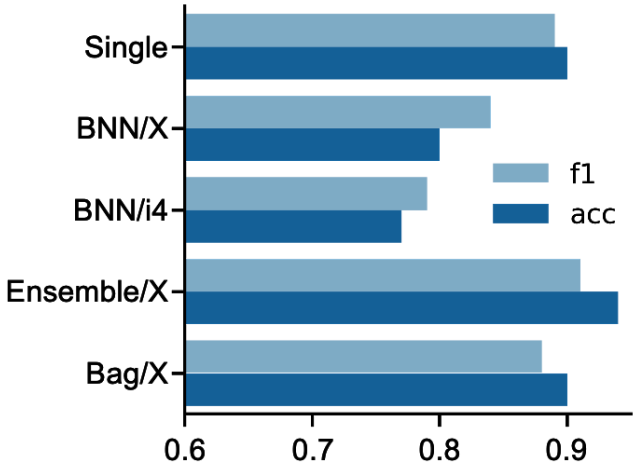




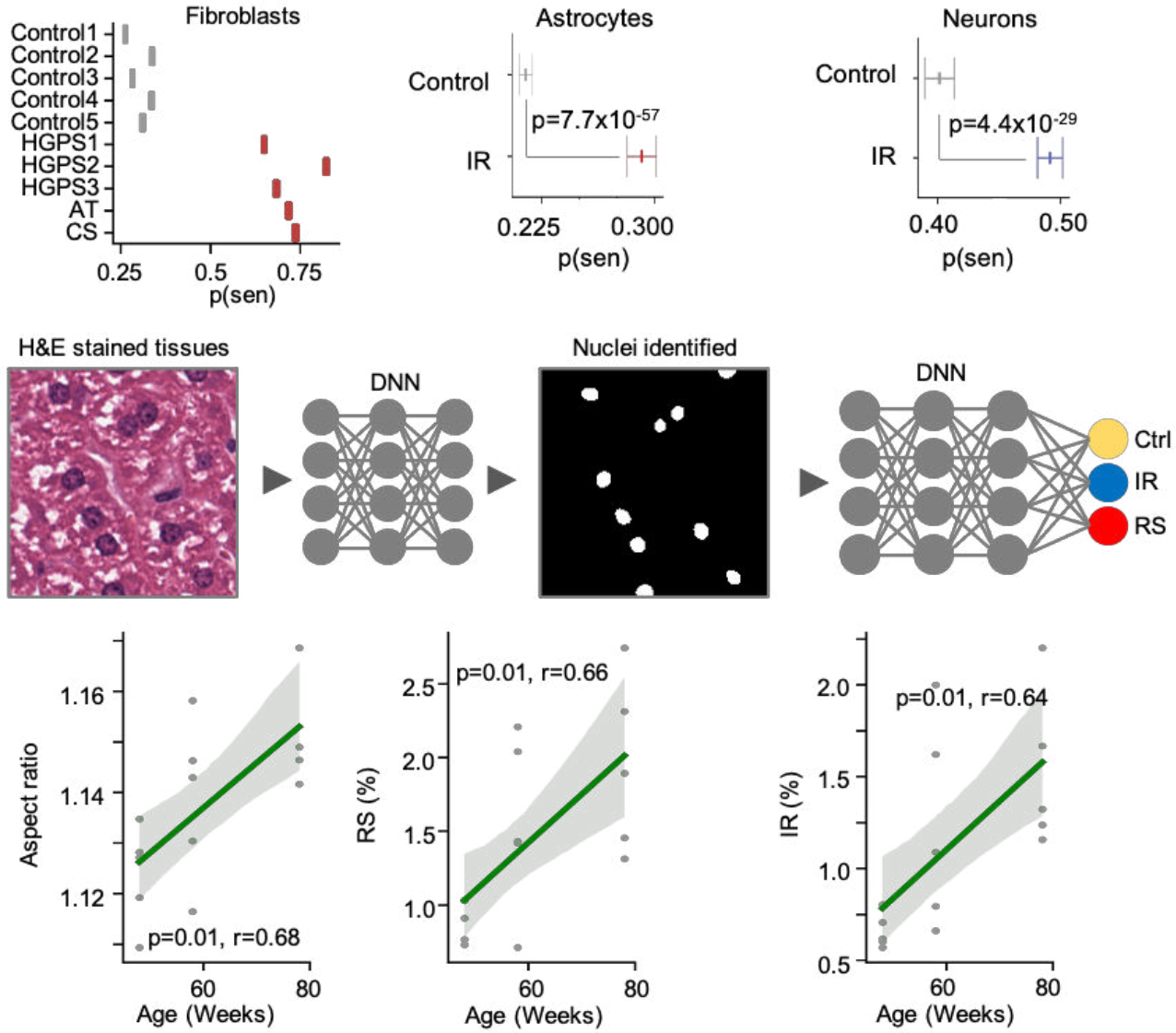
The wisdom of the AI crowd



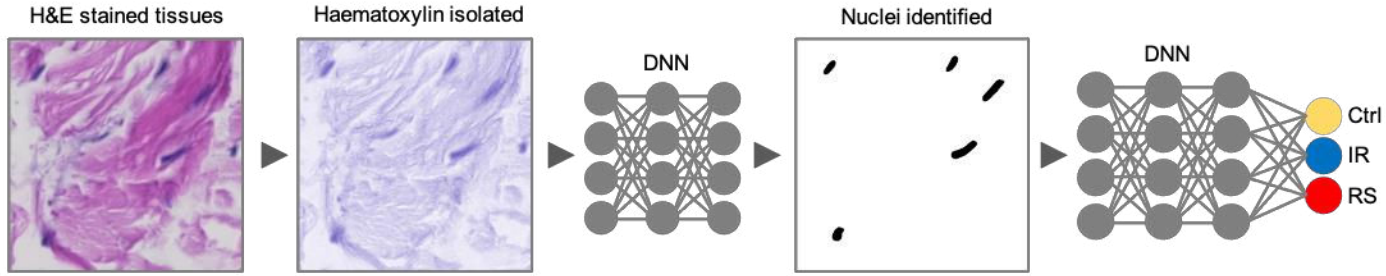


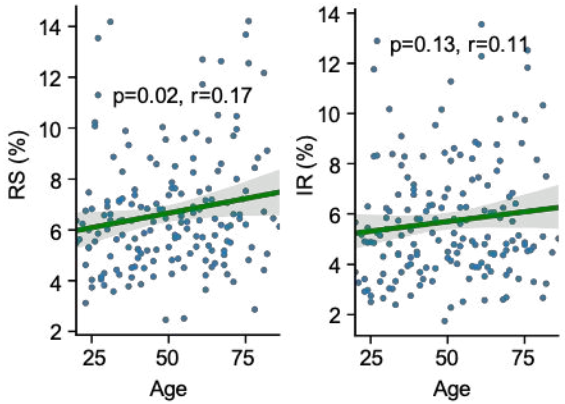


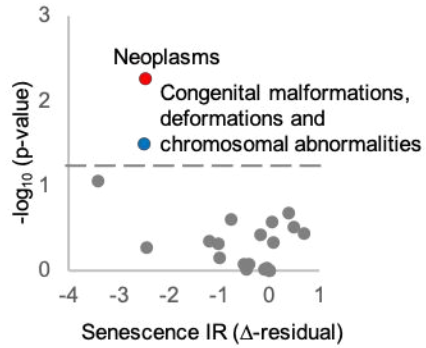
Nuclear morphology is a universal senescence marker

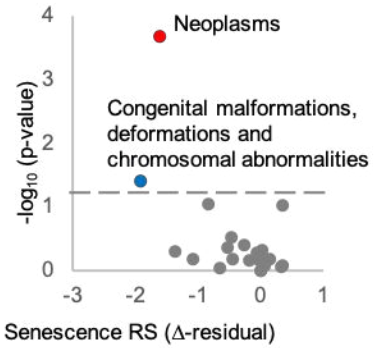


Senescence is a barrier to cancer





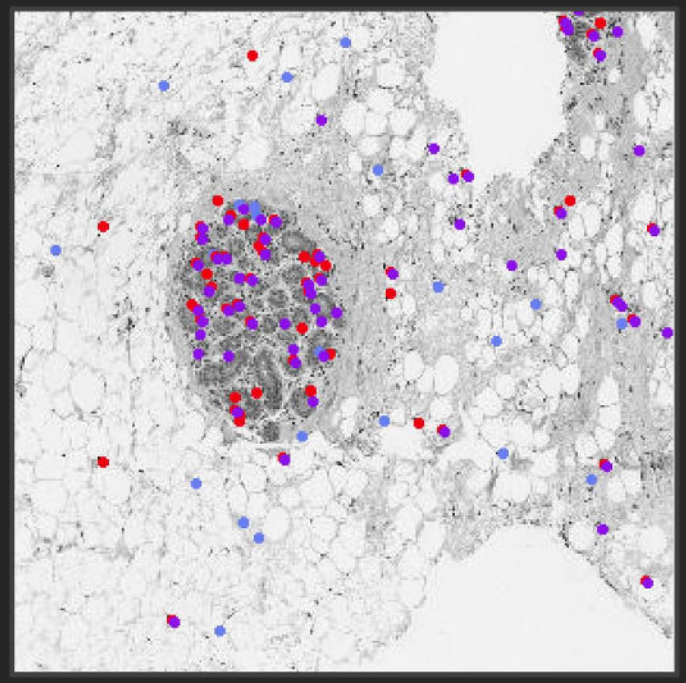


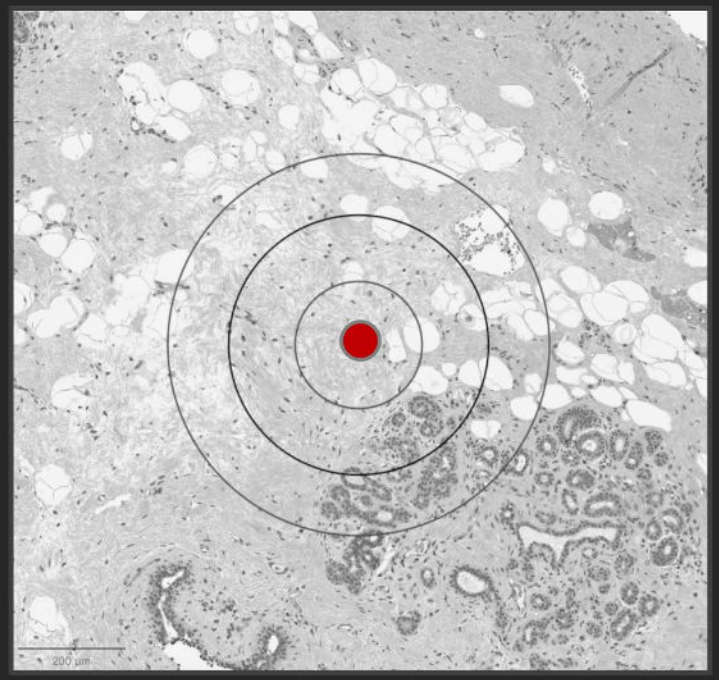


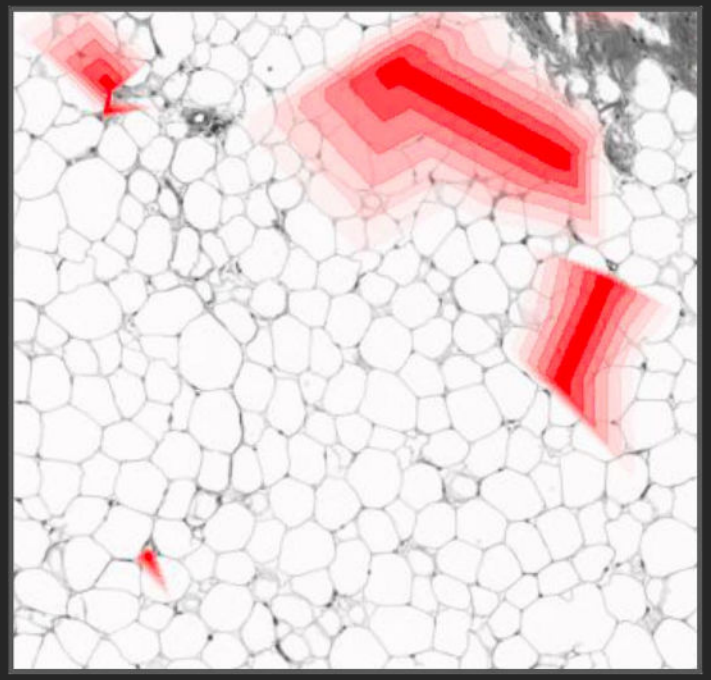
	Neg	Pos	p-value	Relative Risk Ratio
Neoplasm (RS)	85.39%	65.00%	0.002	0.76
Malignancy (IR)	61.63%	42.37%	0.018	0.70
Hypertension (Anti%)	15.66%	30.23%	0.029	1.93
Hypercholesteremia (Anti)	0.00%	5.33%	0.047	3.62
Hyperlipidemia (Unified)	3.57%	12.94%	0.037	*n.s.*
Hearing loss (ATV/r)	7.14%	0.00%	0.014	*n.s.*
Osteoporosis (IR%)	0.00%	4.82%	0.025	*n.s.*
Osteoarthritis (Unified)	0.00%	5.33%	0.031	*n.s.*
Cerebral Infarction (Doxo%)	0.00%	5.81%	0.013	*n.s.*
Sciatica (RS)	0.00%	6.67%	0.022	*n.s.*
Dyspnea (Anti)	9.09%	1.19%	0.034	*n.s.*

Heckenbach et al., Nat Aging 2022

Spatial senescence prediction







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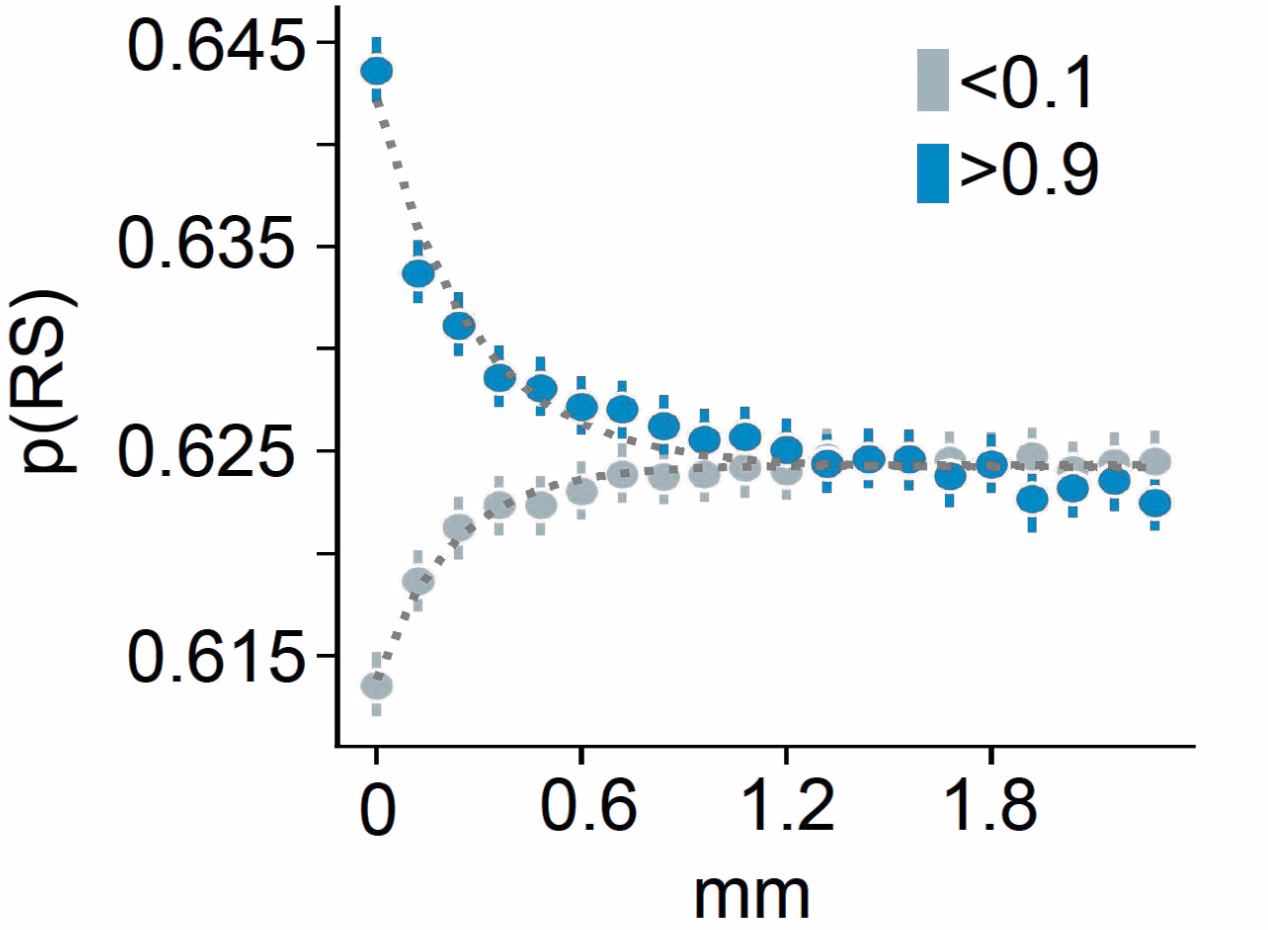
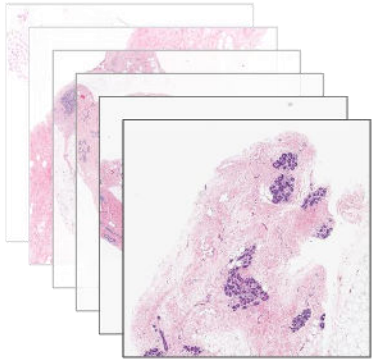
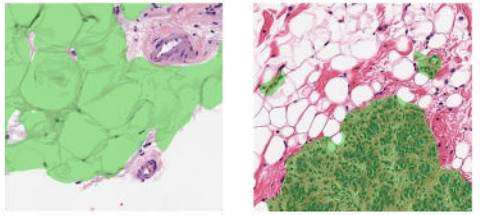


By analysing more than 4000 normal biopsies we find that senescence predicts breast cancer risk

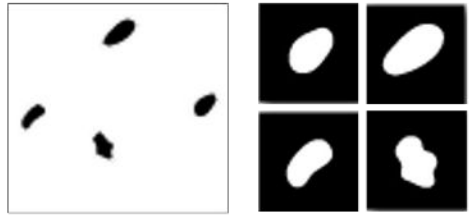
4411 breast biopsies from healthy women



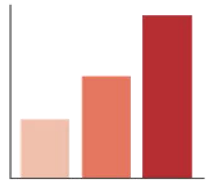
Neural networks detect tissue type



Neural networks detect cell senescence

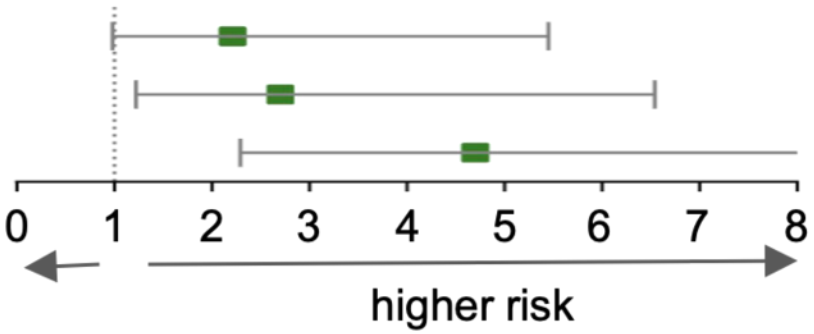


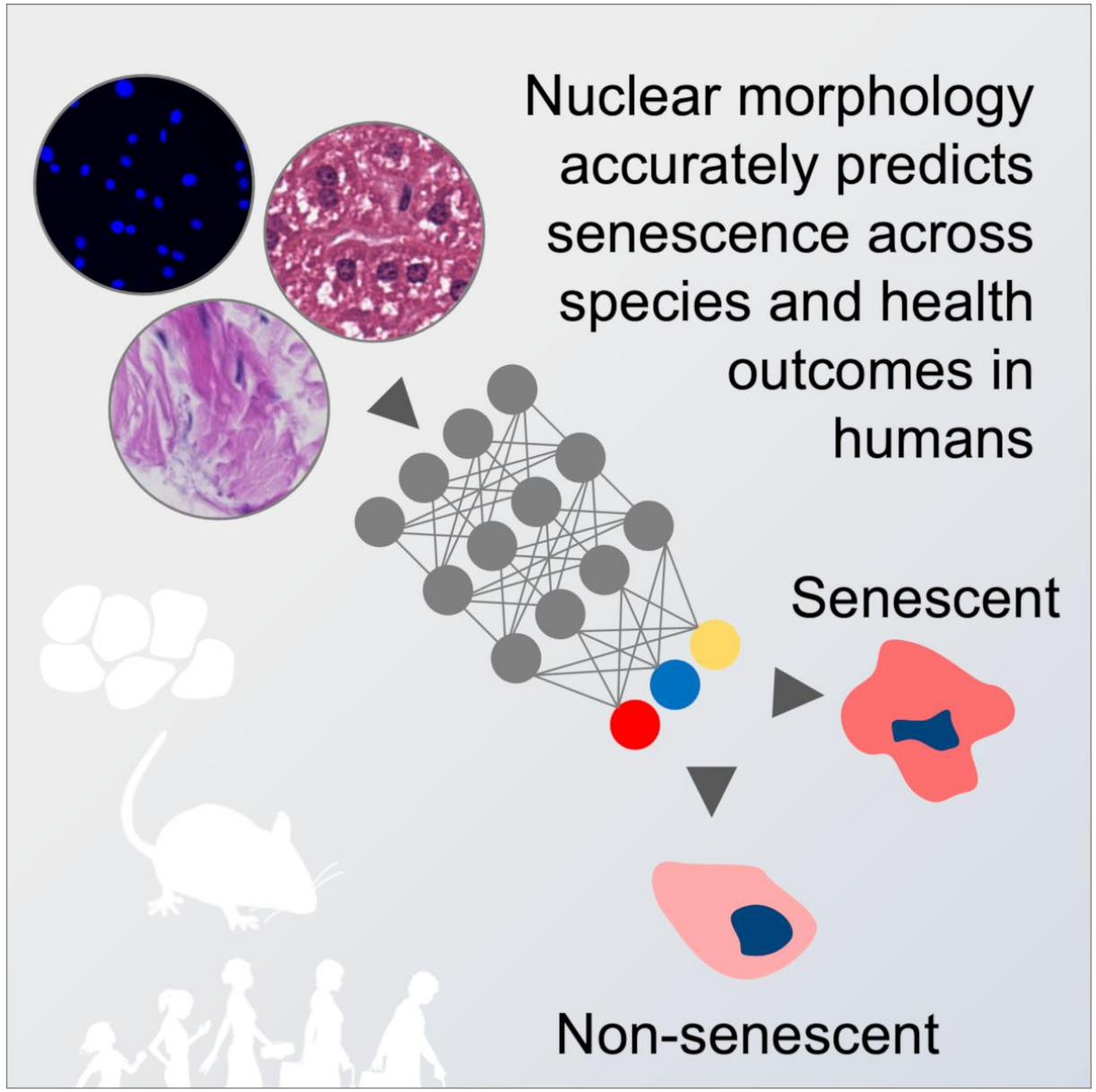
Senescence predicts future cancer risk



OR: 4.7 in histologically normal breast tissue

	OR (95% CI)	p value
No risk factor (N=809)	--	--
AAD/fat only (N=787)	2.21 (0.98 - 5.45)	0.066
Gail only (N=763)	2.70 (1.22 - 6.54)	0.019
AAD+Gail (N=803)	4.70 (2.29 - 10.9)	<0.001





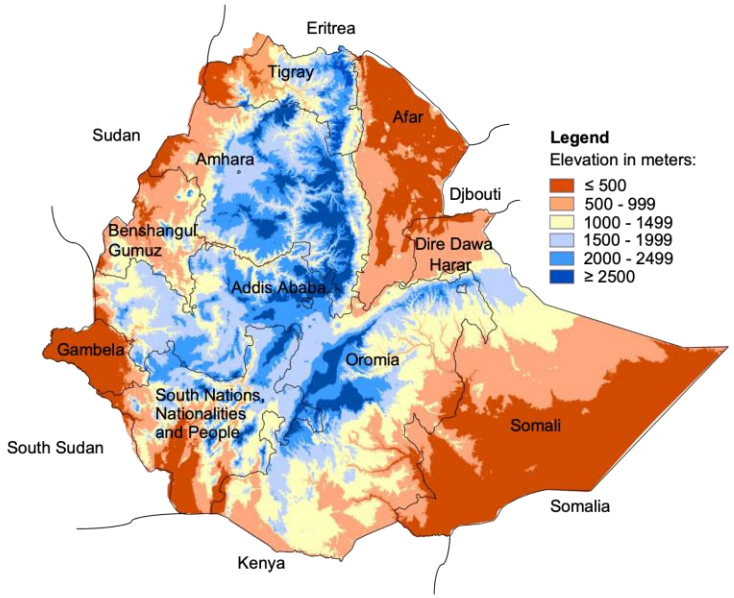
Heckenbach et al., Nat Aging 2022

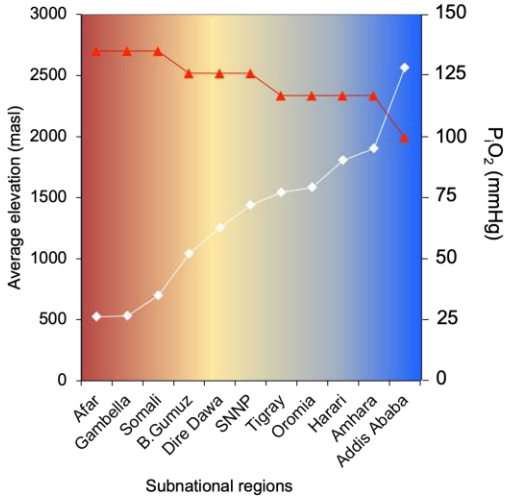
Utility of the senescence predictor

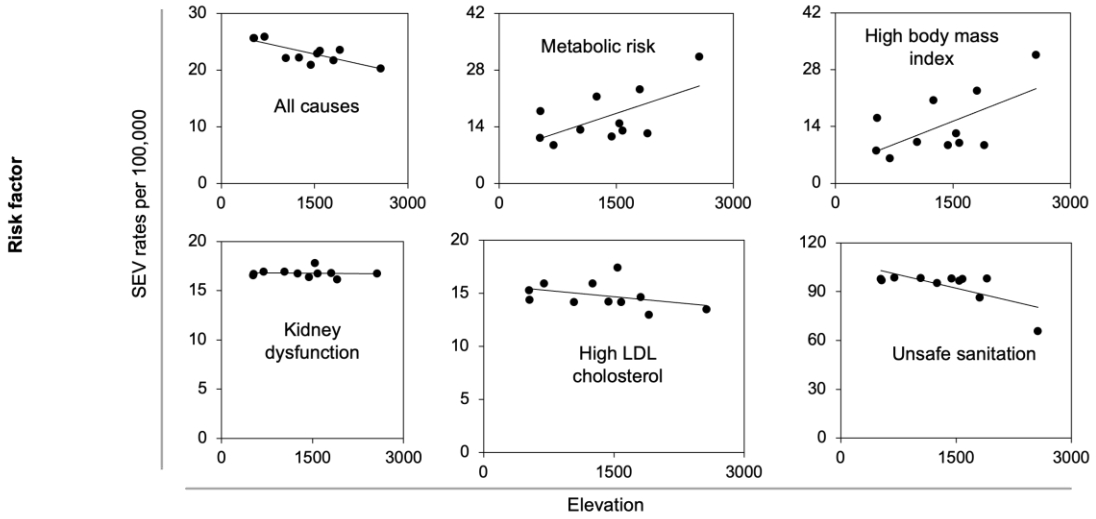
Chronic hypoxia in aging

IKON trial - Double blinded RCT targeting COPD with NR

Chronic hypoxia and health

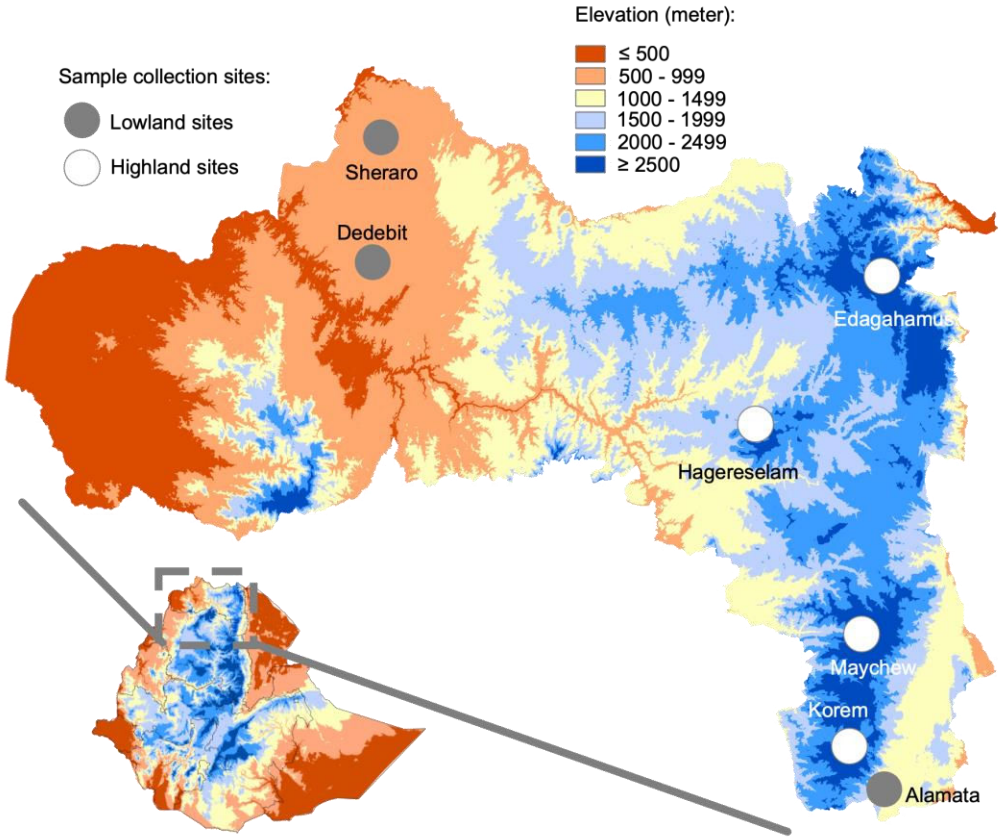


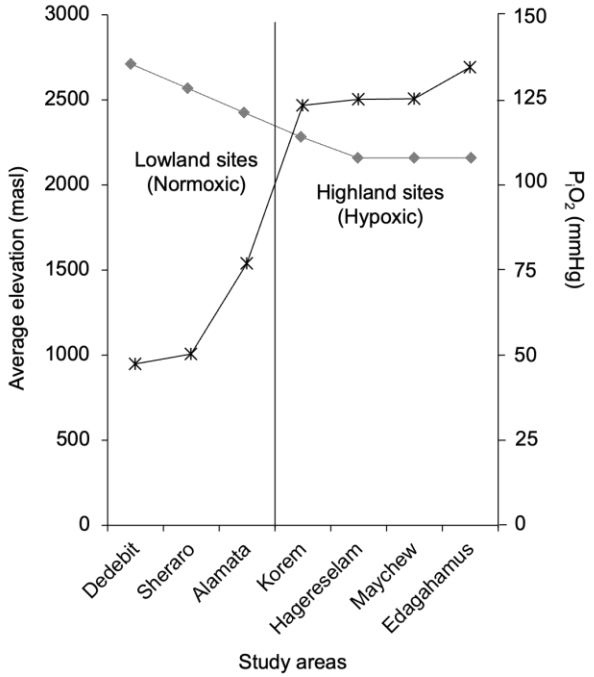




Amanuel Teklu

Chronic hypoxia and senescence





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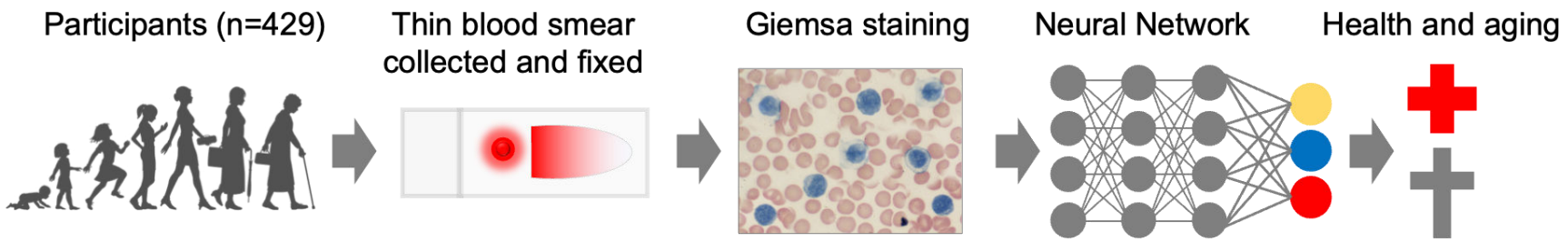
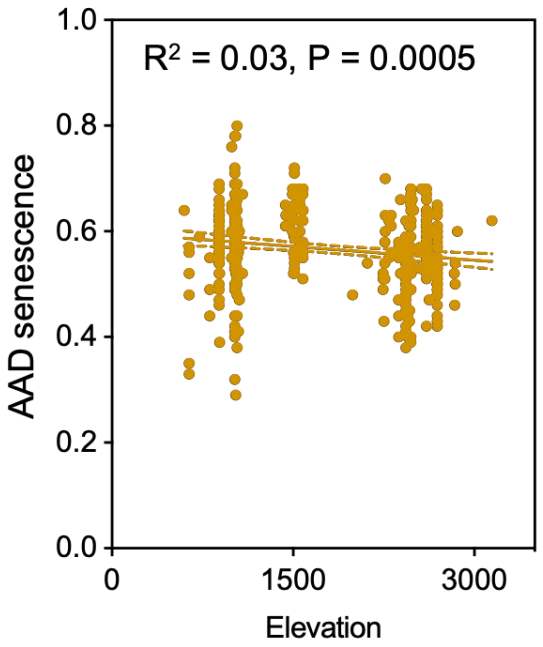
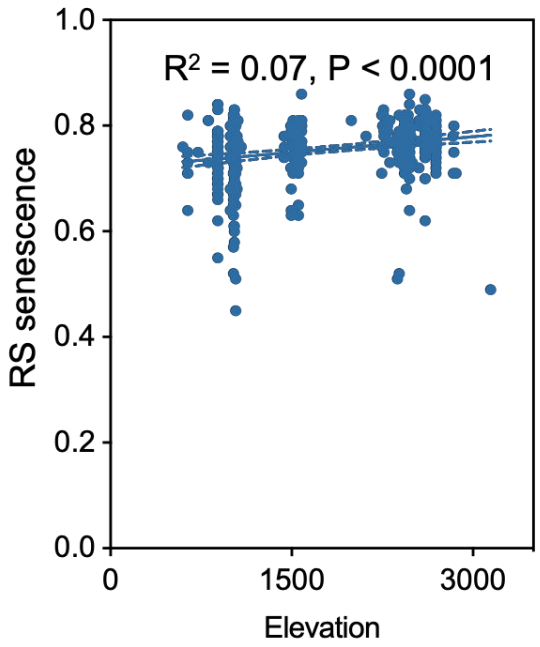
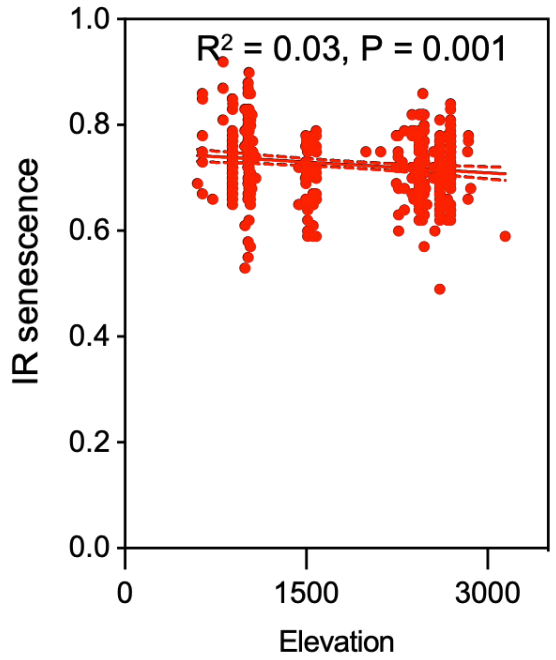
Chronic hypoxia and senescence









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Utility of the senescence predictor

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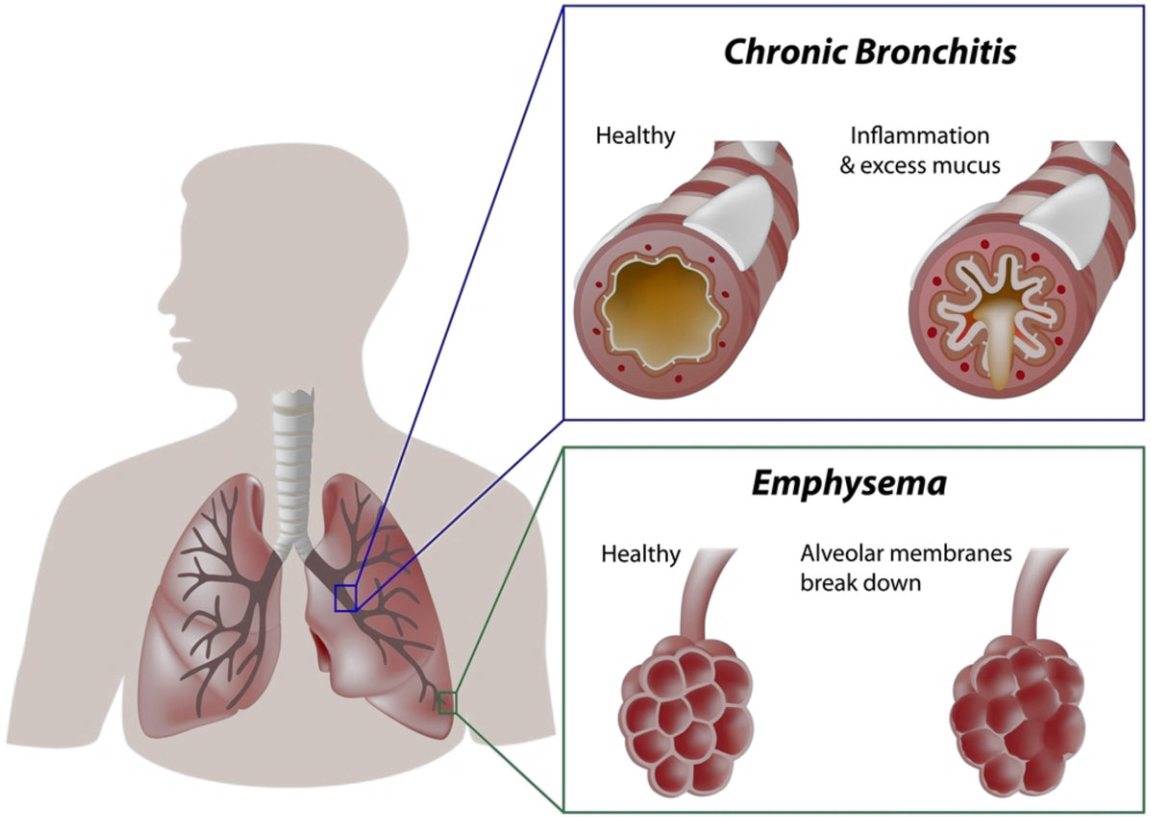
Why Chronic Obstructive Pulmonary Disease?

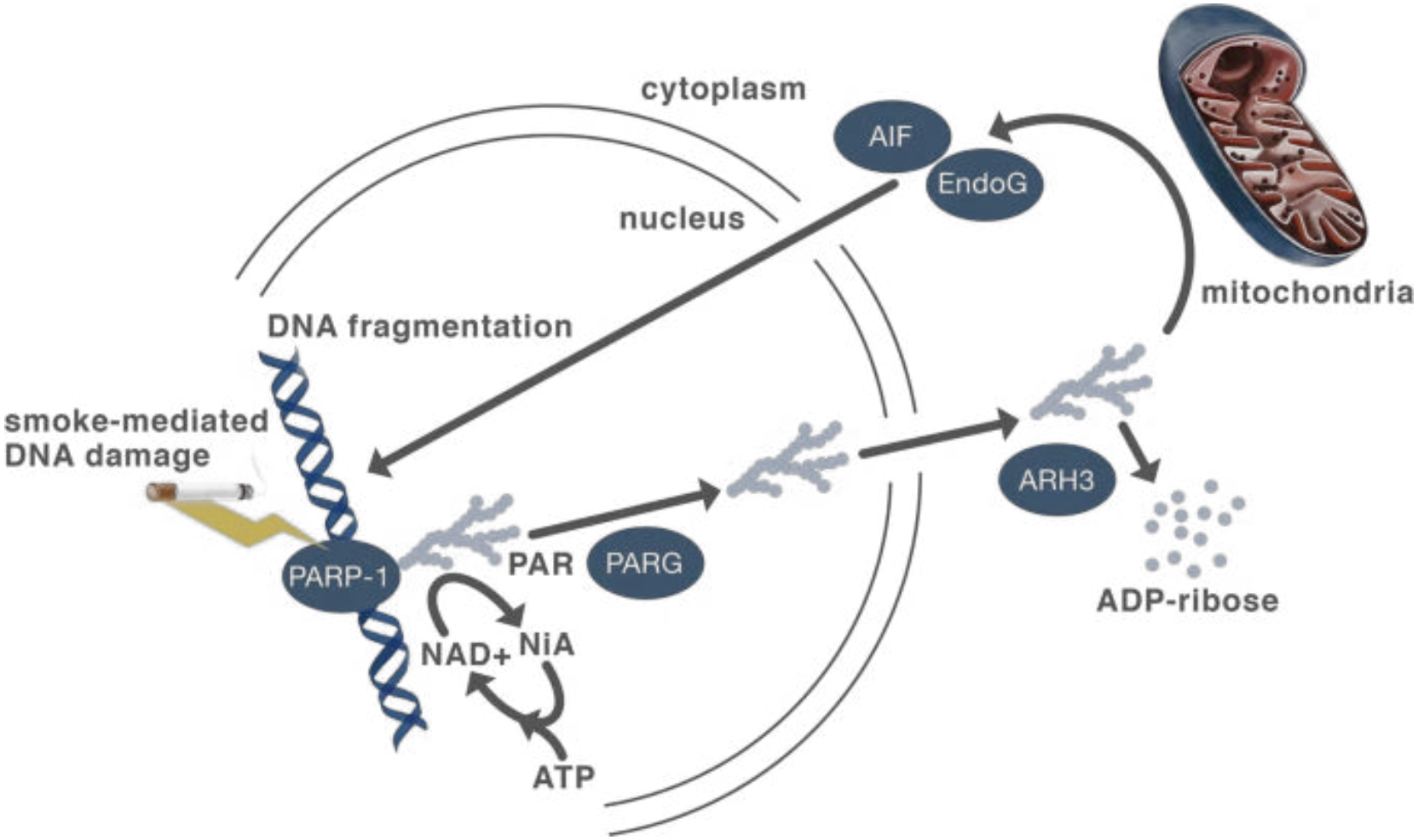
Third leading cause of death globally

3.3 million deaths per year



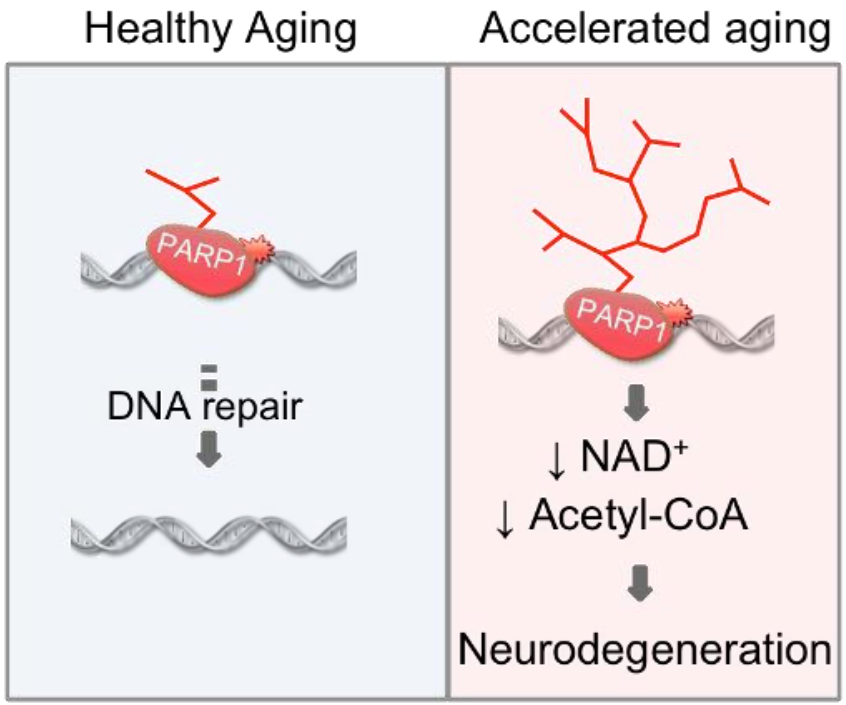
World Health Organization (WHO), 2019

Smoking causes DNA damage and PARP1 activation



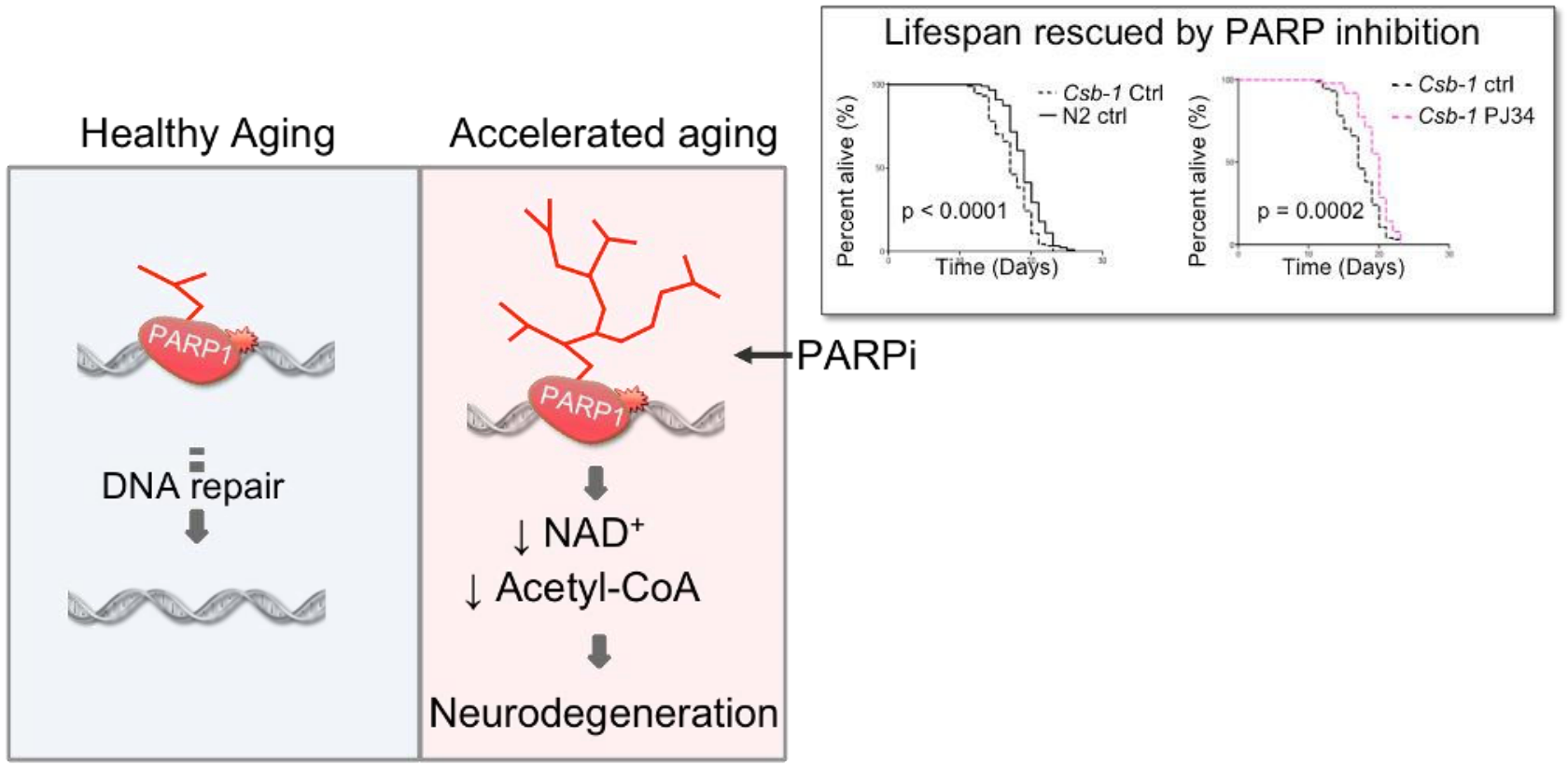
Künzi & Holt, CCD, 2019

DNA damage drives NAD loss and premature aging



Scheibye-Knudsen et al. PNAS, 2016
Fang*, Scheibye-Knudsen* et al. Nature Reviews, 2016
Scheibye-Knudsen et al. TiCB,2015
Scheibye-Knudsen et al. Cell Metabolism, 2014
Scheibye-Knudsen*,Fang,* et al., Autophagy, 2014
Fang*, Scheibye-Knudsen* et al. Cell, 2014
Scheibye-Knudsen et al. Aging 2013
Scheibye-Knudsen et al. J. Exp. Med. 2012

DNA damage drives NAD loss and premature aging



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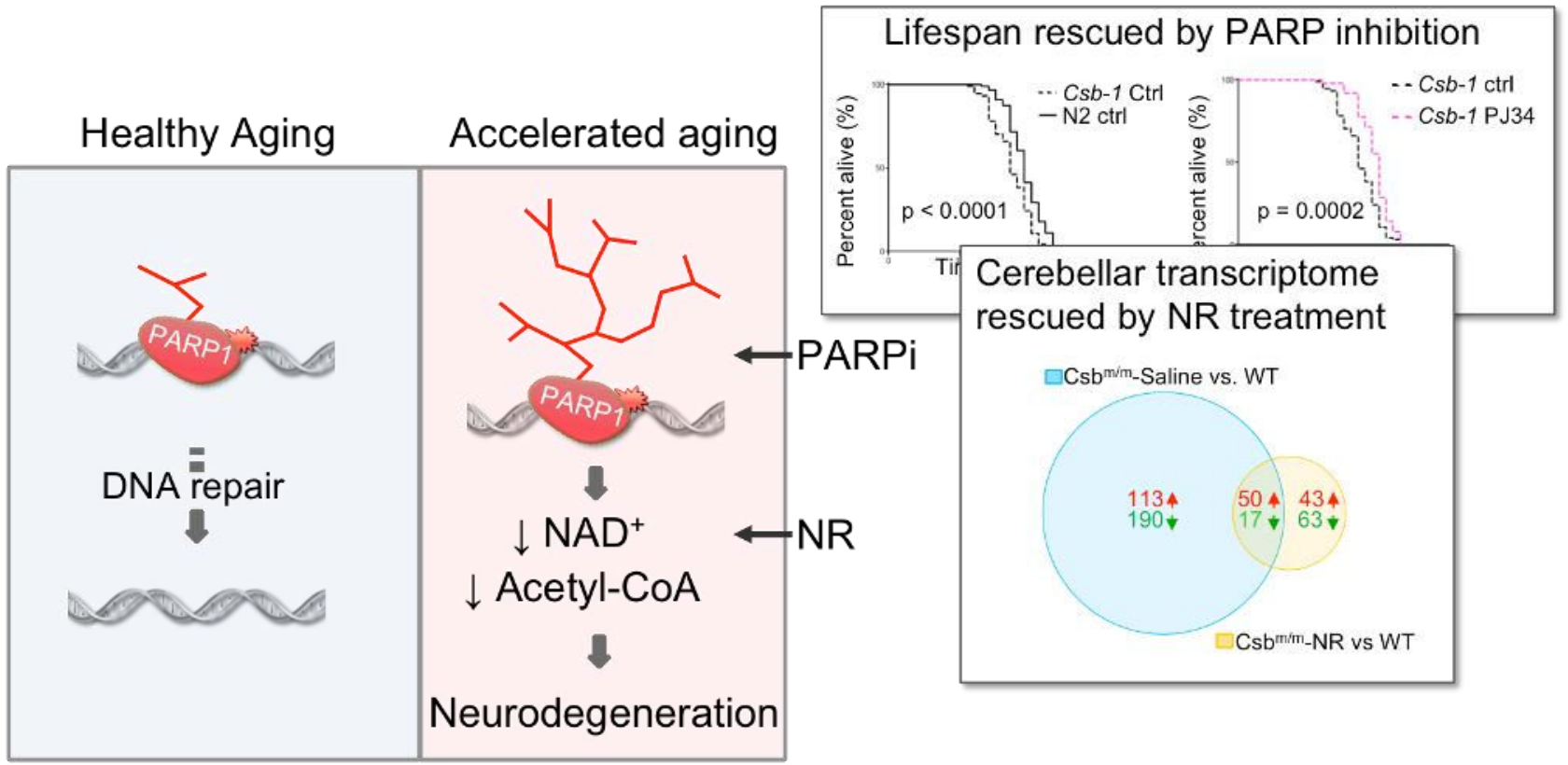

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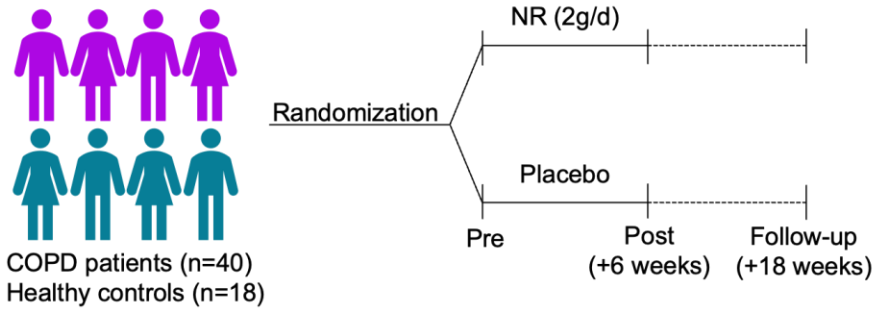
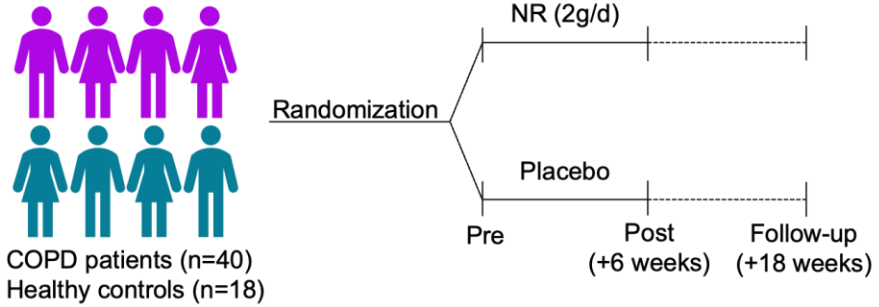
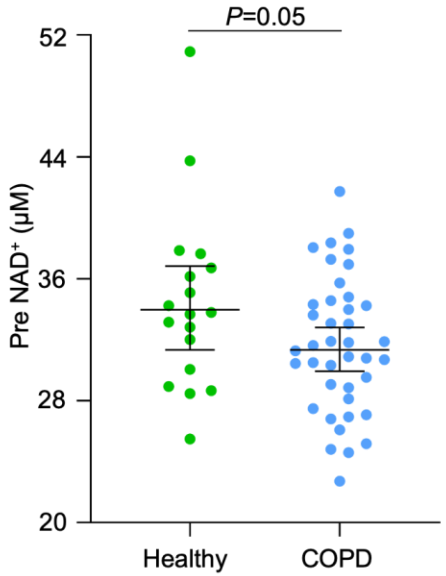
Scheibye-Knudsen et al. Cell Metabolism, 2014
Scheibye-Knudsen*,Fang,* et al., Autophagy, 2014
Fang*, Scheibye-Knudsen* et al. Cell, 2014
Scheibye-Knudsen et al. Aging 2013
Scheibye-Knudsen et al. J. Exp. Med. 2012

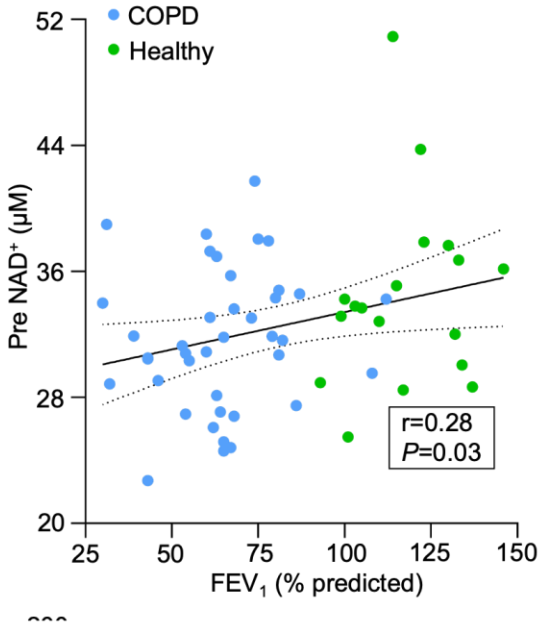
Trial design



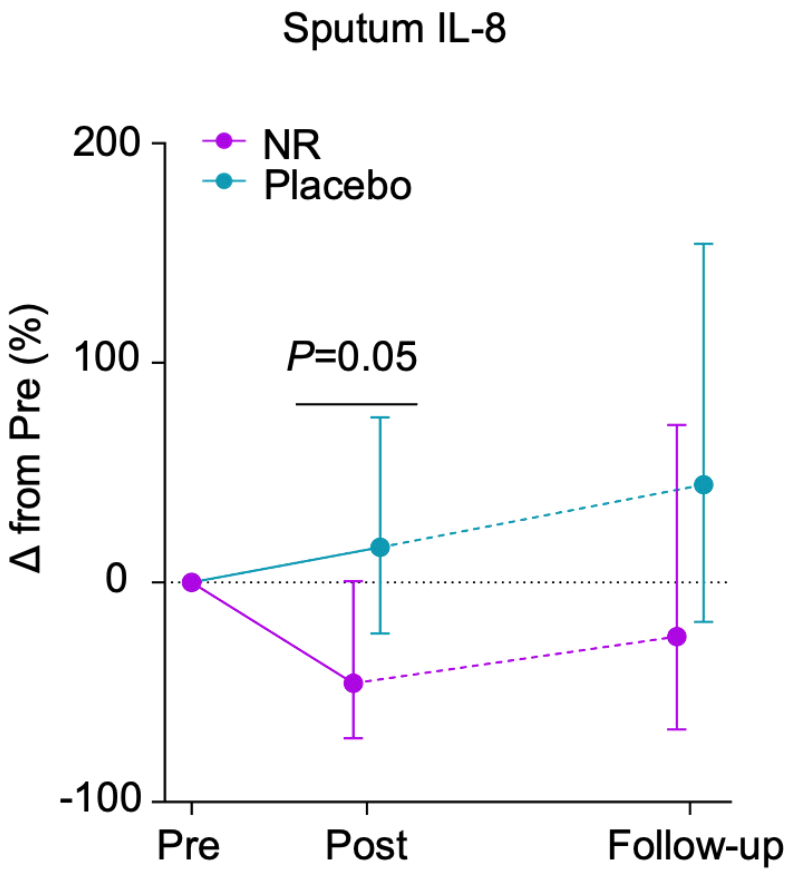
NAD loss in COPD

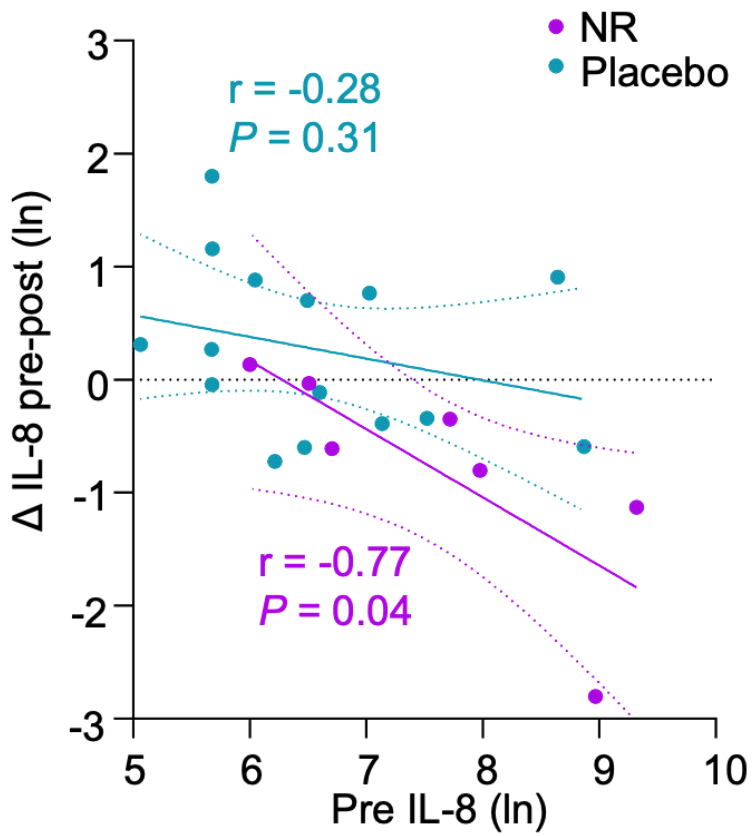


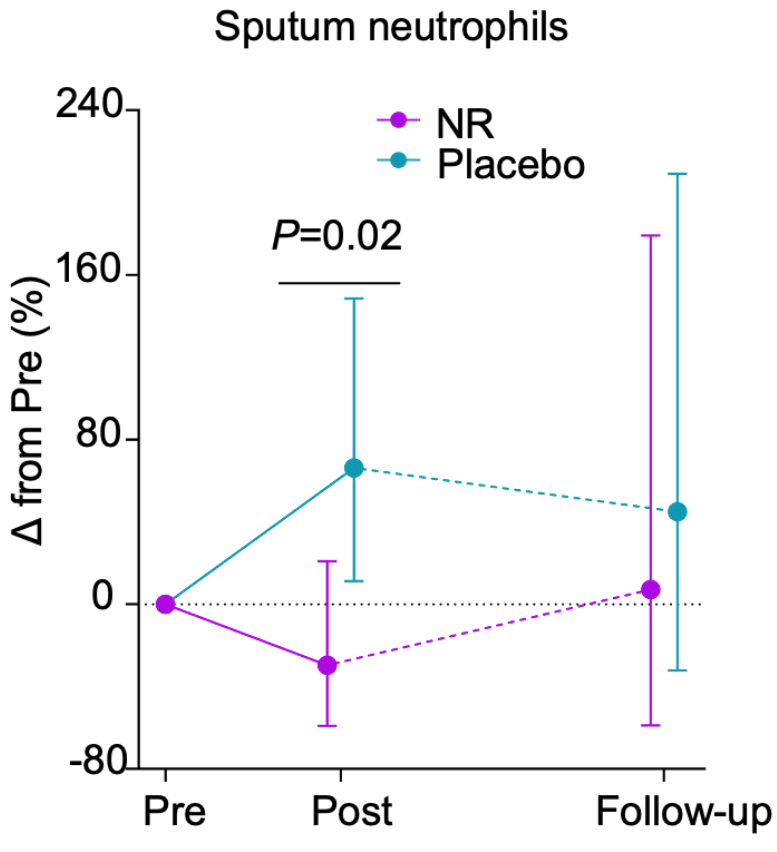




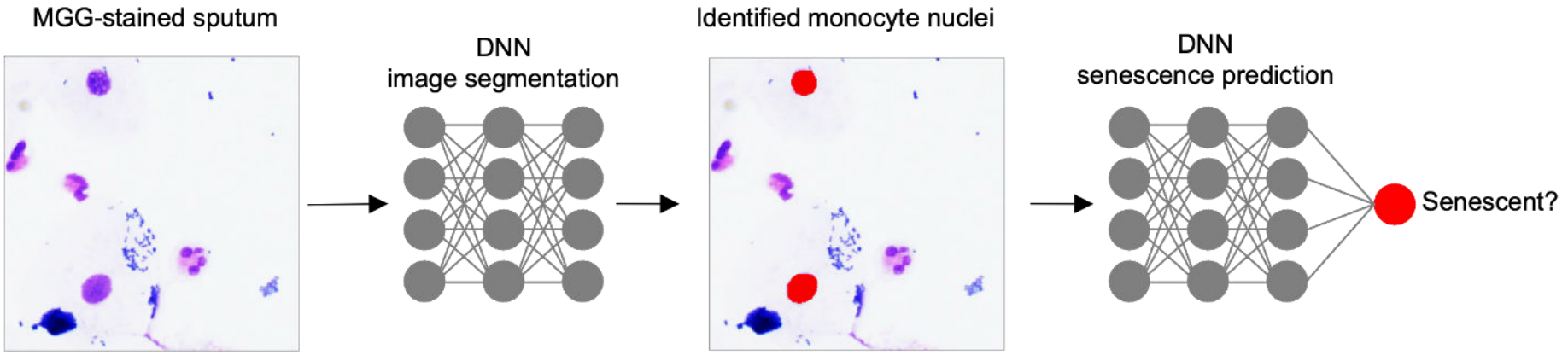
Primary outcome measure: IL-8

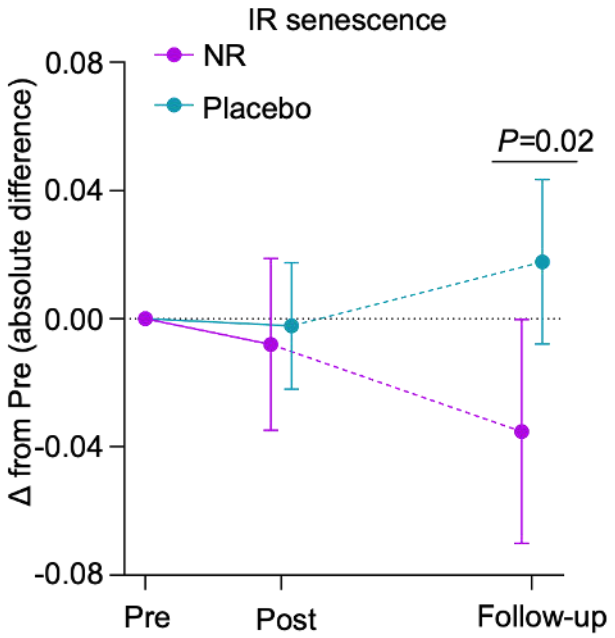


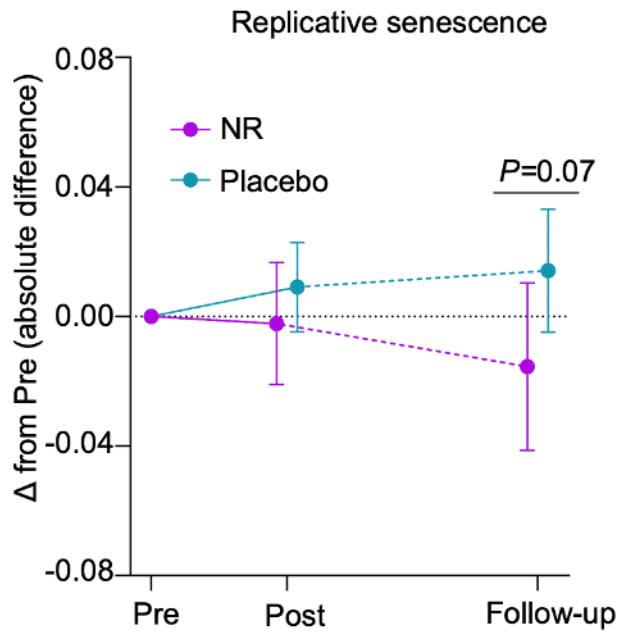


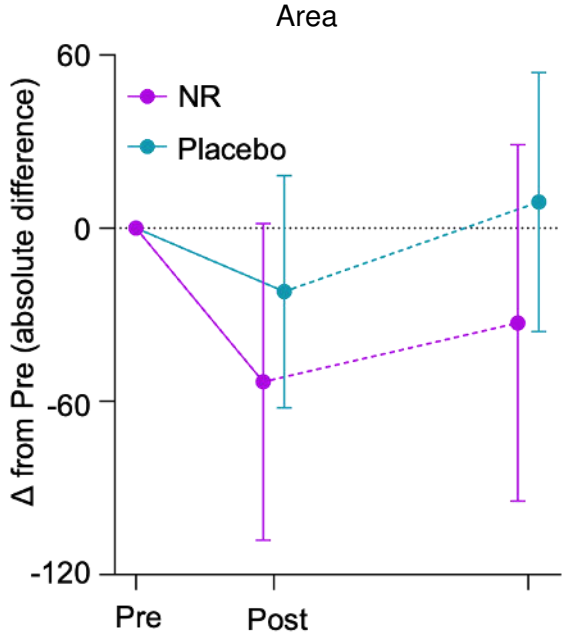


NR reduces cellular senescence in the lung of COPD patients

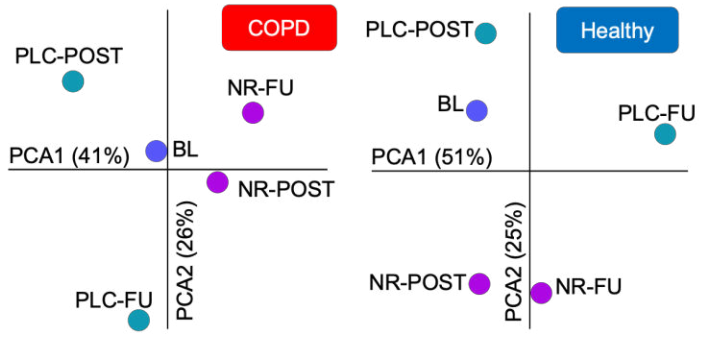


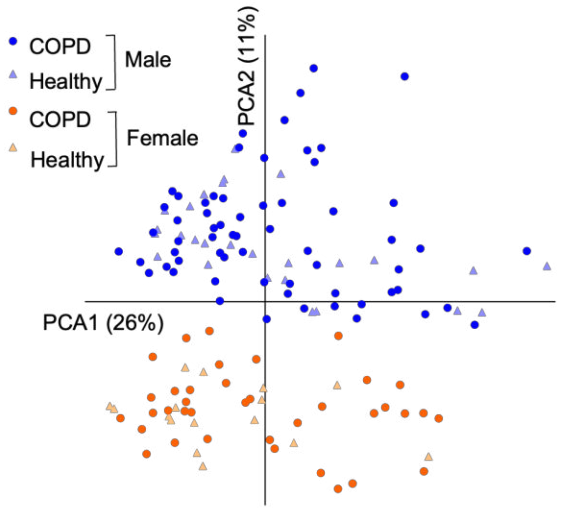


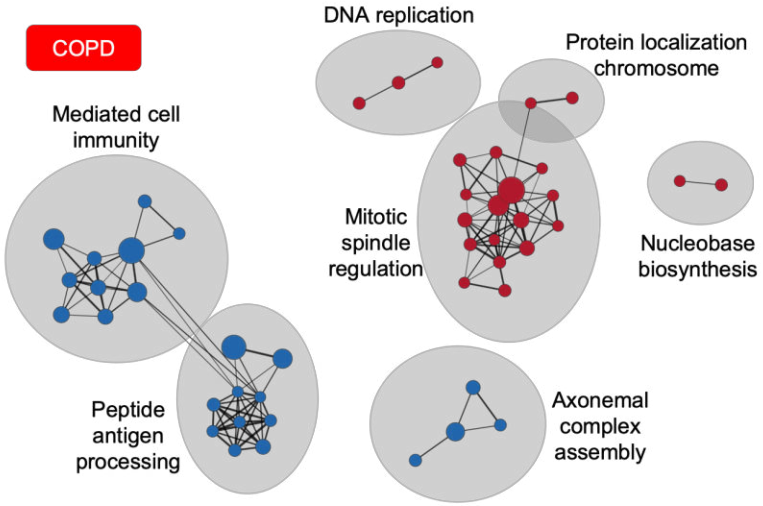


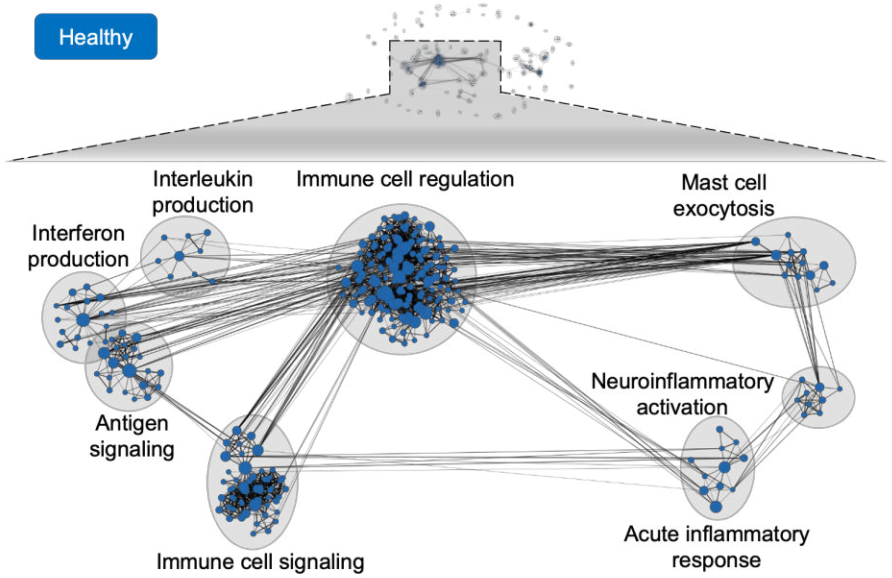


NR reduces inflammatory pathways in airway epithelium in COPD patients









NR reduces airway senescence and inflammation in COPD patients

Kristoffer Norheim

To sum up...

We have thousands of biomarkers of aging

One biomarker, cellular senescence, predicts cancer

We can impact biomarkers of aging and disease with interventions

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