OVERLINE

**To help aging populations,**

**classify organismal senescence**

Comprehensive disease classification and staging is required

to address unmet needs of aging populations.

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Globally, citizens exist for sustained periods in states of ageing-related disease and multi-morbidity. Given the urgent and unmet clinical, healthcare, workforce, and economic needs of aging populations, we need interventions and programs that regenerate tissues and organs, and prevent and reverse aging-related damage, disease, and frailty (*1*). In response to these challenges, the World Health Organization (WHO) has called for a comprehensive public-health responsewithin an international legal framework based on human rights law *(1)*. Yet for a clinical trial to be conducted, a disease to be diagnosed, intervention prescribed, and treatment administered, a corresponding disease classification code is needed, adopted nationally from the WHO International Classification of Diseases (ICD). Such classifications and staging are fundamental for healthcare governance among governments and intergovernmental bodies. We describe a systematic and comprehensive approach to the classification and staging of organismal senescence and aging-related diseases at the organ and tissue levels, in order to guide policy and practice, and enable appropriate interventions and clinical guidance, systems, resources, and infrastructure.

Through the ICD, the WHO oversees the international approval of disease classifications and staging that are subsequently adopted by governmental and regulatory bodies at the national level for use in epidemiological, clinical, and management contexts. Classification submission information is structured to describe the temporality, severity, and pathology of a disease, covering components such as aetiology, manifestation, function, treatment, and diagnosis.

Organ and tissue senescence and age-related damage, disease, and frailty are currently classified and staged within the ICD, but in a non-systematic and non-comprehensive manner, including via classification codes for skin aging, geriatric, time in life and senility, the old age code, in addition to aging-related diseases including cancers, cardiovascular diseases, and dementias. Within this system a patient may have a disease classified in one organ that exists unclassified in another organ, with the possibility of non-recorded drug effects in distal organs. Due to lack of classifications and staging, developing pathology may not be registered or treated. Drugs that prevent or reverse this pathology may be left sitting on the shelf.

Current practices include incomplete and imprecise approaches of, categorization of patients as “at risk of disease”, and via pre-disease and advanced pathology classifications. Our aim is to augment and, where appropriate, replace these approaches. To not classify diseases and stages comprehensively is arbitrary, which may give legal justification for action.. Governments and the WHO may have a duty to ensure that the classification systems are systematic and comprehensive.

**SYSTEMATIC AND COMPREHENSIVE**

In our view, the systematic and comprehensive classification and staging of organismal senescence and aging-related diseases at the system, organ, tissue, and metabolic level is readily achievable via synthesis of the existing knowledge base *(2-10)*. Tissue and organ senescence are defined similarly to organismal senescence at the tissue and organ level and involve pathologic and pathogenic hallmarks of organismal and cellular senescence, including: reduced organ function, cell loss, stem cell dysfunction and niche decline, telomere shortening, senescence-associated-secretory-phenotype-related pathology, inflammation, nuclear and mitochondrial mutation burden, matrix composition dysregulation, protein aggregation, reduced genomic stability, epigenetic dysregulation and extracellular crosslinks, steatosis and polyploidization (*2-10*).

 Organismal senescence at the tissue and organ level, which may involve replicative cellular senescence, has pathologic and pathogenic characteristics *(2-10).* Though replicative cellular senescence may have a protective effect in relation to oncogenesis, we submit that replicative cellular senescence may be pathogenic (*2-4, 8, 9*), which may be targeted, in specific tissues, and removed in relation to pathologic and pathogenic disease states of tissue and organ senescence, treatment of co-morbid conditions, and any preventative and regenerative approaches. Circulating DNA can be traced to tissue of origin (*11*), which may enable organ and tissue specific biomarkers for aging-related diseases and syndromes by severity stage. Senescent cell burden and senescence-associated secretory factors have also been assessed from plasma protein (*9*), in addition to studies in humans with the removal of senescence cells demonstrating an alleviation of physical dysfunction (*10*). Comparative biology demonstrates that cellular and organismal senescence vary across cell types and species, with some cell types being biologically immortal, and some organisms being negligibly senescent, retaining their regenerative capabilities and being cancer resistant (*12-13*).

 Potential benefits of such a staging and classification system include improvements in: (i) understanding of tissue and organ biology and pathology, including accelerated organ and tissue senescence from progeroid disorders, metabolic diseases, and exogenous causes such as chemotherapy and radiotherapy, via the meeting of clinical diagnostic criteria development requirements, enhancement of diagnostic criteria, and via clinical studies, (ii) drug development and repurposing through more accurately described diseases and stages, including increased accuracy and comprehensiveness of indications, staging, and the increased availability and comprehensiveness of functional endpoints, (iii) drug development through regulatory pathway development, (iv) pre-clinical trial models corresponding to the proposed classifications and staging, (v) clinical trials via patient stratification and selection related to indications, multi-indications, multi-staged indications, combination drug regimens, multi-modal therapies, enhanced endpoints, and differential responses, (vi) personalized medicine strategies, (vii) early diagnosis and early prevention, rehabilitation and regeneration, (viii) diagnosis in general, (ix) medical records and digital twins, (x) intervention capability in complex late stage indications and multi-morbidities, (xi) mitigation of age-related risk factors in prescribing and surgery, (xii) preventative, regenerative and rehabilitative approaches and treatment planning, (xiii) patient outcomes, and (xiv) public health statistics, policy, and resourcing.

**PROPOSED SYSTEMS**

We propose that organ and tissue senescence and related disease classification and staging systems be instantiated as WHO ICD disease codes with appropriate corresponding general extension codes, as they relate to senescing, atrophic, pathologically remodeled, calcified, and otherwise metabolically dysfunctional tissue. This should include sub-classifications for each tissue and disease sub-type, and associated extension codes for staging and severity from effectively zero tissue senescence, atrophy, pathologic remodeling, calcification and metabolic dysfunction. Codes should be classified under aetiology and pathology, with tissue and cellular sub-classifications to account for differences in rates of aging at the tissue, organ, and organism level, the existence of aging damage during development and across life, and for the development of a chronologic-age-agnostic organ and tissue pathology framework with associated phenotypes and biomarkers. A comprehensive set of classifications, ICD-Aging-related (ICD-A) or otherwise ICD-Senescent (ICD-S), should be used for senescing, atrophic, remodeled, calcified and metabolically dysfunctional tissue for each organ and gland.

Similar to codes relating to cancer classifications, we propose *Senescent*, *Senescent Secretory*, *Atrophic*, *Calcified* and *Uncertain whether Senescent or Effectively Zero Senescence*. We envisage that organ-by-organ, tissue-by-tissue, senescing, atrophic, pathologic remodelling, calcification and metabolic dysfunction codes, with cell specific sub-classifications comparable to ICD-O (oncology) classifications, would work in concert with existing age-related disease codes such as dementias, cancers, and cardiovascular disease and other systemic, metabolic and infectious disease codes to provide a comprehensive and systematic disease classification framework. Hyperactive and hyperproliferative tissues should be appropriately coded within such a framework. Any such classifications relating to aging tissue that have been developed on an ad hoc basis, such as skin aging, should be formatted and combined with the proposed comprehensive and systematic classification and staging and structure outlined herein, including classification of the ‘ageing-related’ extension code as an aetiology and causality code *(14)*(see supplementary materials for WHO ICD classification submissions by S.R.G.C and B.L.B.).

A 0-V staging system for senescing tissue, and a 0-X severity scale for atrophy, remodeling, calcification and aging-related metabolic dysfunction classifications are appropriate, with 0 being effectively zero tissue senescence and zero pathologic atrophy, remodeling, calcification, or metabolic dysfunction. A staging system for senescent tissue comparable to the TNM Classification of Malignant Tumors (TNM) may be useful for the inflammatory and pathologic secretory phenotype of senescing tissue. We propose that a *Senescing*, *Secretory*, and *pathologic Atrophy*, *Remodelling* and *Calcification* (SSeARC) Classification of Senescing Tissue system be developed.

The rationale for proposing a staging severity scale and a pathogenic stage system for organ and tissue senescence has its basis in oncology classifications, where cells that escape the pathologic phenotype of cellular senescence become cancerous with progressive and distal tissue effects. These cells have both the TNM and the Stage 0-IV systems.

Specific markers are envisaged to differ per tissue, organ, and location within the body, and by the corresponding staging and severity scales. The staging system would classify senescing tissue from effectively zero presence of organ and tissue senescence pathology, and any appearance, features and diagnostic criteria. Stage I may include cells nearing senescence with minimal pathological effect, stage II may include senescent cell presence with minimal pathological effect, stage III may include senescent cell presence and extracellular crosslinking with emerging pathological effect, stage IV may include senescent cell and extracellular crosslinking with onset of age-related disease, and stage V may include hallmarks of organ, tissue and replicative senescence able to cause fatality.

Characterization of atrophic tissue pathology and pathologic remodeling, and the related staging thresholds, may include histopathologic and functional studies in combination with population-based epidemiologic and personalized medicine metrics, with tissue and organ specific disease classifications, including relevant structural, functional and clinical criteria.

We envisage aging-related atrophic, pathologic remodelling, calcification, systemic and metabolic dysfunction disease classifications to be classified and staged in a similar manner. Diagnostic criteria may involve a range of non-invasive and minimally invasive tests and include functional, imaging, fluid- needle- or tissue-based biopsy tests, biomarkers and biomarker panels, with histopathology and tissue omics as required (*7,9,10,15*).

Classification pathology, appearance, features, and diagnostic criteria would include similarities between organs and tissues relating to fundamental processes of tissue senescence, and commonalities in organ and tissue damage and organ-specific and tissue-specific criteria. Clinical biomarkers should be developed to classify tissue senescence to the quality of classification and staging appropriate for clinical practice.

To illustrate the proposed classification and staging system, a 55-year-old Caucasian male patient at a general medical checkup may present a range of multi-morbidities including stage III ageing-related muscle atrophy and stage II muscle senescence, stage IV vascular senescence with risk of rupture, thresholded with arterial stiffness measured from pulse wave velocity, and atherosclerosis type III, diagnosed by MRI and blood test. The clinical response includes the following: Treatment recommendations with one or more senolytic interventions which act on vascular or muscle senescence and the atherosclerotic plaque, which takes into account organ specific disease staging differentials, and an exercise regimen aimed at reversal of ageing-related muscle atrophy and atherosclerosis whilst also preventing senescence stage progression.

Sarcopenia should be included in a systematic and comprehensive manner alongside the senescence, atrophy, remodeling and calcification of each and every tissue, gland, and organ. We submit that tissue atrophy and remodeling has pathological effects, such as can be seen in pineal gland, and heart muscle atrophy, thymic involution and remodelling, We propose that a systematic and comprehensive framework cover all tissues, organs, and glands across all functional scales, including the heart and vasculature, neural lobes and architecture, glia, the pineal gland and the blood-brain barrier. Senescence, atrophy, remodeling, and calcification, should be looked to in relation to glands, lymph nodes and bone marrow in addition to any corresponding blood cell populations relating to immunosenescence, and tissues that function as barriers or are associated with filtration and microbial burden.

Metabolic diseases should be appropriately classified toward trials and treatment, including diseases that accelerate organ and tissue senescence, and for patients with both senescent tissues and organs, and co-morbid metabolic and infectious diseases that affect multiple tissues and organs in combination. “At Risk of Age-Related Disease” should be considered in relation to each and all ageing-related indications in relation to items herein and otherwise, to enhance approaches to the treatment of those at risk of disease and with pre-disease conditions.

An overall scoring system should be developed for each organ and for patients that combines organ and tissue senescence, pathologic remodelling, metabolic damage, atrophy and aging-related disease classifications and stages for aggregate scoring of organ damage and integrity, and patient status.

There are challenges to be surmounted for the comprehensive characterization of disease including sub-types, stages, molecular mechanisms, and biomarkers. However, diseases such as tumors were classified as neoplasms and staged as benign or malignant prior to any genetic characterization. Skin aging is already classified in the ICD, and staged, in the absence of a complete mechanistic understanding and molecular characterization of organ and tissue senescence. Limitations prior to a comprehensive molecular characterization of a disease may be present in relation to (i) the molecular metabolic disease classifications, (ii) disease severity staging based solely on molecular mechanisms and biomarkers, and (iii) molecular biomarker development in relation to WHO ICD classifications and diagnostic criteria.

**IMPLEMENTATION**

The United Nations and WHO should support classification and staging efforts as part of the WHO policy focus on Healthy Ageing and Life Course. The WHO, the International Agency for Research on Cancer (IARC) and relevant other groups should develop such classifications and staging systems including the underlying pathology, appearance, features and diagnostic criteria towards improving health globally in relation to organismal senescence. Given the global importance of an aging society, governments and intergovernmental bodies should engage in the development of, and support for, appropriate classifications and staging with aligned healthcare policy and resourcing. Governments should consider bringing such a motion before the World Health Assembly for ratification, to replicate the successes of ICD-O and the IARC for organ and tissue senescence. We submit that a WHO body commensurate to the IARC should be established for aging, and for the development of aging classifications and staging, or otherwise the IARC remit be expanded to include organ and tissue senescence and related diseases in addition to cancer. Policy and resourcing requirements for organ and tissue senescence and aging-related organ and tissue damage and frailty involve similar considerations as with oncology classifications and staging.

As a counterpart to WHO ICD classifications and staging systems, corresponding pre-clinical models should be developed, including development of organism, organ, and tissue specific counterparts to the WHO ICD classifications and stages for disease pathology characterization and drug development, with aligned government resourcing and policy. Comprehensive and systematic classification and staging of organ and tissue senescence, pathologic remodelling, atrophy, calcification, and aging-related metabolic disease is an urgent and unmet need.

The classification and staging frameworks proposed are intended to be utilised independently or in combination with existing classification codes in a complimentary manner, across disease diagnosis, prevention, management and reversal. The proposed approach will complement existing codes for diseases and syndromes already recognized to improve patient outcomes, and will add value to overall patient care by addressing gaps in international healthcare governance.

We invite governments and the World Health Organization to act on the items herein, and welcome members of the scientific, medical, and patient advocacy communities to contribute to this effort including via feedback, consensus development, and the development and utilisation of the proposed classification, staging and disease criteria frameworks.

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Supplementary materials

url

SUPPLEMENTARY MATERIALS

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Competing interests: The author(s) declare the

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is a shareholder in GlaxoSmithKline plc and Syncona Limited. Professor Graham Pawelec has received research support from Immatics Biotechnologies GmbH, speaker’s honoraria from Celgene, Pfizer, Sanofi, 4DPharma, Clasado and Seqirus, and is a consultant to Repair Biotechnologies Inc. Dr Alexander

Fleming is the Chairman of Kinexum, advising companies focused on age related diseases Professor Jesus Gil owns equity and is a consultant for Unity Biotechnology Inc and Geras Bio. Unity Biotechnology

Inc funds research on senolytics with Professor Jesus Gil. Professor Jesus Gil is a named inventor on a filed Medical Research Council patent related to senolytic therapies (PCT/GB2018/051437) licensed to Unity Biotechnology Inc. Dr Gary Small owns a US patent,

6,274,119, which has been licensed to Ceremark Pharma LLC, is among the inventors, is a co-founder of and has equity interest in Ceremark Pharma LLC. Dr Small reports having served as a consultant and/or

having received lecture or writing fees from AARP, Acadia, Allerga Inc, Avanir, Forum Pharmaceuticals Inc, Gerontological Society of America, Handok Inc, Herbalife International, Herbalife Nutrition, Janssen Pharmaceuticals Inc, lily, Lundbeck Inc, Newsmax Media, Novartis Pharmaceuticals Corporation,

Otsuka Pharmaecuticals Corporation Ltd, Pfizer Inc, RB Health and Theravalues. Professor Tony-Wyss Coray and Professor Karoly Nikolich are founders and board members of Alkahest a regenerative medicine company developing products for age-related diseases. Dr João Pedro de Magalhães is or has recently been an advisor/consultant for 4D Pharma Plc, Aviva, Longevity Vision Fund, Centaura, Xobaderm Ltd, Five Alarm Bio, BioViva and is the founder of Magellan Science Ltd. Professor Judith Campisi is a founder and shareholder of Unity Biotechnology Inc, which has licensing rights to certain patents filed by the Buck Institute. Professor George Church is a founder and advisor to a number of regenerative medicine and diagnostics companies focused on age-related diseases url: http://arep.med.harvard.edu/gmc/tech.html .

Exemplar submissions to the World Health

Organization International Classification of

Diseases:

Submissions to WHO ICD-11 related to comprehensive and systematic classification of ageing-related diseases at the systemic, organ, tissue and metabolic level. Illustrative submissions include senescence, pathologic remodelling, atrophy, calcification and metabolic pathology classifications. Proposal contributions may be viewed via the WHO ICD-11 Maintenance Platform url: http://icd.who.int/dev11/l-m/en

Ageing-related extension code, reclassification

Identifiers: #1Z9X & #1Z9Y

Submissions to entities: 459275392 &

1698138964

Ageing-related histopathology

Identifiers: #1Z5W#1Z9Z, #2001, #2002,

#2003, #2882 & #2881

Submissions to entities: 411368752 &

1295816090

ICD-Ageing/ICD-Senescence

Identifier: #1Z5V

Submissions to entity: 77159832

Biological age

Identifier: #2883

Submissions to entity: 1390117811

Old age, reclassification

Identifiers: #241G, #241H

Submissions to entities: 835503193, 1596590595

Liver senescence

Identifier: #240I

Submissions to entity: 328366540

Cerebrovascular pathologic remodelling

Identifier: #2895

Submissions to entity: 843843448

Pineal atrophy

Identifier: #240N

Submissions to entity: 112148603

Vascular calcification, arteries, bone marrow

Identifier: #2871

Submissions to entity: 1164983645

Immunosenescence

Identifier: #290R

Submissions to entity: 978368870

Ceroid lipofuscinosis, ageing-related

Identifier: #290A

Submissions to entity: 21500692

Nonhereditary metabolic lipidosis

Identifier: #2406

Submissions to entity: 155258022

Glycatosis

Identifier: #2909

Submissions to entity: 393047701

Fatty heart disease

Identifier: #241N

Submissions to entity: 1986774235