Response

Zhavoronkov questions the timing of our Policy Forum's publication in relation to the release and adoption of the International Classification of Diseases 11 (ICD-11), but the World Health Organization accepts ICD submissions and updates on a rolling basis across the review and maintenance phases and is regularly revised, versioned and updated(*1*). Zhavoronkov also posits that senescence cannot be added to ICD without substantial further research. We challenge this view: Given the World Health Organization's decision making history, classification and staging consensus, development, and submissions to ICD are needed now.

Organismal senescence at the organ level has already been classified in the ICD as "Intrinsic aging of the skin" and "Photo-aging of the skin," with an accompanying staging scale for aging skin (*2*). It is therefore entirely feasible to classify organismal senescence across the organs and tissues of the body, along with all other aging-related diseases and disorders. Our Policy Forum cites the substantial literature that already exists for such an effort [e.g., (*3*, *4*)].

We agree with Zhavoronkov that there is still much to learn about aging-related diseases. However, many diseases within the ICD were not comprehensively understood before classification. Our understanding of skin aging increased after classification (*5*) as a result of improved recognition and further study. Alzheimer's disease was recognized as a leading cause of death only after its inclusion in ICD-9 led to improved epidemiology and statistics (*6*). If diseases and disorders are identifiable, distinct, and associated with a substantial body of knowledge, they should be classified.

In contrast to Zhavoronkov, we see a place for staging senescence in the ICD framework. It is common for diseases to be classified and staged before the approval of clinical biomarkers. An initial staging of organismal senescence could be achieved for all organs based on macroscopic and histologic measures, similar to the Glogau scale for skin (*5*). Longitudinal studies in animals and humans will be required, as Zhavoronkov states, to further develop the staging of organismal senescence across organs for clinical endpoints and precision medicines. Organismal senescence may be a continuous process that begins early in life, but the ICD classification should be able to distinguish between early age-related degenerative change and any initial processes of organismal development.

Zhavoronkov is correct that severity staging systems do not require ICD approval. However, "severity scale value" may be appended in the ICD for statistical purposes. Staging systems are usually developed and maintained by international disease-specific medical societies. We would welcome the development of international initiatives to develop a comprehensive set of staging systems, biomarkers, and interventions for senescence and aging-related diseases.

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