MEDICAL UNIVERSITY OF VIENNA

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Enabling Whole Person Research: The Transformative Impact of Total Body PET, Complexity Science and Network Medicine

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Total-Body PET: A Window into **Health** and Disease

canton de vaud

Plan

Health & well-being

Live longer and better

Longevity and anti-ageing

Total-body PET

Senescence, ageing and inflammaging

Using real-world data

Summary / roadmap

Constitution of the WHO (1946)

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity

22-06-1946, last update 15-09-2005, https://www.who.int/about/governance/constitution

Health and well-being

Healthcare and treatment

- Through hospitals and the medical system

Health promotion and prevention

- Area of growing interest
- Health risks and protective factors
- Interventions can be designed for individuals, specific groups or whole populations
- Can be supported through legislation and regulation, organizational strategies, training and interventions
- Promoting child and adolescent health is also a priority

https://www.who.int/data/gho/data/major-themes/health-and-well-being

Health vs. Wellness

Health

Absence or presence of disease
Hypertension?

Hypercholesterolemia?

Cancer?

Does not indicate how well a life you are leading

Wellness

How well is your sleep?

How often do you exercise?

How healthful are your meals

How many close family members do you have?

What is the quality of your relationship?

Are you financialy secure?

More hollistic sense of health

https://www.lhsfna.org/health-and-wellness-explained/

Wellness

Several dimensions:

- physical
- social
- intellectual
- emotional
- mental
- financial
- vocational
- *spiritual*

Spiritual wellness

One Piece in a Larger Puzzle

Many of the behaviors associated with overall wellness are key components of spiritual wellness. Examples include volunteering, being positive and optimistic, contributing to society, connecting with others, feeling a sense of belonging and practicing self-care.

Difficult to measure and include as co-variables in a study

https://www.lhsfna.org/health-and-wellness-explained/

Live longer and better

Lifespan has doubled in 4 generations

By 2050, 20% of will be >60y and 426 million will be >80y

Wish to extend lifespan quality in good health more than lifespan in total:

"add life to years rather than years to life"

https://www.who.int/news/item/14-12-2020-decade-of-healthy-ageing-a-new-un-wide-initiative

Longevity and Anti-senescence Therapy Market

Market worth $25.1 billion, to reach $44.2 billion by 2030

Compound annual growth rate of 6.5% from 2021–2030 owing government initiatives and rise in adoption of anti-aging products

Leading players:

AgeX Therapeutics, BMS, Calico Life Sciences, CohBar, Life Biosciences, Merck, Oisin Biotechnologies, Pfizer, T.A. Sciences, Unity Biotechnology

Interest from non-pharma industry such as

L'Oréal, LVMH, Nestlé, among others

Capital Venture Funds ready to be launched

https://www.bloomberg.com/press-releases/2022-04-19/longevity-and-anti-senescence-therapy-market-to-reach-44-2-bn-globally-by-2030-at-6-1-cagr-allied-market-research

Urolothin A as anti-ageing molecule

- Urolithin A stimulates mitophagia (removal of deficient mitochondries) helping to prevent sarcopenia
- Not all individuals have enough Urolithin A levels (microbiote-produced)
- Nutritional supplement approved in US, soon in Europe

Amazentis

https://www.rts.ch/info/sciences-tech/10507362-une-molecule-antivieillissement-prometteuse-decouverte-a-lepfl.html

Urolithin A as nutritional supplement

nature medicine

Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents

Dongryeol Ryu[1,5], Laurent Mouchiroud[1,5], Pénélope A Andreux[1,2,5], Elena Katsyuba[1], Norman Moullan[1], Amandine A Nicolet-dit-Félix[1], Evan G Williams[1], Pooja Jha[1], Giuseppe Lo Sasso[1], Damien Huzard[3], Patrick Aebischer[4], Carmen Sandi[3], Chris Rinsch[2] & Johan Auwerx[1]

The biological effects of urolithins remain poorly characterized, despite wide-spread human exposure via the dietary consumption of their metabolic precursors, the ellagitannins, which are found in the pomegranate fruit, as well as in nuts and berries. We identified urolithin A (UA) as a first-in-class natural compound that induces mitophagy both *in vitro* and *in vivo* following oral consumption. In *C. elegans*, UA prevented the accumulation of dysfunctional mitochondria with age and extended lifespan. Likewise, UA prolonged normal activity during aging in *C. elegans*, including mobility and pharyngeal pumping, while maintaining mitochondrial respiratory capacity. These effects translated to rodents, where UA improved exercise capacity in two different mouse models of age-related decline of muscle function, as well as in young rats. Our findings highlight the health benefits of urolithin A and its potential application in strategies to improve mitochondrial and muscle function.

The evolution of society from its hunter-gatherer origins to its present form has come with a marked shift in dietary behavior. Berries, nuts, acorns and tree leaves, all found in the wild, serve as an important dietary staple of animals today and humans long ago[1]. Natural compounds known as ellagitannins (ETs) are a common denominator uniting, from a phytochemistry viewpoint, many of these ancestral foods[2]. For humans, the pomegranate fruit is a prominent source of ellagitannins in general and of punicalagin in particular[3]. ETs are hydrolyzed in the gut to release ellagic acid (EA), which is further processed by the microflora into urolithins through the loss of one of its two lactones and by successive removal of hydroxyl groups[4] (**Fig. 1a**). In the species investigated to date (including humans), urolithin A (UA), urolithin B (UB), urolithin C (UC) and urolithin D (UD) are the redundant measurable metabolites that are thought to be the end-products of both ETs and EA[4,5].

Until now, there has not been an in-depth investigation into the mechanism of action of urolithins and their benefits following chronic administration. Most studies exploring urolithins *in vivo* have focused on their metabolism by administering a source of ETs (either mixed or pure) and subsequently monitoring their conversion into either EA or urolithins[5–8]. Notably, it has been observed that intestinal biotransformation of EA into urolithins is heterogeneous across individuals, with individuals showing high or low conversion rates, as well as those who do not convert at all[9]. A few studies have documented biological effects of urolithins *in vitro*, including antiproliferation in cancer cell models[10], anti-inflammation[11] and benefits on lipid metabolism[12], although a clear biological pathway has not yet been described. Here we characterized the biological effects of urolithins, and UA in particular, using *C. elegans* as a model organism. We subsequently investigated the activity of UA in mammalian cells and explored their health benefits in rodents.

RESULTS

Urolithins extend lifespan and improve fitness in *C. elegans*

We found that feeding worms from eggs until death with UA, UB, UC or UD at a standard concentration of 50 μM extended lifespan by 45.4, 36.6, 36.0 and 19.0%, respectively, as compared to the vehicle-treated population (**Fig. 1b**). In contrast, treatment with EA at the same concentration had no effect on lifespan (**Fig. 1b**). Thus, we decided to continue with a deeper investigation of urolithins, and we focused on UA, as it is the most prevalent EA-derived metabolite observed in humans[5,9]. We found a clear dose-response effect on lifespan when UA concentrations were increased from 10 to 50 μM (**Fig. 1c**). At 50 μM, UA significantly delayed the mortality observed at advanced ages (**Fig. 1d**; $P \leq 0.001$).

Similar to other organisms, fasting is one of the well-known mechanisms by which worm lifespan can be extended[13]. Fasting can be induced if a compound affects bacterial growth, thereby reducing the amount of food available or modifying key nutrient amounts[14], or acts as repellent for the worms and prevents food intake. To test the first possibility, we measured the effect of UA on bacterial metabolism by measuring the growth of two *Escherichia coli* strains, OP50 and HT115, after treatment with UA. We found that UA had a very modest effect on the growth of these two strains (**Supplementary Fig. 1a,b**).

- Urolithin A is produced via dietary consumption of ellagitannins their precursor found in the pomegranate fruit
- Extended the lifespan of C. elegans and improved exercise capacity in mouse models and rats
- Improves mitochondrial and muscle function

https://www.nature.com/articles/nm.4132

Urolithin A as nutritional supplement

nature metabolism

LETTERS

https://doi.org/10.1038/s42255-019-0073-4

The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans

Pénélope A. Andreux[1], William Blanco-Bose[1], Dongryeol Ryu[1,2,5], Frédéric Burdet[3], Mark Ibberson[3], Patrick Aebischer[4], Johan Auwerx[2], Anurag Singh[1,6] and Chris Rinsch[1,6]*

Urolithin A (UA) is a natural dietary, microflora-derived metabolite shown to stimulate mitophagy and improve muscle health in old animals and in preclinical models of aging[1]. Here, we report the results of a first-in-human clinical trial in which we administered UA, either as a single dose or as multiple doses over a 4-week period, to healthy, sedentary elderly individuals. We show that UA has a favourable safety profile (primary outcome). UA was bioavailable in plasma at all doses tested, and 4 weeks of treatment with UA at doses of 500 mg and 1,000 mg modulated plasma acylcarnitines and skeletal muscle mitochondrial gene expression in elderly individuals (secondary outcomes). These observed effects on mitochondrial biomarkers show that UA induces a molecular signature of improved mitochondrial and cellular health following regular oral consumption in humans.

During aging, there is progressive decline in the cell's capacity to eliminate its dysfunctional elements by autophagy[1]. Accumulating evidence has highlighted the decrease in the specific autophagy, or recycling, of dysfunctional mitochondria, known as mitophagy, in aging skeletal muscle[1]. This can result in poor mitochondrial function in the skeletal muscle, and has been closely linked to slow walking speed and poor muscle strength in elderly individuals[2,3]. Consequently, improving mitochondrial function in elderly people by restoring levels of mitophagy represents a promising approach to halt or delay the development of age-related decline in muscle health.

UA is a first-in-class natural food metabolite that stimulates mitophagy and prevents the accumulation of dysfunctional mitochondria with age, thereby maintaining mitochondrial biogenesis and respiratory capacity in cells, and, in the nematode *Caenorhabditis elegans*, improving mobility and extending lifespan[1]. In rodents, UA improves endurance capacity in young rats and in old mice either fed a healthy diet or placed under conditions of metabolic challenge[1]. Recently, UA was shown to have a favourable safety profile following a battery of standardized toxicological tests, including subchronic exposure for 90 d in rodent models[4], and received a favourable review by the US Food and Drug Administration under the agency's generally recognized as safe (GRAS) notification program[5].

In this report, we detail the outcome of a first-in-human, randomized, double-blind, placebo-controlled clinical study with UA in healthy, sedentary elderly individuals, and describe its safety, bioavailability and beneficial impact on key biomarkers of mitochondrial health (NCT02655393). Physiological endpoints were not evaluated as part of this study, as the 4-week intervention was considered too short in comparison to the extended protocols (minimum 3 months) deemed necessary to improve muscle strength or physical performance parameters in elderly individuals[2].

This phase 1 study was a two-part study, with a single ascending dose (part A) followed by a multiple ascending dose (part B). As the first objective of the study was safety assessment, the dose escalation was designed to progress from the lowest to the highest UA dose investigated in both parts of the study. Dose escalation to the next higher UA dose was always twofold higher than the previous dose (see Methods and Supplementary Table 1 for the decision tree and stopping rule criteria to advance to the next higher UA dose). During part A of the study, three cohorts of eight subjects each (24 subjects) received either placebo or UA in a two-period design separated by a minimum 3-week wash-out period and at single ascending doses of 250, 500, 1,000 or 2,000 mg, either in soft gels or admixed with food (Fig. 1a, also the CONSORT diagram in Supplementary Fig. 1). In part B of the study, three cohorts of 12 elderly subjects were given either placebo or UA at 250, 500 or 1,000 mg once daily in soft gels for 28 d (Fig. 1a and Supplementary Fig. 1). The lowest dose of 250 mg was chosen on the basis of preclinical studies, where the equivalent daily dosing of 50 mg per kg (mpk) of body weight in mice demonstrated efficacy on mitochondrial and muscle function after a 6-week oral intervention[1]. Clinical study treatment groups were evenly matched for age, sex and body mass index, and all of the subjects were sedentary at the time of inclusion in the study (Supplementary Tables 2 and 3). All enrolled subjects completed the study, there were no major deviations in the clinical protocol or in product intake, and no subjects were excluded in the final analysis for the main study endpoints (Supplementary Fig. 1).

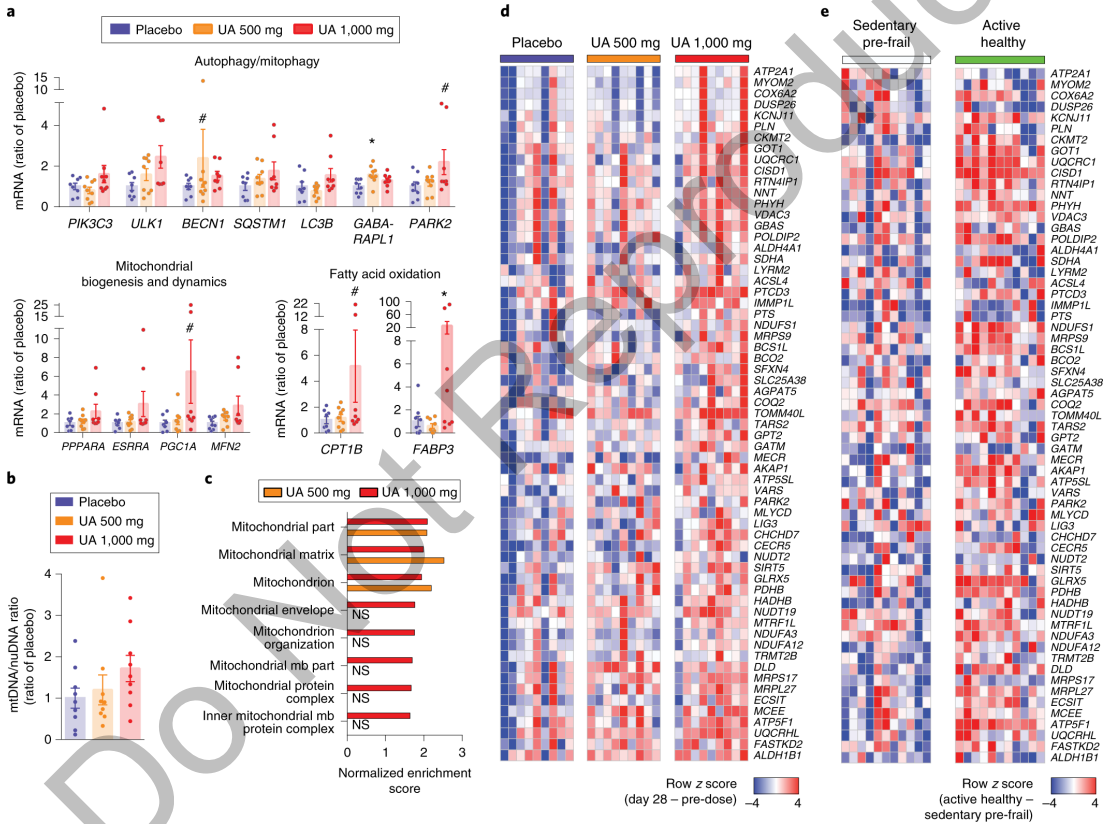
As the study was a single and multiple dose escalation phase 1 study, designed according to guidelines and recommendations for first-in-human studies[7] and following standard dose escalation safety trial design[8–10], it was powered to meet the primary outcome of safety and tolerability of UA in elderly humans to provide sufficient information on human safety and pharmacokinetic profile and to allow dose selection for future phase 2 efficacy trials (see also Methods).

Confirmed in clinical trials that Urolithin A induces molecular signature of improved mitochondrial and cellular health following regular oral consumption in humans

Not all humans are equal and only 30% of us have enough Urolithin A levels (generated by their microbiota)

https://www.nature.com/articles/s42255-019-0073-4

Urolithin A positively impacts markers of mitochondrial function after 28d



https://www.nature.com/articles/s42255-019-0073-4

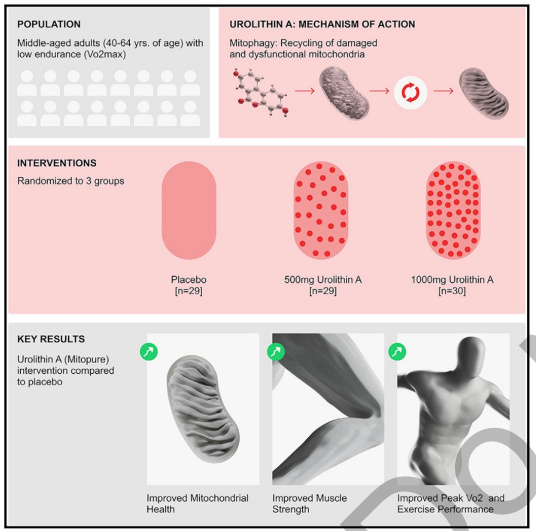
Effect of Urolithin A in middle-aged adults

Cell Reports
Medicine

Article

Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults

Graphical abstract



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In brief

Singh et al. investigate the impact of oral supplementation with Urolithin A, a gut microbiome postbiotic known to activate mitophagy, in a randomized clinical trial in middle-aged adults. Results show that supplementation results in improvements in muscle strength and exercise-performance measures along with an impact on mitochondrial biomarkers.

Highlights

- Oral supplementation with Urolithin A increases muscle strength
- High dose of Urolithin A positively impacts exercise-performance measures
- An increase in mitophagy proteins in human skeletal muscle observed in parallel
- Supplementation is safe and increases circulating levels of Urolithin A

N=88 (placebo, 500 mg, 1000mg)

https://doi.org/10.1016/j.xcrm.2022.100633

Effect of Urolithin A in older adults

JAMA Network | Open.

Original Investigation | Nutrition, Obesity, and Exercise

Effect of Urolithin A Supplementation on Muscle Endurance and Mitochondrial Health in Older Adults
A Randomized Clinical Trial

Sophia Liu, PhD; Davide D'Amico, PhD; Eric Shankland, PhD; Saakshi Bhayana, BS; Jose M. Garcia, MD, PhD; Patrick Aebischer, MD; Chris Rinsch, PhD; Anurag Singh, MD, PhD; David J. Marcinek, PhD

Abstract

IMPORTANCE Aging is associated with a decline in mitochondrial function and reduced exercise capacity. Urolithin A is a natural gut microbiome-derived food metabolite that has been shown to stimulate mitophagy and improve muscle function in older animals and to induce mitochondrial gene expression in older humans.

OBJECTIVE To investigate whether oral administration of urolithin A improved the 6-minute walk distance, muscle endurance in hand and leg muscles, and biomarkers associated with mitochondrial and cellular health.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, placebo-controlled randomized clinical trial in adults aged 65 to 90 years was conducted at a medical center and a cancer research center in Seattle, Washington, from March 1, 2018, to July 30, 2020. Muscle fatigue tests and plasma analysis of biomarkers were assessed at baseline, 2 months, and 4 months. Six-minute walk distance and maximal ATP production were assessed using magnetic resonance spectroscopy at baseline and at the end of study at 4 months. The analysis used an intention-to-treat approach.

INTERVENTIONS Participants were randomized to receive daily oral supplementation with either 1000 mg urolithin A or placebo for 4 months.

MAIN OUTCOMES AND MEASURES The primary end point was change from baseline in the 6-minute walk distance and change from baseline to 4 months in maximal ATP production in the hand skeletal muscle. The secondary end points were change in muscle endurance of 2 skeletal muscles (tibialis anterior [TA] in the leg and first dorsal interosseus [FDI] in the hand). Cellular health biomarkers were investigated via plasma metabolomics. Adverse events were recorded and compared between the 2 groups during the intervention period.

RESULTS A total of 66 participants were randomized to either the urolithin A (n = 33) or the placebo (n = 33) intervention group. These participants had a mean (SD) age of 71.7 (4.94) years, were predominantly women (50 [75.8%]), and were all White individuals. Urolithin A, compared with placebo, significantly improved muscle endurance (ie, increase in the number of muscle contractions until fatigue from baseline) in the FDI and TA at 2 months (urolithin A: FDI, 95.3 [115.5] and TA, 41.4 [65.5]; placebo: FDI, 11.6 [147.4] and TA, 5.7 [127.1]). Plasma levels of several acylcarnitines, ceramides, and C-reactive protein were decreased by urolithin A, compared with placebo, at 4 months (baseline vs 4 mo: urolithin A, 2.14 [2.15] vs 2.07 [1.46]; placebo, 2.17 [2.52] vs 2.65 [1.86]). The mean (SD) increase from baseline in the 6-minute walk distance was 60.8 (67.2) m in the urolithin A group and 42.5 (73.3) m in the placebo group. The mean (SD) change from baseline to 4

Key Points

Question What is the effect of supplementation with urolithin A, a natural gut microbiome-derived food metabolite, on skeletal muscle performance and mitochondrial health in older adults?

Findings In this randomized clinical trial of 66 older adults, those who received supplementation with 1000 mg of urolithin A had a significant improvement in muscle endurance (number of muscle contractions until fatigue) for both hand and leg skeletal muscles compared with those who used placebo. Plasma levels of several acylcarnitines, ceramides (biomarkers of mitochondrial health), and C-reactive protein were decreased after urolithin A supplementation.

Meaning These findings indicate that urolithin A was safe and well tolerated as well as beneficial for muscle endurance and mitochondrial health in older adults; it may also be a promising approach to counteracting age-associated muscle decline.

+ Visual Abstract

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Effect urolithin A supplement on skeletal muscle performance + mitochondrial health in older adults

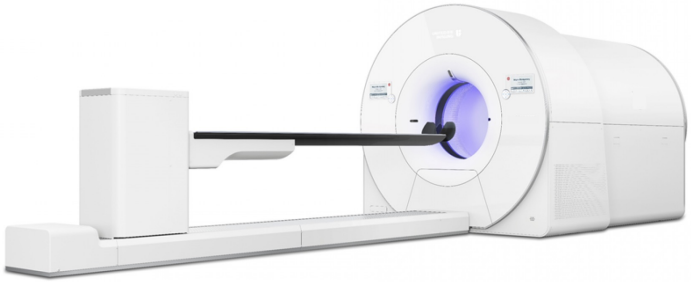
→ Significant improvement in muscle endurance and

→ Decreased C-reactive protein

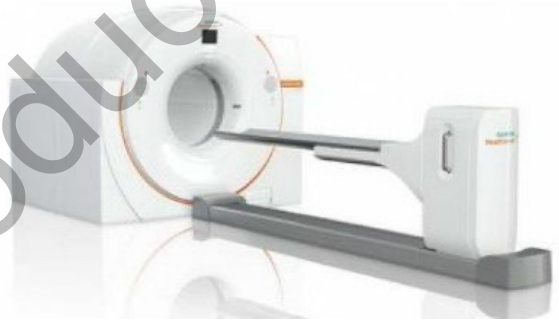
Promising approach to counteracting age-associated muscle decline

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2788244

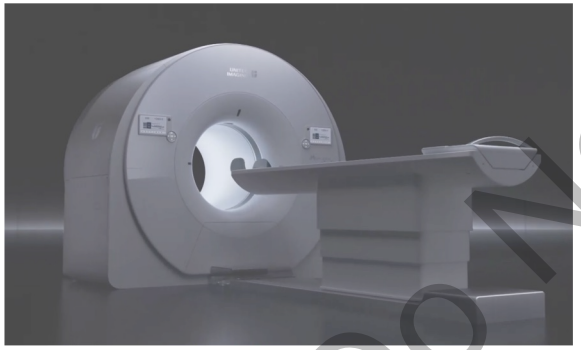
Total-body PETs



https://explorer.ucdavis.edu



https://www.siemens-healthineers.com/



https://usa.united-imaging.com/products/molecular-imaging/umi-panorama#tab-2

https://www.wt-pet.org

Atlas of glucose uptake by the total-body PET/CT

JOURNAL ARTICLE

An atlas of glucose uptake across the entire human body as measured by the total-body PET/CT scanner: a pilot study

Weizhao Lu, Zhaoping Cheng, Xue Xie, Kun Li, Yanhua Duan, Min Li, Chao Ma, Sijin Liu, Jianfeng Qiu ✉ Author Notes

Life Metabolism, Volume 1, Issue 2, October 2022, Pages 190–199,
https://doi.org/10.1093/lifemeta/loac030
Published: 27 October 2022 **Article history** ▾

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Abstract

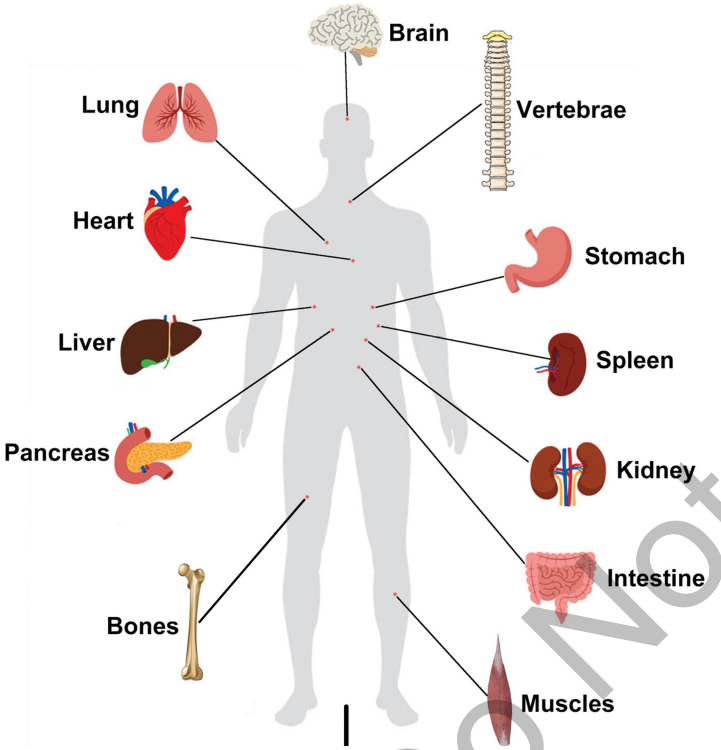
Glucose uptake differs in organs and tissues across the human body. To date, however, there has been no single atlas providing detailed glucose uptake profiles across the entire human body. Therefore, we aimed to generate a detailed profile of glucose uptake across the entire human body using the uEXPLORER positron emission tomography/computed tomography scanner, which offers the opportunity to collect glucose metabolic imaging quickly and simultaneously in all sites of the body. The standardized uptake value normalized by lean body mass (SUL) of 18F-fluorodeoxyglucose was used as a measure of glucose uptake. We developed a fingerprint of glucose uptake reflecting the mean SULs of major organs and parts across the entire human body in 15 healthy-weight and 18 overweight subjects. Using the segmentation of organs and body parts from the atlas, we uncovered the significant impacts of age, sex, and obesity on glucose uptake in organs and parts across the entire body. A difference was recognized between the right and left side of the body. Overall, we generated a total-body glucose uptake atlas that could be used as the reference for the diagnosis and evaluation of disordered states involving dysregulated glucose metabolism.

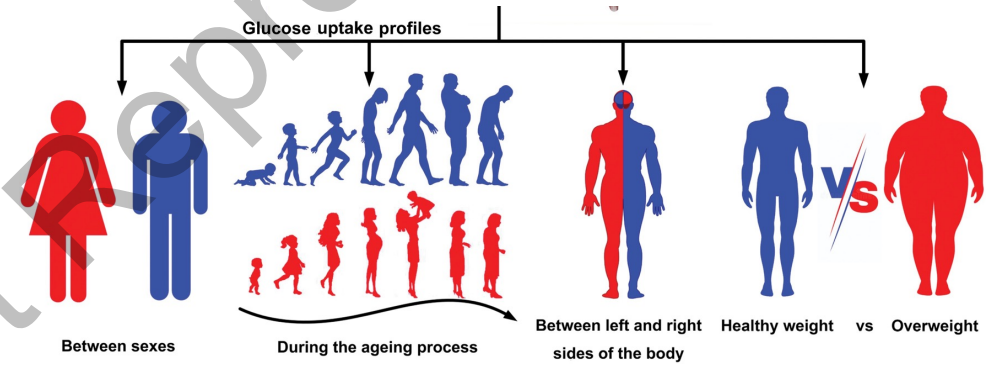
Keywords: glucose uptake, PET/CT, glucose uptake atlas, uEXPLORER
Issue Section: Original Articles

- N=15 healthy-weight + 18 overweight subjects
- Effect of age, sex, and obesity on glucose uptake in organs and parts across the entire body
- Difference was seen between the right and left side of the body.
- Generation of total-body glucose uptake atlas as reference for diagnosis and evaluation of disordered states involving dysregulated glucose metabolism

https://academic.oup.com/lifemeta/article/1/2/190/6775914

Atlas of glucose uptake by the total-body PET/CT





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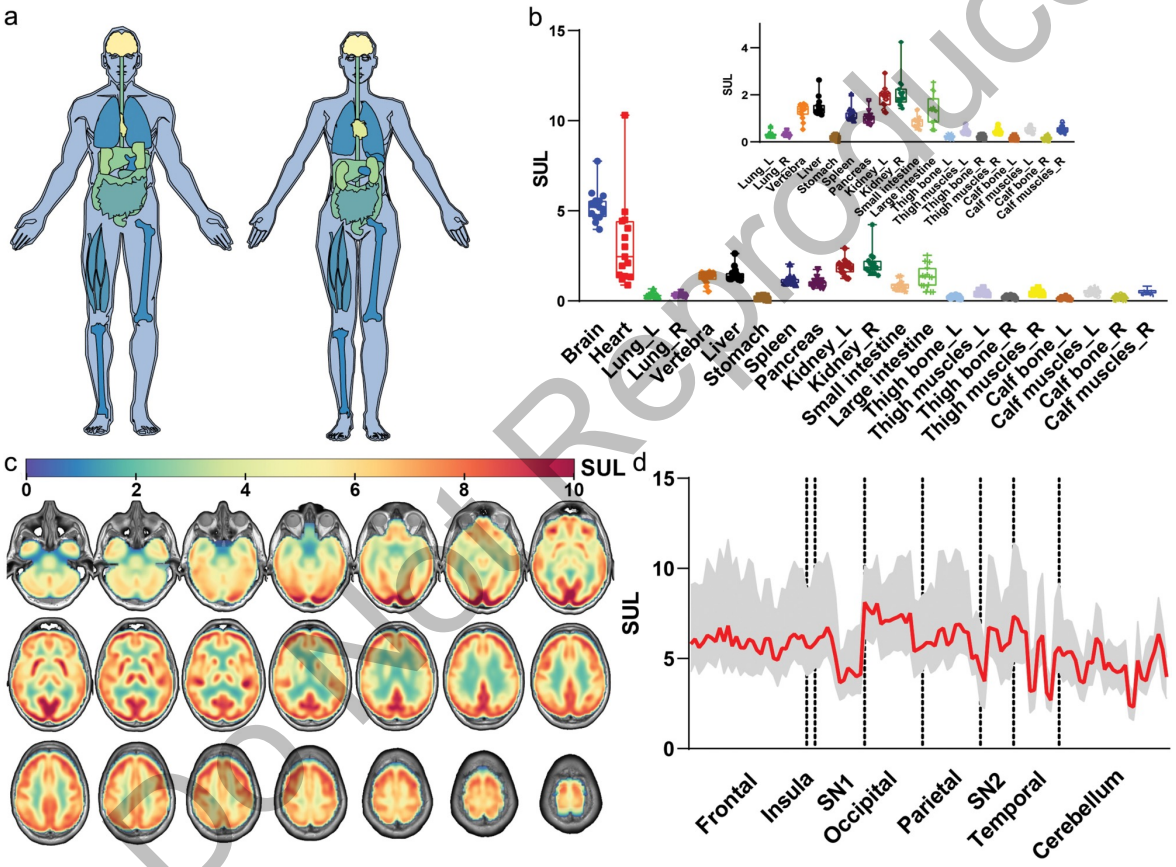
Atlas of glucose uptake by the total-body PET/CT



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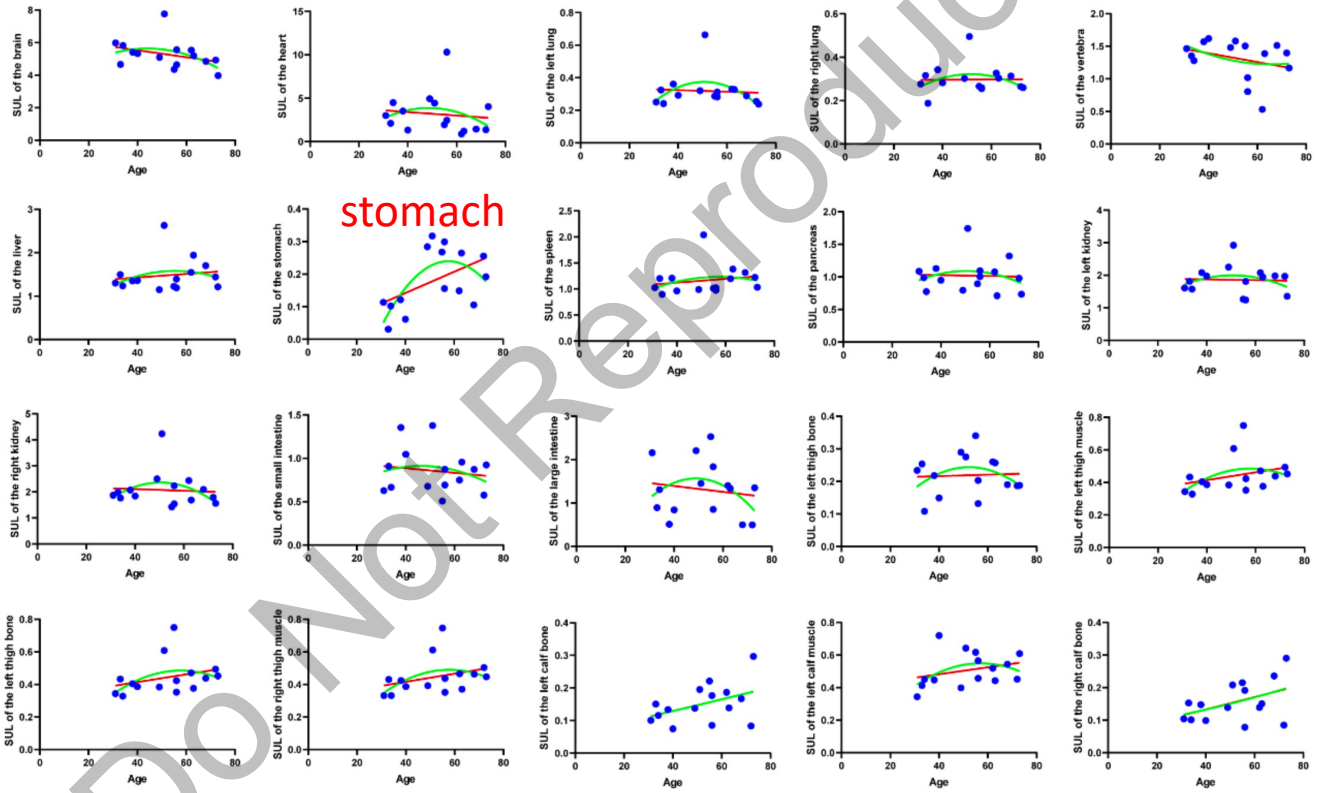
Atlas of glucose uptake by the total-body PET/CT

Effect of age



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Atlas of glucose uptake by the total-body PET/CT

15 healthy subjects

18 overweighted subjects

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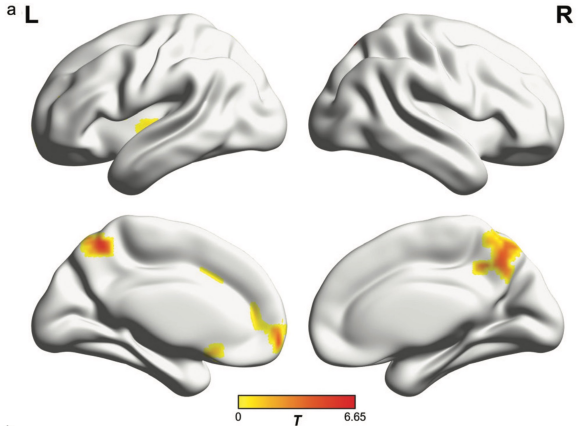
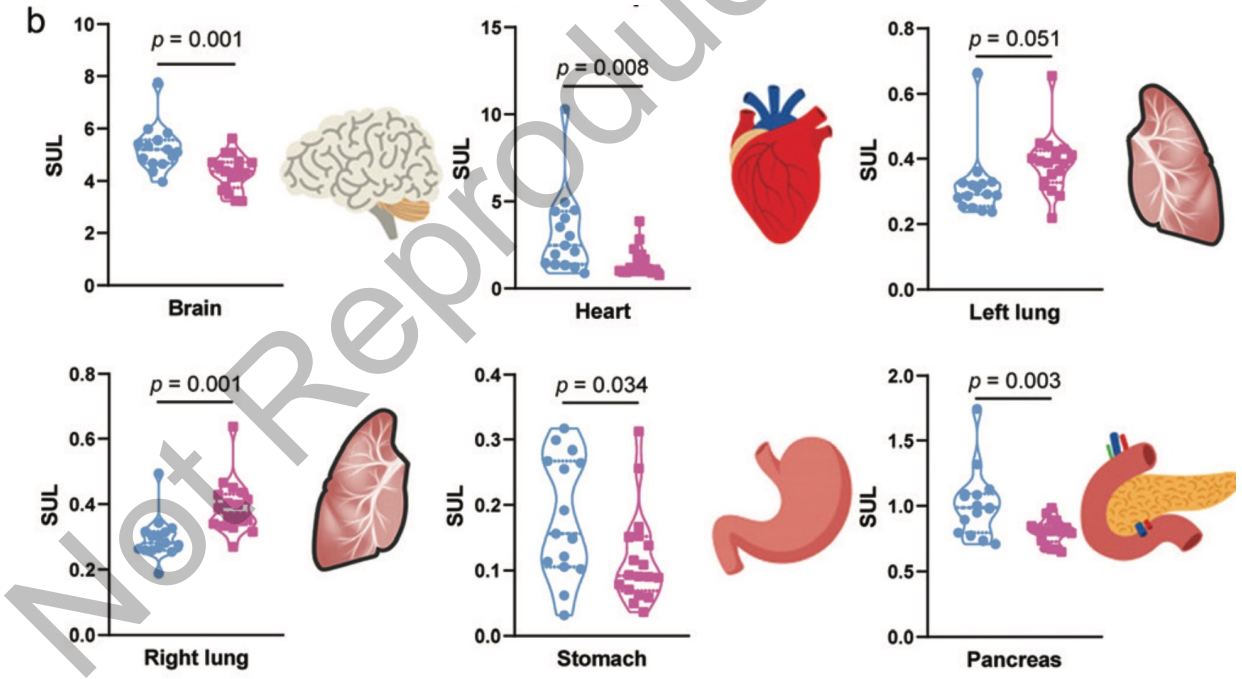
Healthy vs. overweigthed subjects





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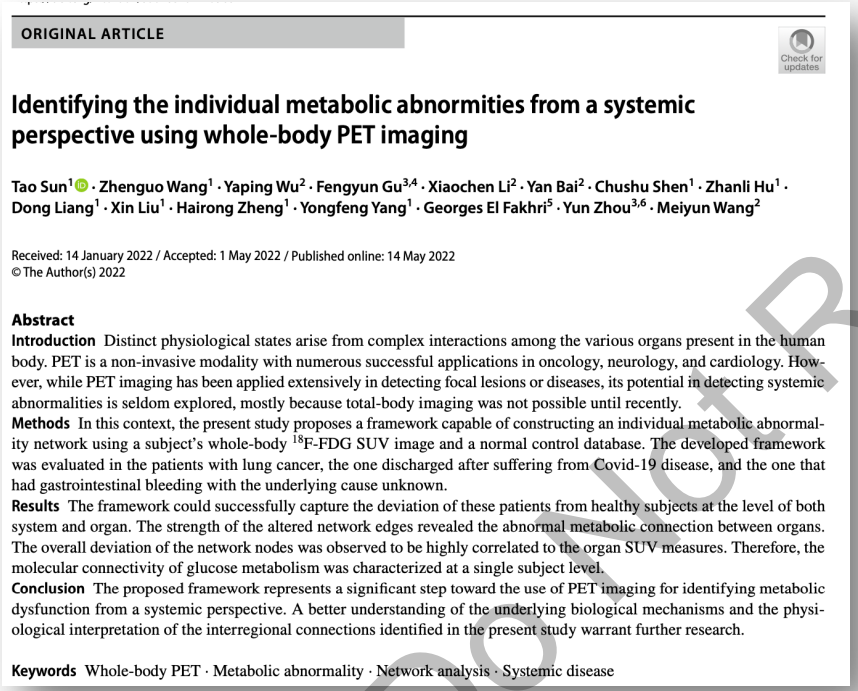
Whole-Body PET insights about individual metabolic abnormalities



ORIGINAL ARTICLE

Check for updates

Identifying the individual metabolic abnormities from a systemic perspective using whole-body PET imaging

Tao Sun[1] · Zhenguo Wang[1] · Yaping Wu[2] · Fengyun Gu[3,4] · Xiaochen Li[2] · Yan Bai[2] · Chushu Shen[1] · Zhanli Hu[1] · Dong Liang[1] · Xin Liu[1] · Hairong Zheng[1] · Yongfeng Yang[1] · Georges El Fakhri[5] · Yun Zhou[3,6] · Meiyun Wang[2]

Received: 14 January 2022 / Accepted: 1 May 2022 / Published online: 14 May 2022

Abstract

Introduction Distinct physiological states arise from complex interactions among the various organs present in the human body. PET is a non-invasive modality with numerous successful applications in oncology, neurology, and cardiology. However, while PET imaging has been applied extensively in detecting focal lesions or diseases, its potential in detecting systemic abnormalities is seldom explored, mostly because total-body imaging was not possible until recently.

Methods In this context, the present study proposes a framework capable of constructing an individual metabolic abnormality network using a subject's whole-body ^{18}F-FDG SUV image and a normal control database. The developed framework was evaluated in the patients with lung cancer, the one discharged after suffering from Covid-19 disease, and the one that had gastrointestinal bleeding with the underlying cause unknown.

Results The framework could successfully capture the deviation of these patients from healthy subjects at the level of both system and organ. The strength of the altered network edges revealed the abnormal metabolic connection between organs. The overall deviation of the network nodes was observed to be highly correlated to the organ SUV measures. Therefore, the molecular connectivity of glucose metabolism was characterized at a single subject level.

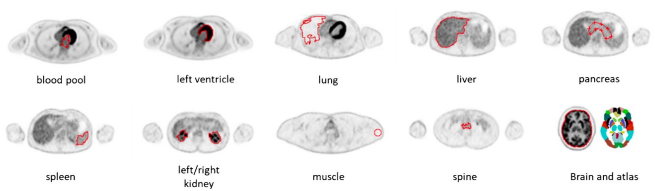
Conclusion The proposed framework represents a significant step toward the use of PET imaging for identifying metabolic dysfunction from a systemic perspective. A better understanding of the underlying biological mechanisms and the physiological interpretation of the interregional connections identified in the present study warrant further research.

Keywords Whole-body PET · Metabolic abnormality · Network analysis · Systemic disease

- Framwork comparing individual patients metabolic F-18-FDG SUV to a normal database
- Looking for interegional connections from a systemic perspective

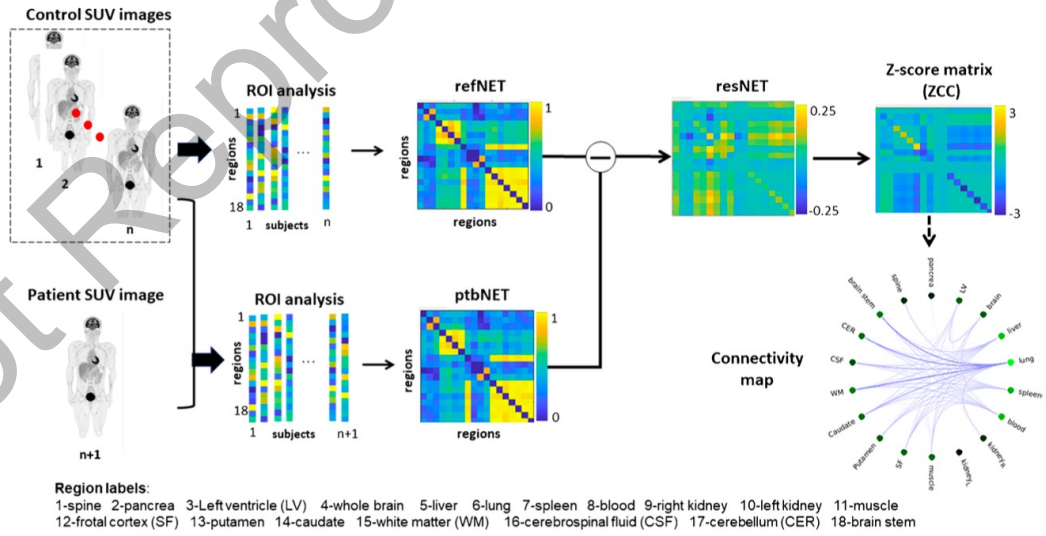
https://doi.org/10.1007/s00259-022-05832-7

Framework for obtaining the individual metabolic network from a patient scan



18 samples regions
(11 organs, 7 brain subregions)

Reference

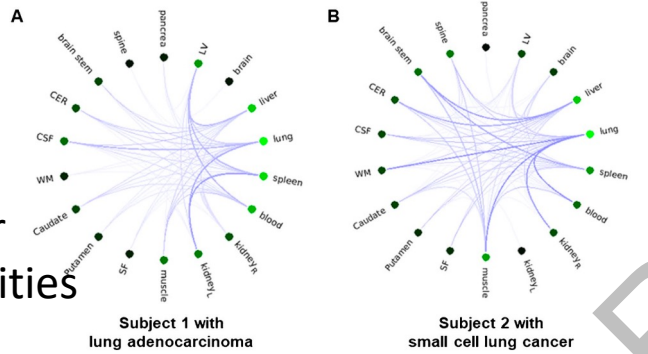


Patient

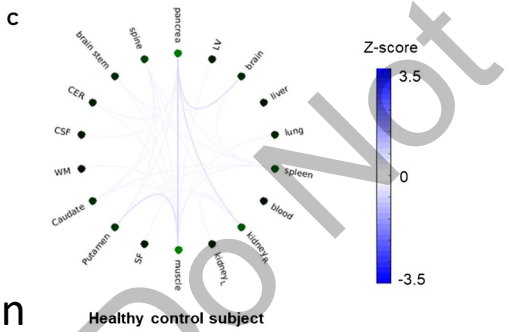
https://doi.org/10.1007/s00259-022-05832-7

Metabolic connectivity plots

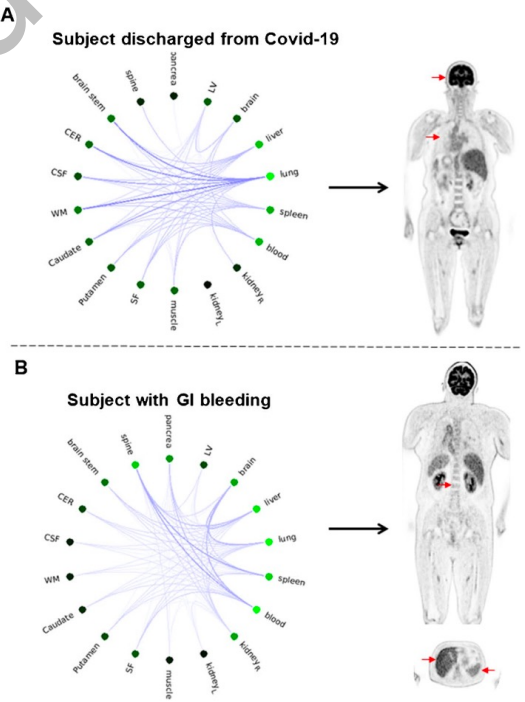
Lung cancer heterogeneities



Healthy control: pancreas-muscle connection



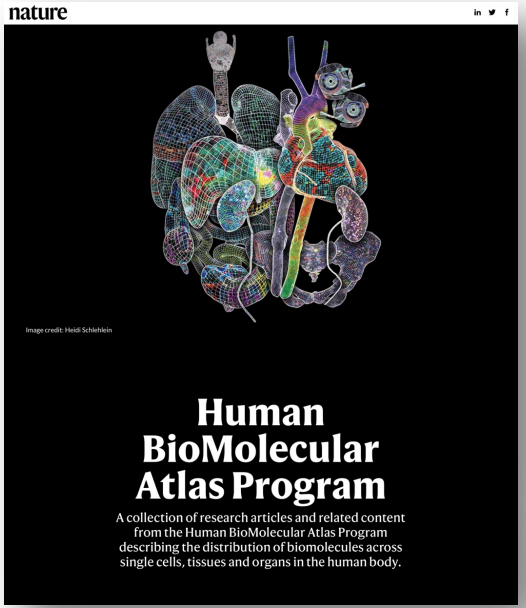
Connectivity plots with denser and stronger conneections in disease

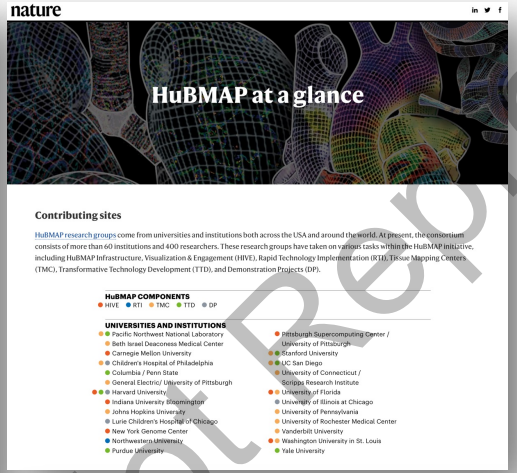


Preliminary step, adaptable to other tracers, Ki, DV, blood flow, etc.

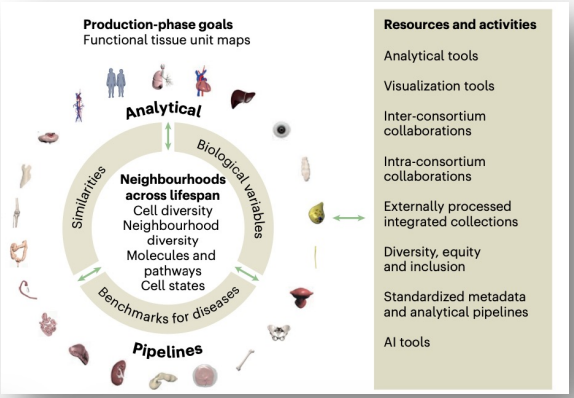
https://doi.org/10.1007/s00259-022-05832-7

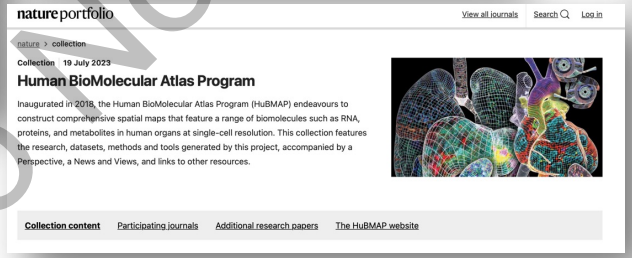
Mapping Health in the human body

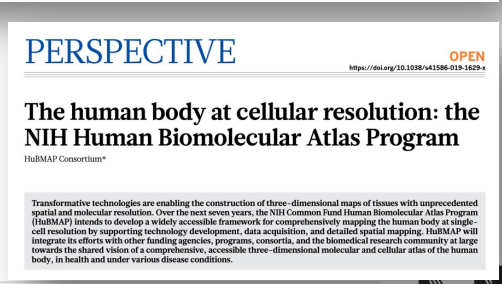




FDG PET = transformative technology



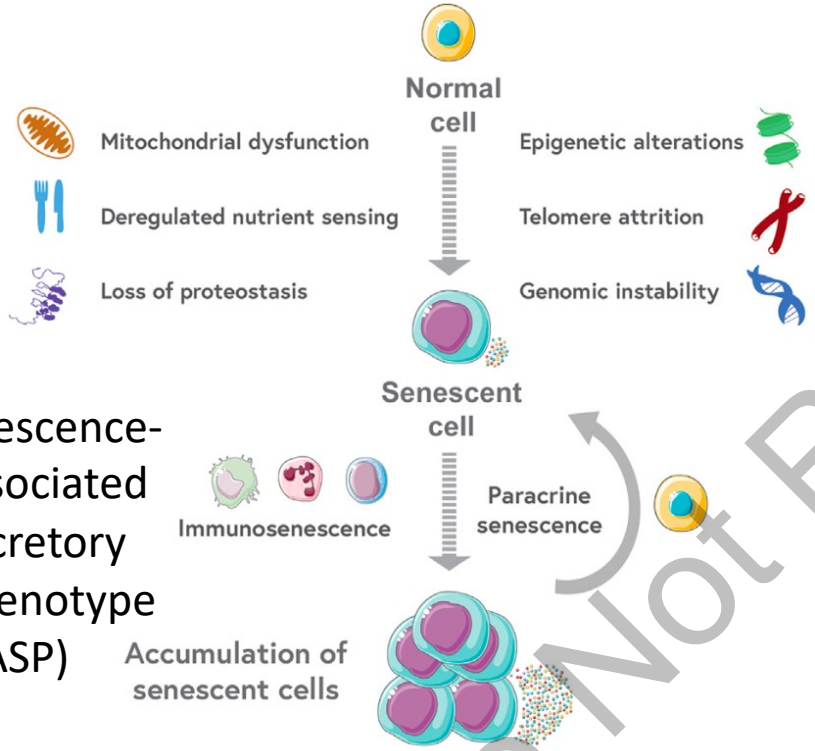




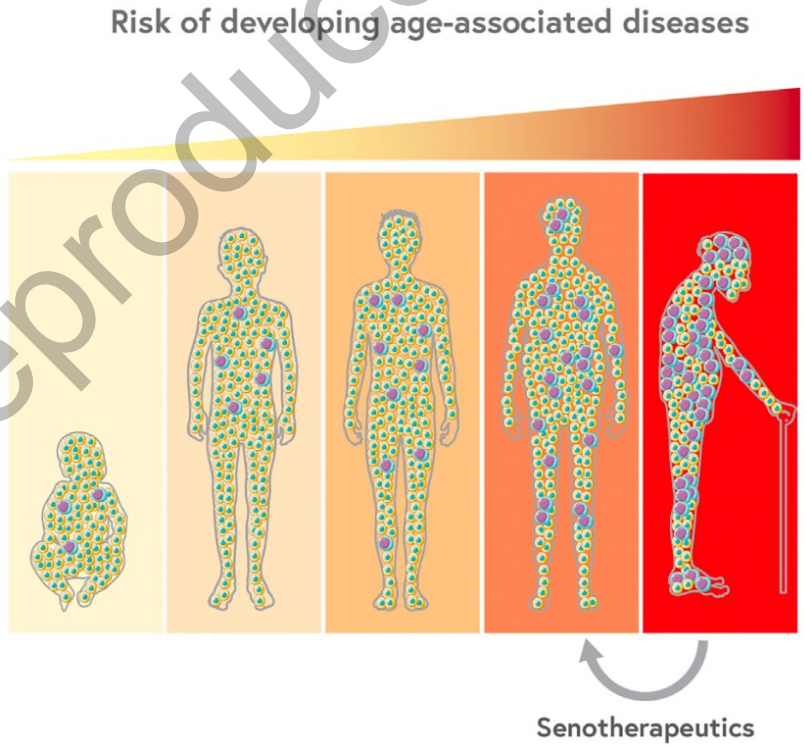
Why not add PET/CT?

https://www.nature.com/immersive/d42859-023-00019-y/index.html and https://www.nature.com/articles/s41556-023-01194-w

A Senescence-Centric View of Aging

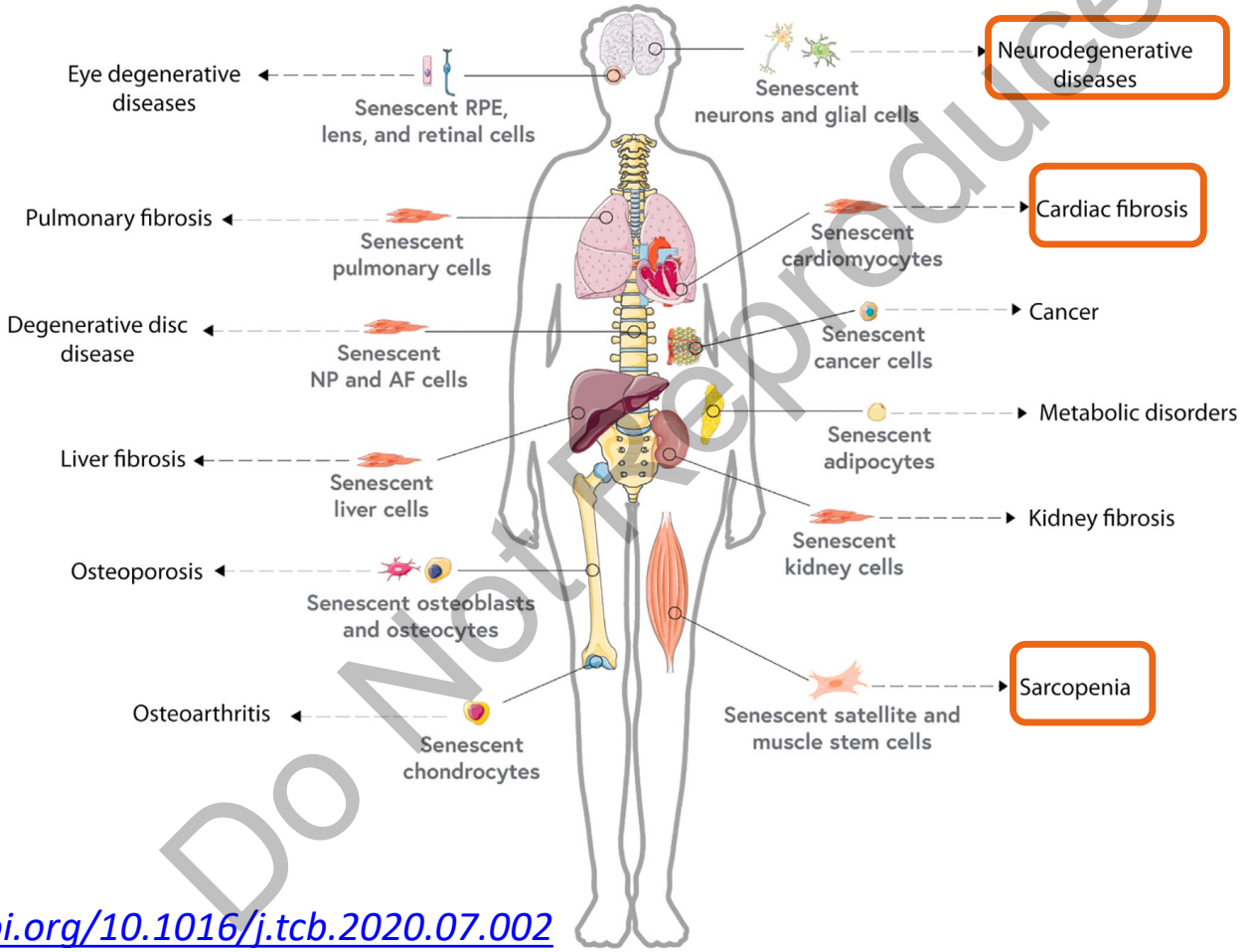


Snescence-associated secretory phenotype (SASP)



https://doi.org/10.1016/j.tcb.2020.07.002

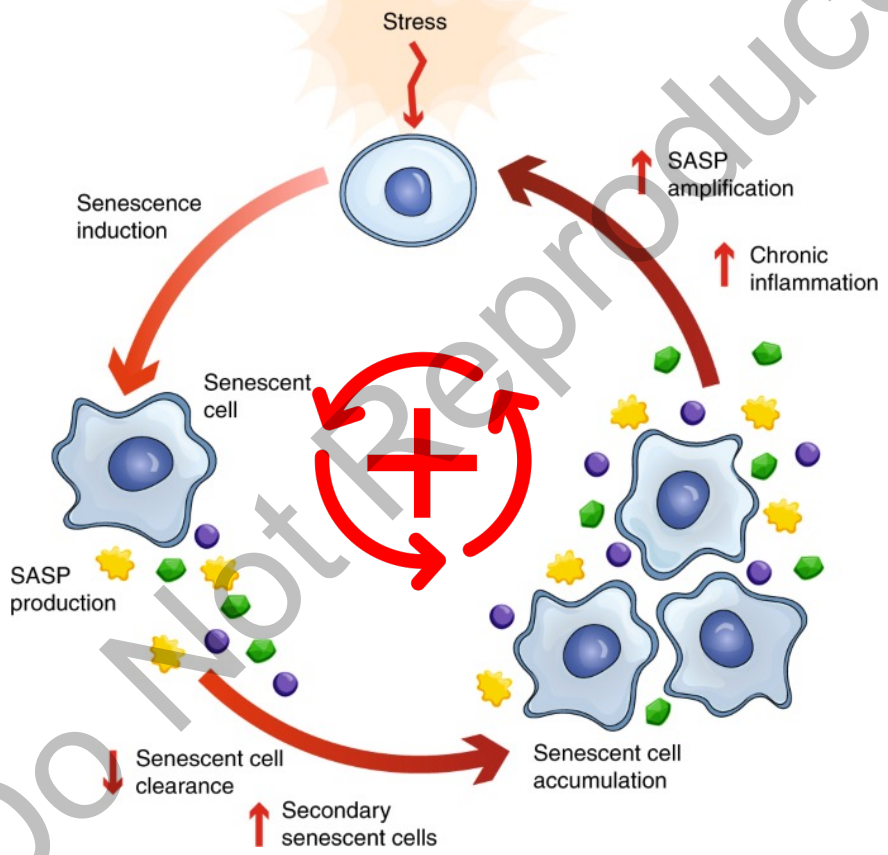
Senescent Cells Play a Role in Age-Associated Diseases



https://doi.org/10.1016/j.tcb.2020.07.002

Senescent cell accumulation

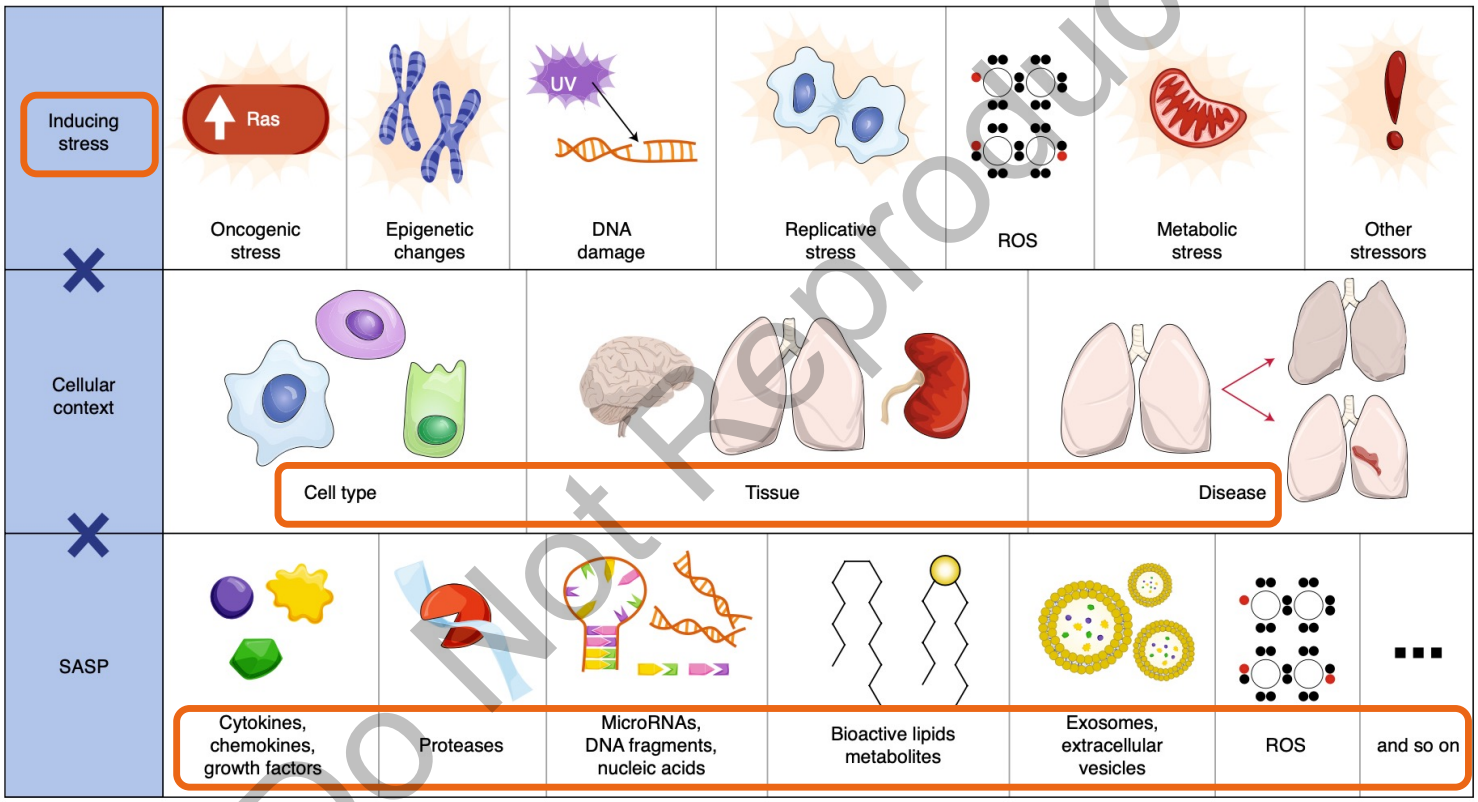
Positive-feedback loop leading to more senescence-associated secretory phenotype (SASP) and more senescent cells



Inflammaging: low-grade chronic inflammation causing higher risk of morbidity and mortality in elderly

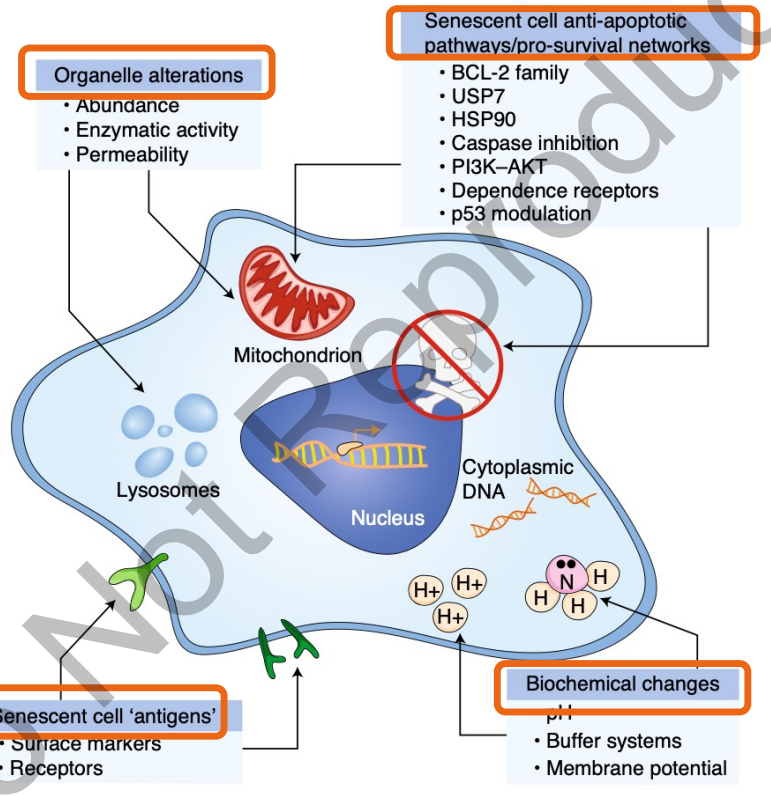
https://www.nature.com/articles/s43587-021-00121-8

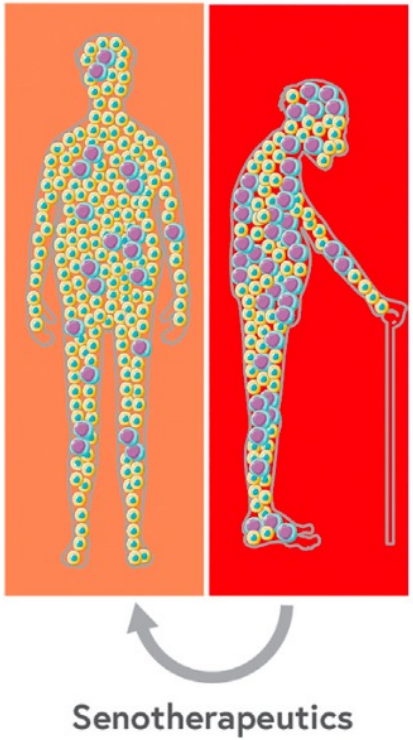
Heterogeneity in cellular senescence



https://www.nature.com/articles/s43587-021-00121-8

Targets of senolytics





https://www.nature.com/articles/s43587-021-00121-8

Clinical Trials with Senotherapeutic Compounds

Study identifier[a]	Type	Condition	Participants	Senolytic
NCT02848131 (Mayo Clinic)	Phase II R[c], OL	Diabetic kidney disease	*n* = 9 (female *n* = 2, male *n* = 7, mean age: 68.7 yr)	D+Q (3 consecutive days) D: 100 mg/day (d) Q: 1000 mg/d
NCT02874989 (Wake Forest University)	Phase I R, OL, P	Idiopathic pulmonary fibrosis	*n* = 14 (≥50 yr)	D+Q (3 consecutive days for 3 wk) D: 100 mg/d Q: 1250 mg/d
NCT02652052 (Mayo Clinic)	Pilot R, OL	Stem cell transplant	*n* = 10 (HSCT survivors ≥18 yr)	D+Q (3 consecutive days) D: 100 mg/d Q: 1000 mg/d
NCT04063124: SToMP-AD (Texas Health Science Center)	Phase I/II OL	AD	*n* = 5 (>65y)	D+Q (intermittent: 2 d on, 14 d off for 12 wk)
NCT04313634 (Mayo Clinic)	Phase II R, OL	Healthy (aging)	*n* = 120 (female ≥70 yr)	D+Q or Fisetin (5 dosing periods repeated every 28 d over 20 wk) D: 100 mg/d (2 d) Q: 1000 mg/d (3 d) Fisetin: 20 mg/kg/d (3 d)
NCT03325322 (Mayo Clinic)	Phase II R, DB, P	CKD	*n* = 30 (40–80 yr)	Fisetin: 20 mg/kg/d for 2 consecutive days
NCT03430037: AFFIRM (Mayo Clinic)	Phase II R, DB, P	Frail elderly syndrome	*n* = 40 (female ≥70 yr)	Fisetin: 20 mg/kg/d for 2 consecutive days/wk (2 mo)
NCT03675724: AFFIRM-LITE (Mayo Clinic)	Phase II R, DB, P	Frail elderly syndrome	*n* = 40 (adult ≥70 yr)	Fisetin: 20 mg/kg/d for 2 consecutive days (single dose)
NCT04210986 (Steadman Philippon Research Institute)	Phase I/II R, DB, P	OA (knee)	*n* = 72 (adult 40–80 yr)	Fisetin: 20 mg/kg/d for 2 consecutive days/wk
NCT03513016 (Unity Biotechnology)	Phase I R, DB, P	OA (knee)	*n* = 78 (adult 40–85 yr)	UBX0101: dose-finding study (single dose)
NCT04129944 (Unity Biotechnology)	Phase II R, DB, P	OA (knee)	*n* = 180 (adult 40–85 yr)	UBX0101: 0.5, 2.0, or 4.0 mg single dose
NCT04349956 (Unity Biotechnology)	Phase II R, DB, P	OA (knee)	*n* = 180 (adult 40–85 yr)	No intervention: Long-term follow-up study patients NCT04129944
NCT04229225 (Unity Biotechnology)	Phase I R, DB, P	OA (knee)	*n* = 36 (adult 40–85 yr)	UBX0101: 8.0 mg single dose or 2 × 4.0 mg repeat dose

Study identifier[a]	Type	Condition	Participants	Senostatic
NCT01649960: CARE (Mayo Clinic)	Phase I OL	Coronary artery disease	*n* = 13 (adult ≥60 yr)	Rapamycin: 0.5, 1, or 2 mg daily for 12 wk
NCT02874924 (The University of Texas Health Science Center)	Phase II R, DB, P	Aging	*n* = 34 (adult 70–95 yr)	Rapamycin (Rapamune/sirolimus): 1 mg daily for 8 wk
NCT03103893 (Drexel University)	Phase I/II OL, P	Dermal atrophy	*n* = 36 (adult 40–100 yr)	Rapamycin (topical on skin) 0.5 ml daily (10 μM cream)
NCT01462006 (NHLBI, University of Virginia)	Pilot R, DB, P	Idiopathic pulmonary fibrosis	*n* = 32 (adult 25–85 yr)	Rapamycin (sirolimus) concentration unknown
NCT04200911: CARPE DIEM (The University of Texas Health Science Center)	Phase I	AD	*n* = 10 (adult 55–85 yr)	Rapamycin (Rapamune/sirolimus): 1 mg orally daily for 8 wks
NCT02432287: MILES (Albert Einstein College of Medicine)	Phase IV R, DB, P	Aging (impaired glucose tolerance)	*n* = 16 (adult ≥60 yr)	Metformin: 1700 mg daily
NCT02570672	Phase II R, DB, P	Frailty	*n* = 120 (adult 65–90 yr)	Metformin: 1000 mg twice daily
NCT03451006 (Mayo Clinic)	Phase II R, DB, P	Frailty	*n* = 12 (adult ≥60 yr)	Metformin: up to 2 g daily for 1 yr
TAME[b]	R, DB, P	Aging and age-associated disease	*n* = 3000 (adult 65–80 yr)	Metformin: 850 mg twice daily
NCT03309007 (University of New Mexico)	Phase III R, DB, P	Prediabetes	*n* = 25 (adult 30–70 yr)	Metformin: 1500 mg daily for 1 mo

Senolytic therapy	Indication	Trial
D + Q	Diabetic kidney disease	NCT02848131
	Alzheimer's disease	ALSENLITE, NCT04785300
		SToMP-AD, NCT04685590
	Accelerated age-like state post bone marrow transplantation	HTSS, NCT02652052
	Accelerated age-like state in childhood cancer survivors	SENSURV, NCT04733534
	Age-related osteoporosis	NCT04313634
Fisetin	Frailty in older women	AFFIRM, NCT03430037
	Diabetic and chronic kidney disease	NCT03325322
	Accelerated age-like state in childhood cancer survivors	SENSURV, NCT04733534
	Age-related osteoporosis	NCT04313634
	Osteoarthritis	NCT04210986
	Coronavirus disease 2019 (COVID-19) in nursing home patients	COVID-FIS, NCT04537299
	COVID-19 in hospitalized patients	COVID-FISETIN, NCT04476953
	COVID-19 in outpatients	COVFIS-HOME, NCT04771611
UBX1325	Diabetic macular edema	NCT04537884

>30 Clinical trials

https://doi.org/10.1016/j.tcb.2020.07.002

https://www.nature.com/articles/s43587-021-00121-8

Immunosenescence and inflammaging in aging

Ageing Research Reviews 71 (2021) 101422

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journal homepage: www.elsevier.com/locate/arr

Immunosenescence and inflammaging in the aging process: age-related diseases or longevity?

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ARTICLE INFO

Keywords:
Aging
Longevity
Centenarians
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Immunosenescence
Inflammaging
COVID-19

ABSTRACT

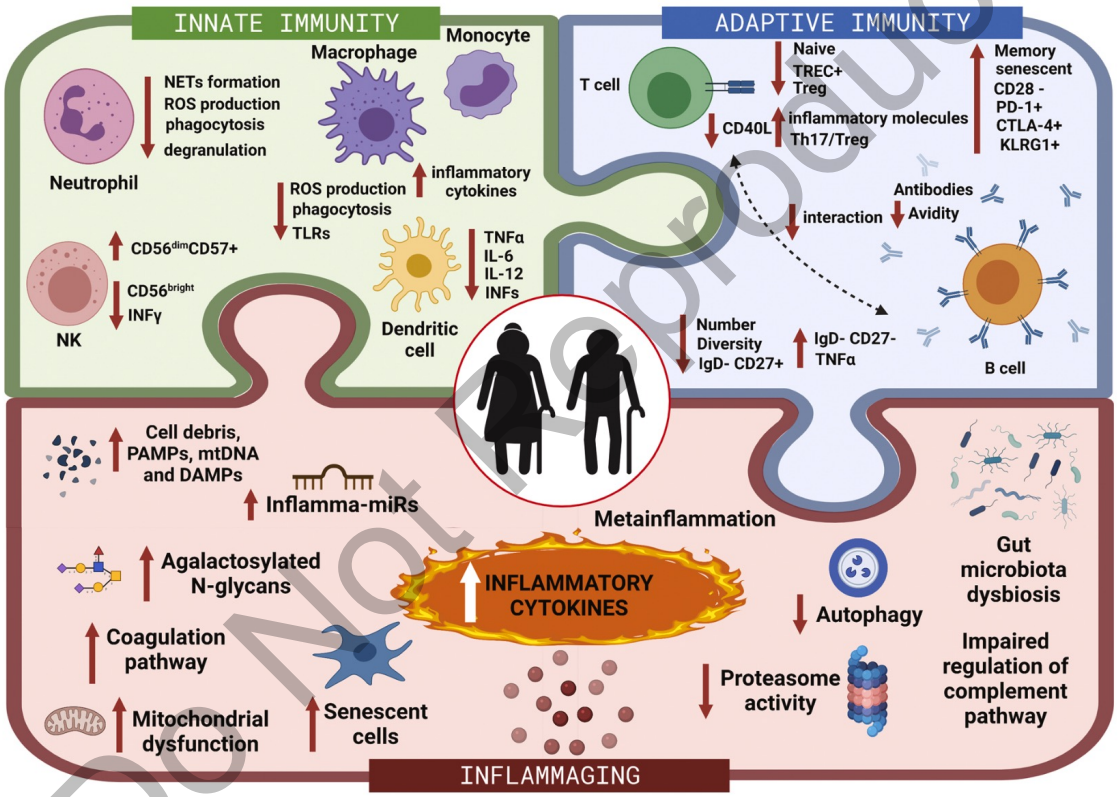
During aging the immune system (IS) undergoes remarkable changes that collectively are known as immunosenescence. It is a multifactorial and dynamic phenomenon that affects both natural and acquired immunity and plays a critical role in most chronic diseases in older people. For a long time, immunosenescence has been considered detrimental because it may lead to a low-grade, sterile chronic inflammation we proposed to call "inflammaging" and a progressive reduction in the ability to trigger effective antibody and cellular responses against infections and vaccinations. Recently, many scientists revised this negative meaning because it can be considered an essential adaptation/remodeling resulting from the lifelong immunological biography of single individuals from an evolutionary perspective. Inflammaging can be considered an adaptive process because it can trigger an anti-inflammatory response to counteract the age-related pro-inflammatory environment. Centenarians represent a valuable model to study the beneficial changes occurring in the IS with age. These extraordinary individuals reached the extreme limits of human life by slowing down the aging process and, in most cases, delaying, avoiding or surviving the major age-associated diseases. They indeed show a complex and heterogeneous phenotype determined by an improved ability to adapt and remodel in response to harmful stimuli. This review aims to point out the intimate relationship between immunosenescence and inflammaging and how these processes impact unsuccessful aging rather than longevity. We also describe the gut microbiota age-related changes as one of the significant triggers of inflammaging and the sex/gender differences in the immune system of the elderly, contributing to the sex/gender disparity in terms of epidemiology, pathophysiology, symptoms and severity of age-related diseases. Finally, we discuss how these phenomena could influence the susceptibility to COVID-19 infection.

- Inflammaging defined as an adaptive process triggering anti-inflammatory response to counteract age-related pro-inflammatory environment
- Centenarians slowed down the aging process and delayed or survived age-associated diseases

https://doi.org/10.1016/j.arr.2021.101422

Innate and adaptive immunity and inflammaging

Innate immunity

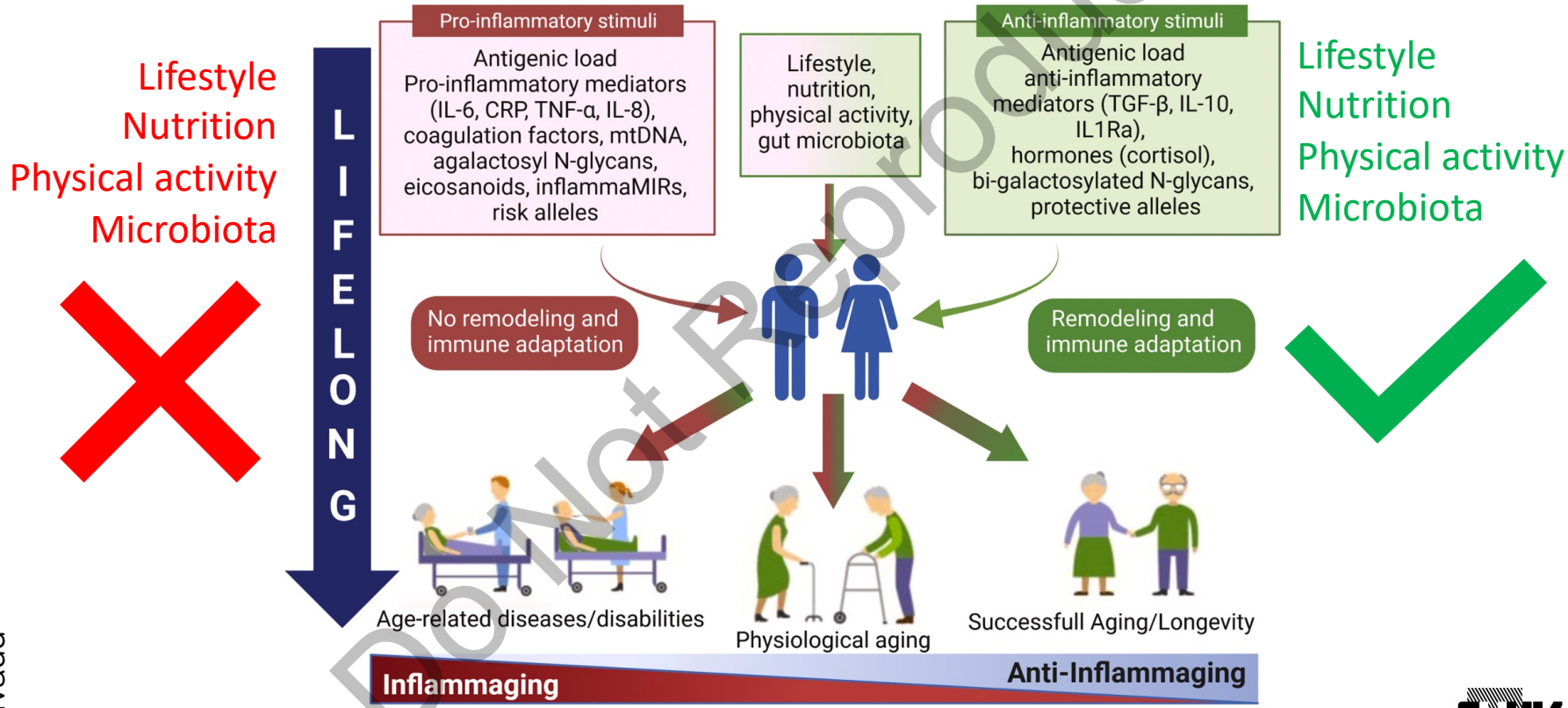


Adaptive immunity

Increase in inflammatory cytokines

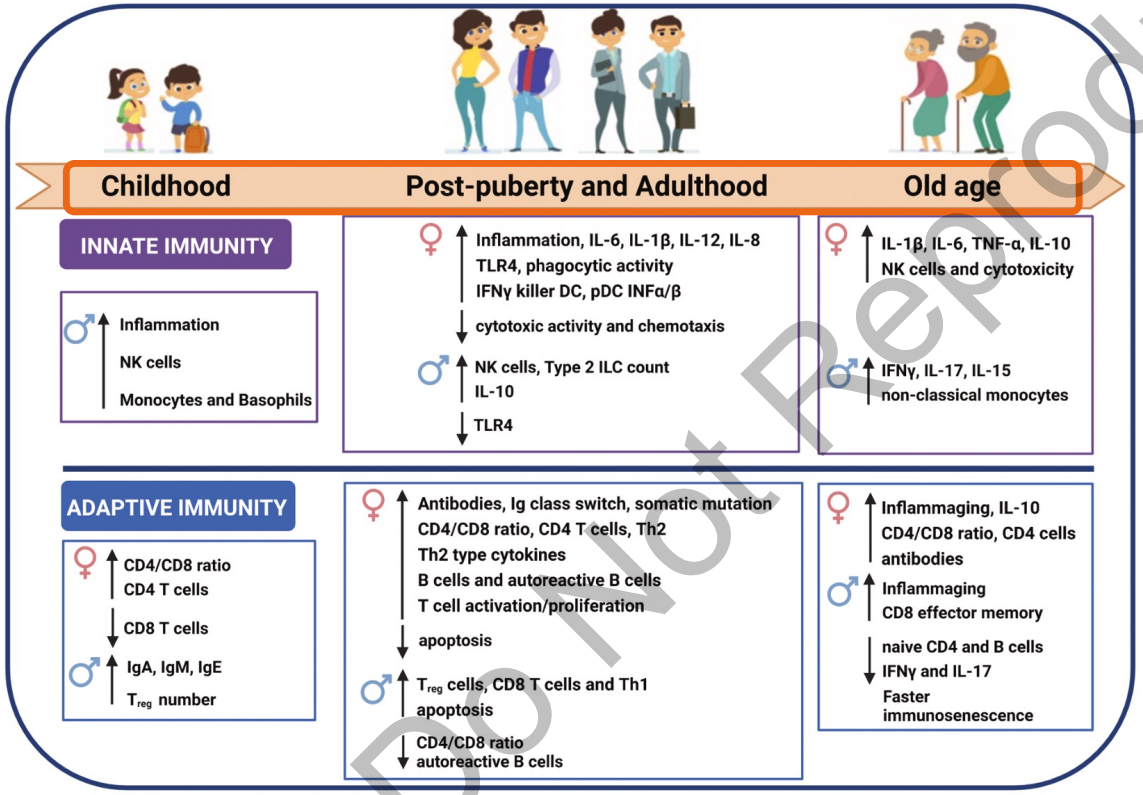
https://doi.org/10.1016/j.arr.2021.101422

Adaptation/maladaptation to lifelong pro- and anti-inflammatory stimuli leads to longevity or diseases.



https://doi.org/10.1016/j.arr.2021.101422

Sex/gender differences in innate and adaptive immunity throughout life

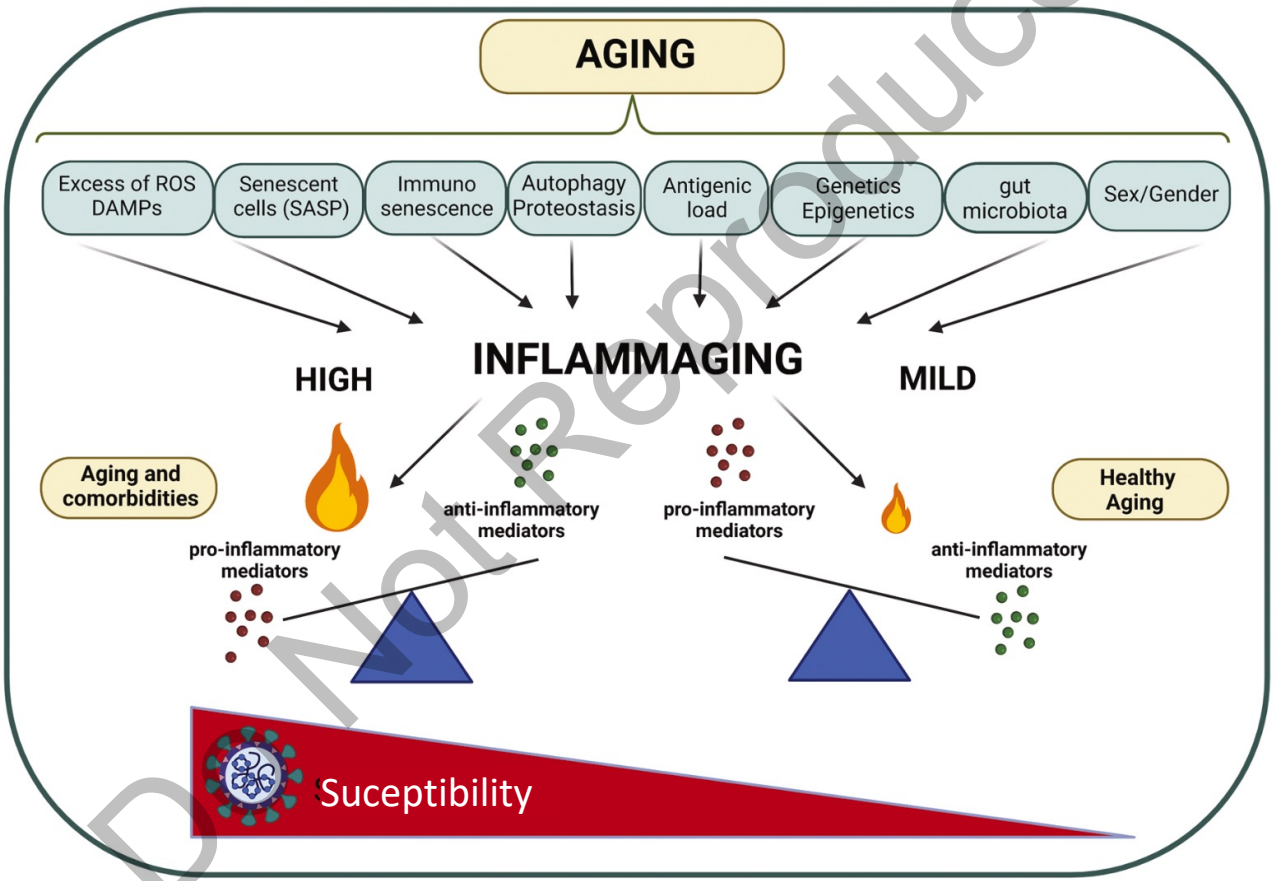


Men have faster progression to immunosenescence than women, highlighted by changes in immune cells and inflammatory mediators

Women's T cells produce more IL-10 than men with age neutralizing adverse effects of inflammaging (but have 2–10-fold more autoimmune disease)

https://doi.org/10.1016/j.arr.2021.101422

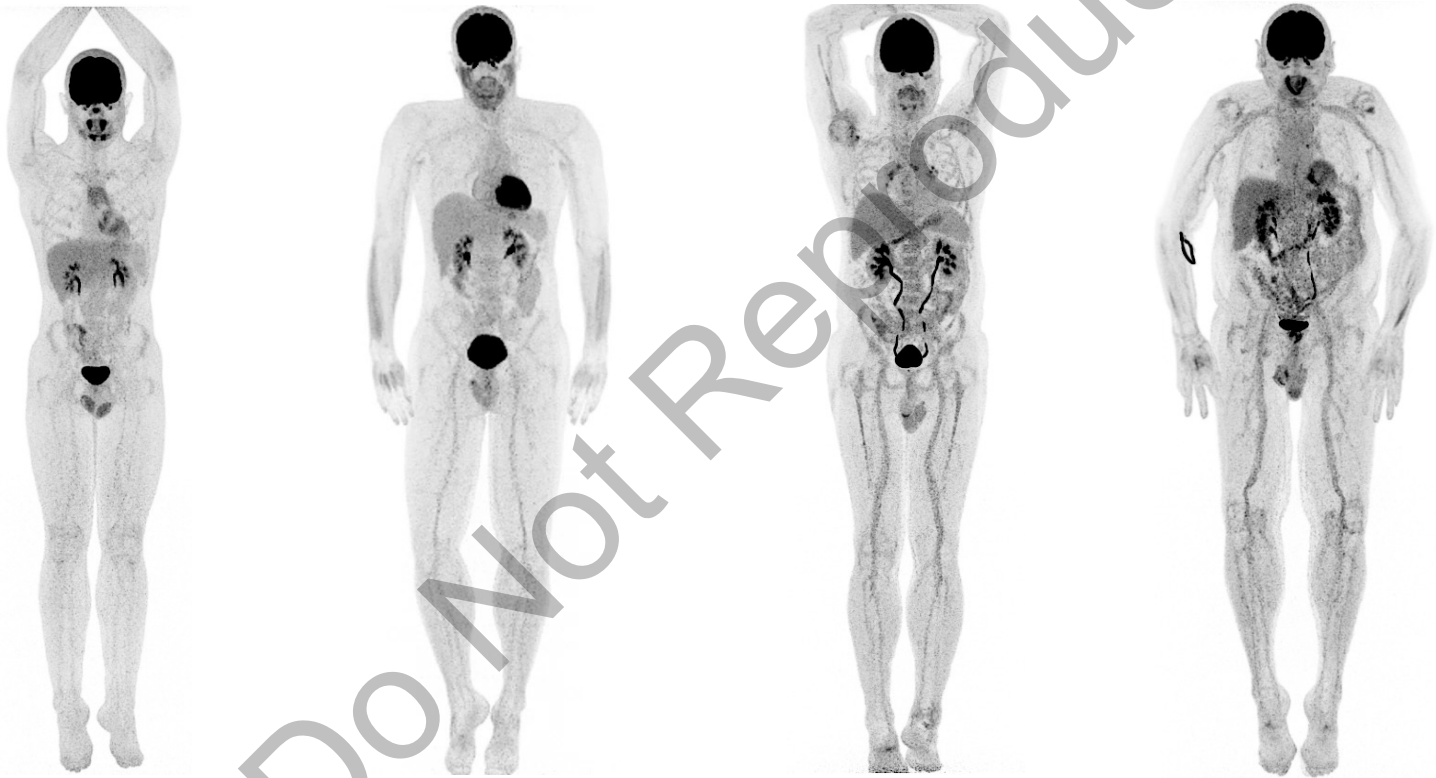
Inflammaging and susceptibility to COVID 19



https://doi.org/10.1016/j.arr.2021.101422

Imaging Inflammaging

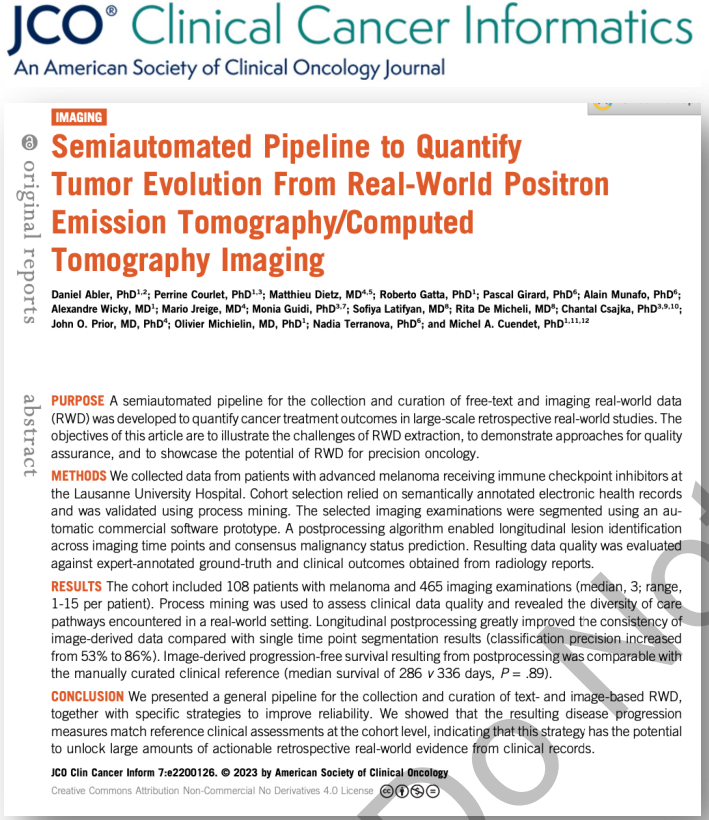
FDG – PET is an ideal marker to depict inflammaging



20 Years 40 Years 60 Years 80 Years

Courtesy of Pr Niklaus Schaefer

Using PACS PET/CT Real-World Data



JCO® Clinical Cancer Informatics
An American Society of Clinical Oncology Journal

IMAGING

Semiautomated Pipeline to Quantify Tumor Evolution From Real-World Positron Emission Tomography/Computed Tomography Imaging

Daniel Abler, PhD[1,2]; Perrine Courlet, PhD[1,3]; Matthieu Dietz, MD[4,5]; Roberto Gatta, PhD[1]; Pascal Girard, PhD[6]; Alain Munafo, PhD[6]; Alexandre Wicky, MD[1]; Mario Jreige, MD[4]; Monia Guidi, PhD[3,7]; Sofiya Latifyan, MD[8]; Rita De Micheli, MD[8]; Chantal Csajka, PhD[3,9,10]; John O. Prior, MD, PhD[4]; Olivier Michielin, MD, PhD[1]; Nadia Terranova, PhD[6]; and Michel A. Cuendet, PhD[1,11,12]

original reports abstract

PURPOSE A semiautomated pipeline for the collection and curation of free-text and imaging real-world data (RWD) was developed to quantify cancer treatment outcomes in large-scale retrospective real-world studies. The objectives of this article are to illustrate the challenges of RWD extraction, to demonstrate approaches for quality assurance, and to showcase the potential of RWD for precision oncology.

METHODS We collected data from patients with advanced melanoma receiving immune checkpoint inhibitors at the Lausanne University Hospital. Cohort selection relied on semantically annotated electronic health records and was validated using process mining. The selected imaging examinations were segmented using an automatic commercial software prototype. A postprocessing algorithm enabled longitudinal lesion identification across imaging time points and consensus malignancy status prediction. Resulting data quality was evaluated against expert-annotated ground-truth and clinical outcomes obtained from radiology reports.

RESULTS The cohort included 108 patients with melanoma and 465 imaging examinations (median, 3; range, 1-15 per patient). Process mining was used to assess clinical data quality and revealed the diversity of care pathways encountered in a real-world setting. Longitudinal postprocessing greatly improved the consistency of image-derived data compared with single time point segmentation results (classification precision increased from 53% to 86%). Image-derived progression-free survival resulting from postprocessing was comparable with the manually curated clinical reference (median survival of 286 *v* 336 days, $P = .89$).

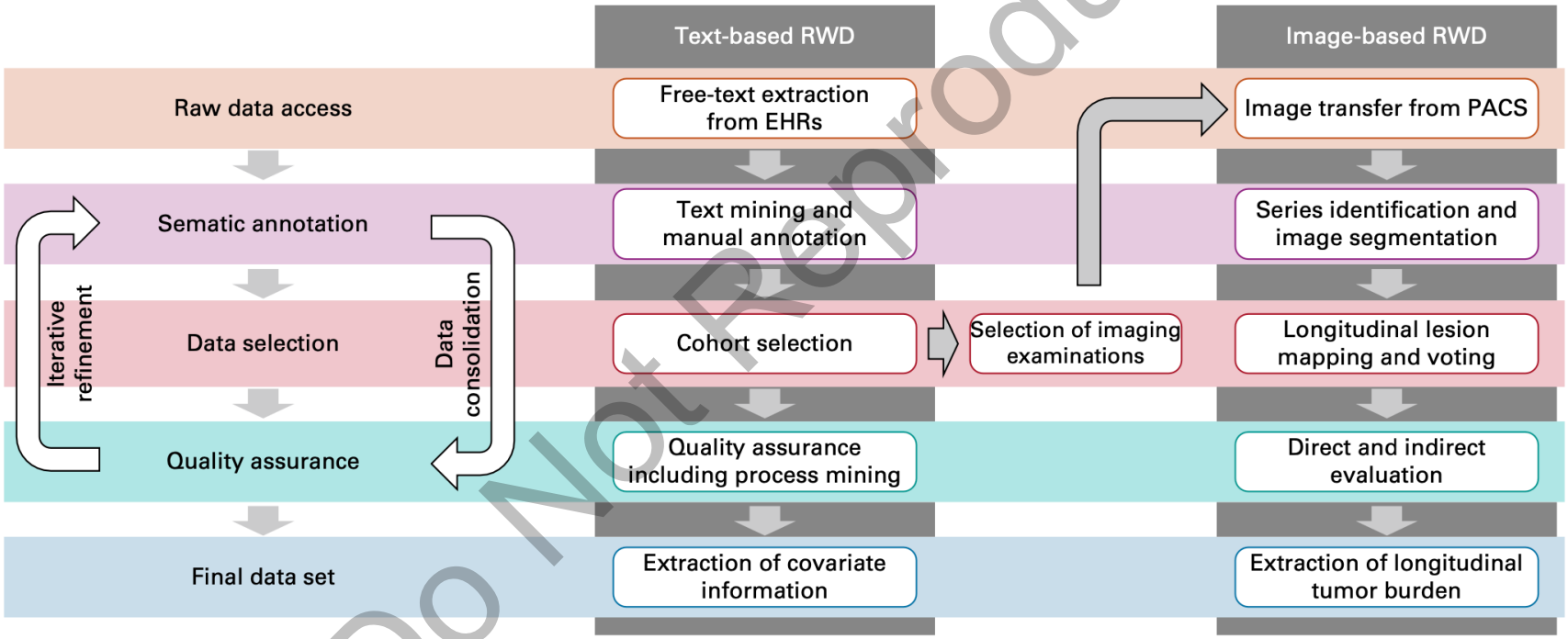
CONCLUSION We presented a general pipeline for the collection and curation of text- and image-based RWD, together with specific strategies to improve reliability. We showed that the resulting disease progression measures match reference clinical assessments at the cohort level, indicating that this strategy has the potential to unlock large amounts of actionable retrospective real-world evidence from clinical records.

JCO Clin Cancer Inform 7:e2200126.

- N=108 patients, 465 PET/CT
- Image-derived progression-free survival
- We developed a general pipeline for the collection and curation of text- and image-based RWD

http://ascopubs.org/doi/full/10.1200/CCI.22.00126

Collection and curation of real-world clinical and imaging data



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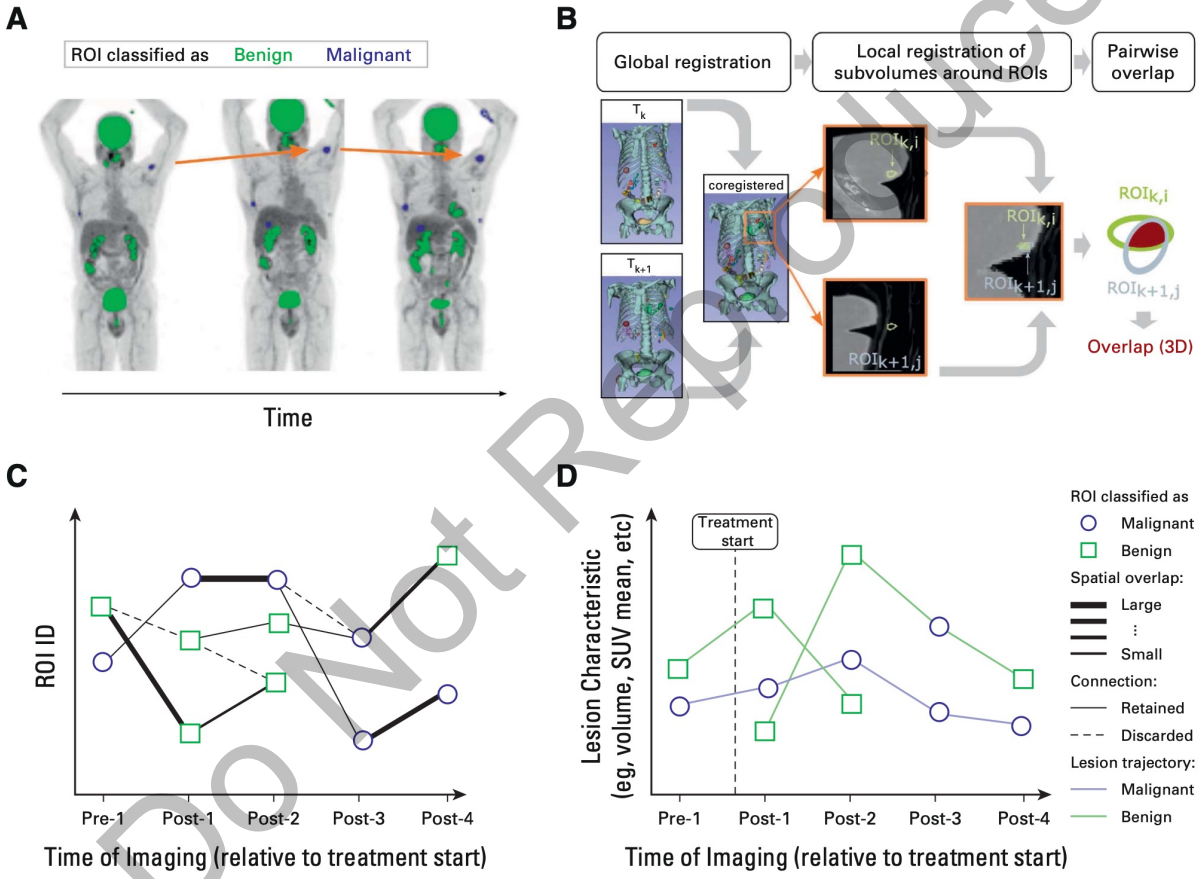
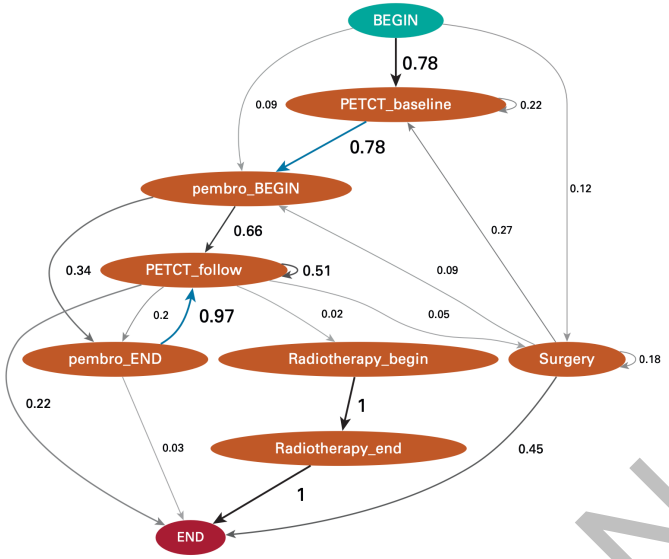
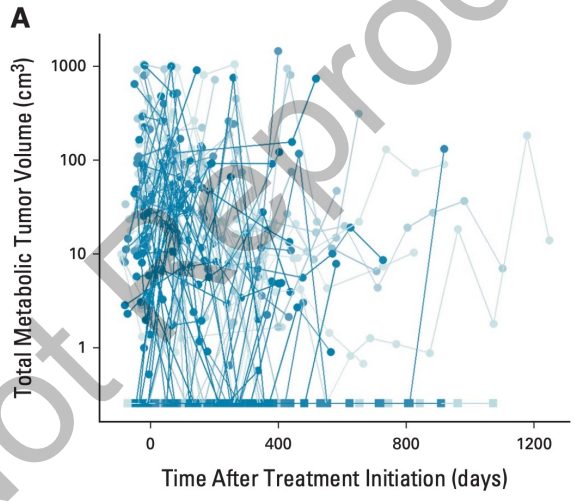
Longitudinal follow-up of individual tumor lesions



http://ascopubs.org/doi/full/10.1200/CCI.22.00126

Using PACS PET/CT Real-World Data for Tumor Dynamics





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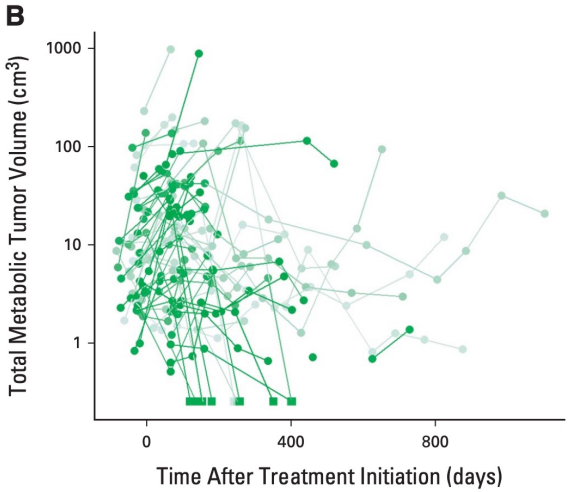
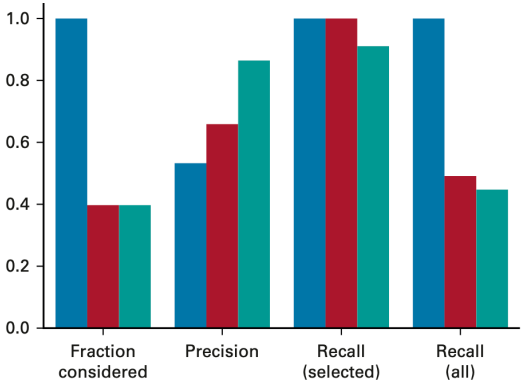
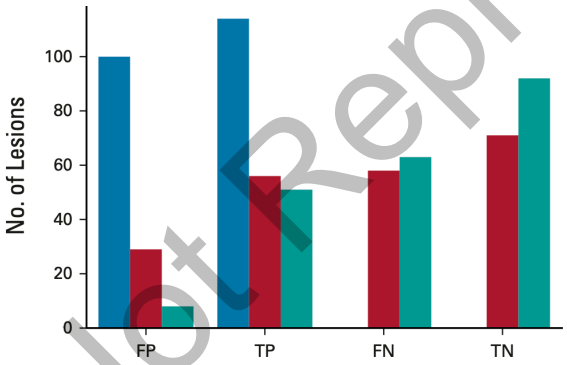
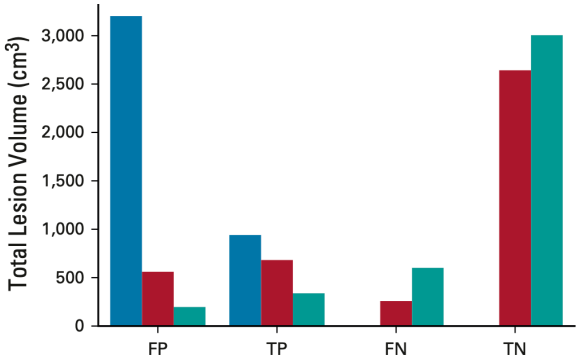


Data-consolidated by experts

Automatic vs. Expert Evaluation of Tumor Lesions





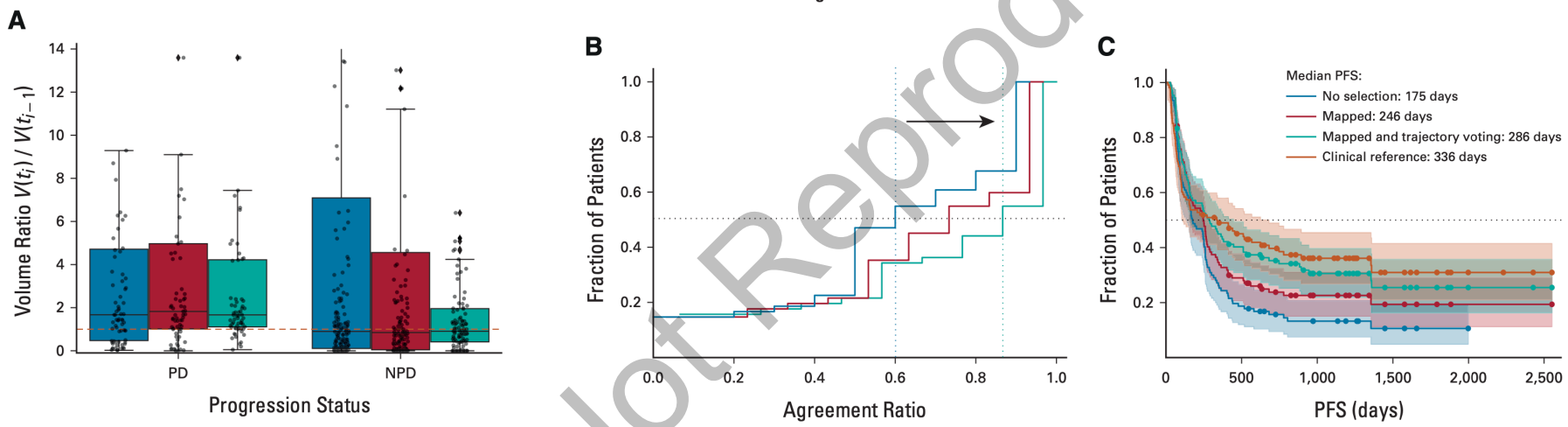


no selection
automatic
expert-anotated

No significant differences

http://ascopubs.org/doi/full/10.1200/CCI.22.00126

Automatic vs. Expert Evaluation of Tumor Lesions



no selection
automatic
expert-anotated

Results closely reproduced the clinically curated PFS (median PFS of 336 days, P = 0.89), whereas unprocessed segmentation results did not (P<0.01)

http://ascopubs.org/doi/full/10.1200/CCI.22.00126

Using PACS PET/CT Real-World Data

Automatic extraction/curation of imaging & EHR real-world data provides important opportunities:

- not only for the confirmation of randomized control trials results but also for biomarker discovery
- can help collect and analyze data in a harmonized way across different hospitals to assemble larger cohorts for real-world multicentric studies

Summary: Roadmap

Need for dynamic total-body PET with parametric imaging and multiple radiopharmaceuticals, starting with FDG (inflammageing), best TOF possible, triple–coincidence welcomed

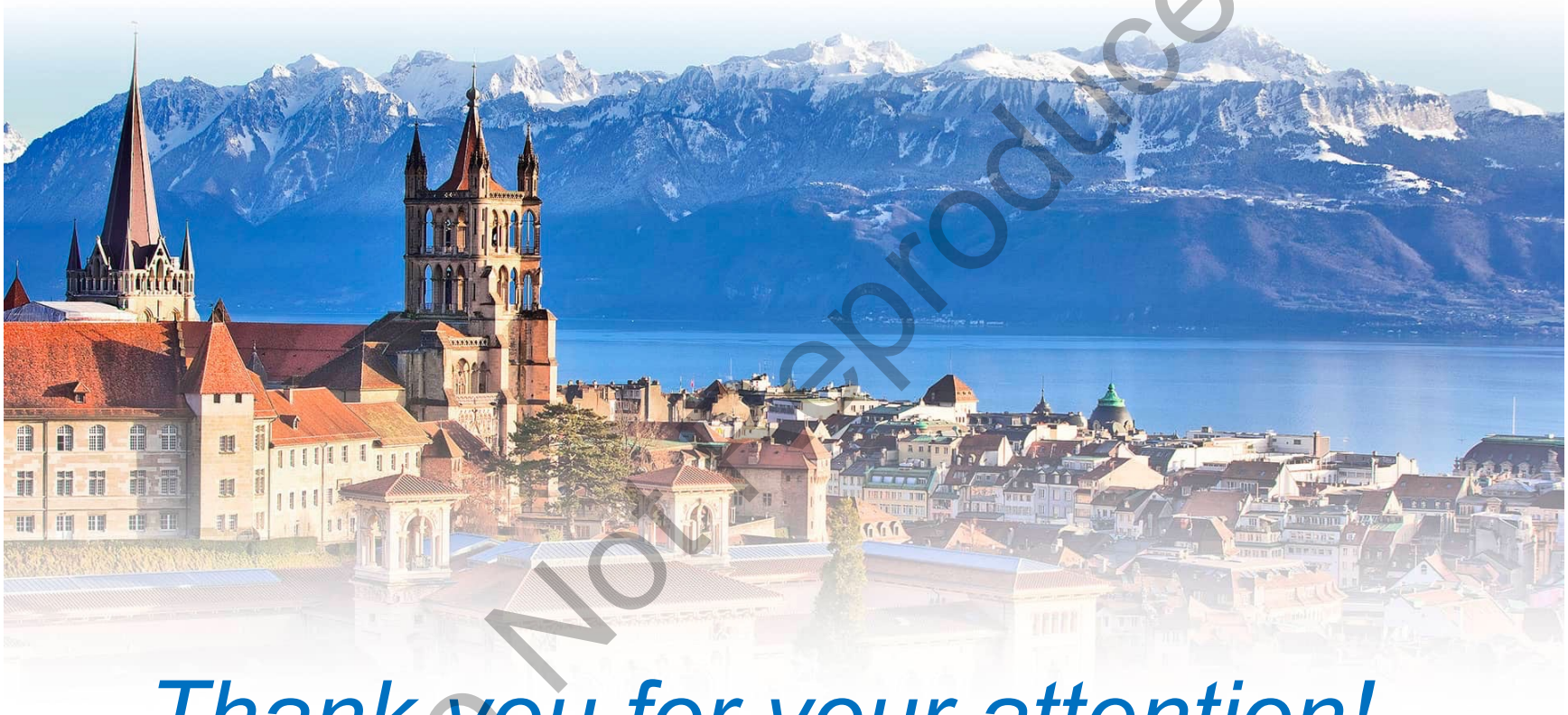
Interrelation of organs, systems, and voxels, but also with any other data at hand (wearables, other imaging CT, MR, US, all –omics, liquid biopsy, etc.) Need for transdisciplinary collaborations!

AI-powered analysis and sharing tools (open access) needed,but also use of real-world data from PACS and EHR

Study the effects of interventions (behaviour, nutrition, medication, etc.) or stress tests (cold-pressor, food, etc.) or why not “wellness” tests

Focus on healthy individuals followed-up longitudally (cohorts over decades) → healthy human total-body PET atlas?

Start in understanding health & disease, but need as next step to include also data on wellness…



Thank you for your attention!

canton de vaud