POLICY FORUM

AGING

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 aging-related disease and multimorbidity. Given the urgent and unmet clinical, health care, 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 response within 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 health care 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 etiology, 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 nonsystematic and noncomprehensive manner, including by means of classification codes for skin aging, geriatric, time in life and senility, and the old age code, in addition to aging-related diseases such as 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 nonrecorded drug effects in distal organs. Because of the 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 and categorization of patients as "at risk of disease" and through predisease 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 through 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, extracellular cross-links, 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*). Although 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 comorbid 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—through the meeting of clinical diagnostic criteria development requirements and enhancement of diagnostic criteria, and with 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 end points; (iii) drug development through regulatory pathway development; (iv) preclinical trial models corresponding to the proposed classifications and staging; (v) clinical trials with patient stratification and selection related to indications, multi-indications, multistaged indications, combination drug

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regimens, multimodal therapies, enhanced end points, and differential responses; (vi) personalized medicine strategies; (vii) early diagnosis and early prevention, rehabilitation, and regeneration; (viii) diagnoses in general; (ix) medical records and digital twins; (x) intervention capability in complex late-stage indications and multimorbidities; (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.

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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 because they relate to senescing, atrophic, pathologically remodeled, calcified, and otherwise metabolically dysfunctional tissue. This should include subclassifications for each tissue and disease subtype 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 etiology and pathology, with tissue and cellular subclassifications 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 remodeling, calcification, and metabolic dysfunction codes, with cell-specific subclassifications comparable with 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 here, including classification of the "aging-related" extension code as an etiology and causality code (*14*) (WHO ICD classification submissions by S.R.G.C. and B.L.B. are provided in the supplementary materials).

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" indicating effectively zero tissue senescence and zero pathologic atrophy, remodeling, calcification, or metabolic dysfunction. A staging system for senescent tissue comparable with 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, Remodeling, 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, in which 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 to 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 cross-linking with emerging pathological effect; stage IV may include senescent cell and extracellular cross-linking 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 remodeling, calcification, systemic, and metabolic dysfunction disease classifications to be classified and staged in a similar manner. Diagnostic criteria may involve a range of noninvasive and minimally invasive tests and

include functional imaging; fluid-, needle-, or tissue-based biopsy tests; biomarker; 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- 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 multimorbidities, including stage III aging-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 with magnetic resonance imaging and blood test. The clinical response includes the following: treatment recommendations with one or more senolytic interventions that 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 aging-related muscle atrophy and atherosclerosis while 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 the pineal gland, heart muscle atrophy, and thymic involution and remodeling. 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 aging-related indications in relation to items here and otherwise to enhance approaches to the treatment of those at risk of disease and with predisease conditions.

An overall scoring system should be developed for each organ and for patients that combines organ and tissue senescence, pathologic remodeling, 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 subtypes, stages, molecular mechanisms, and biomarkers. However, diseases such as tumors were classified as neoplasms and staged as benign or malignant before 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 before a comprehensive molecular characterization of a disease may be present in relation to (i) the molecular metabolic disease classifications, (ii) disease severity staging solely on the basis of 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 Aging 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 toward 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 health care 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 those of oncology classifications and staging.

As a counterpart to WHO ICD classifications and staging systems, corresponding preclinical models should be developed, including the 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 remodeling, atrophy, calcification, and aging-related metabolic disease is an urgent and unmet need.

The classification and staging frameworks proposed are intended to be used independently or in combination with existing classification codes in a complementary 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 health care governance.

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

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SUPPLEMENTARY MATERIALS

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