Acta Biomed 2024; Vol. 95, N. 6: e2024152 DOI: 10.23750/abm.v95i6.16343

Forever Young: mission impossible?

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Abstract. Despite an increase in life span over the last century, most people spend the extra years in poor health. Undoubtedly, older patients will rise to the overall majority of patients accessing social and healthcare systems unprepared to respond to special and complex demands. The future has to undergo a significant transformation, emphasizing a healthier and more active aging process. Looking ahead, prioritizing "health span", not life span. will help us make the most of the opportunities that come with longer lives and practical approaches to increase the number of healthy years (healthy ageing medicine and timely intervention to counteract pathological senescence), highlighting the positive impact a healthier population can have on both the economy and society. (www.actabiomedica.it)

Myths of immortality and extreme longevity were common throughout ancient and medieval times, and many legends demonstrate that youth and lifespan can be extended (1). The current demographic situation in our part of the world is characterized by an increase in average life expectancy, a low birth rate, and an enormous increase in the number of older people, which is why our epoch is called the age of longevity. Last century many investigations were carried out into the mechanisms of aging, and the search for interventions that could prevent diseases and frailty or even restore a youthful state, but until now aging is driving up age-related diseases, comorbidity and dependency. Providing support and appropriate intervention for healthy lifestyles (increased physical activity, improved nutrition, decreased hazardous and harmful drinking/alcohol use, practice positive thinking, improved sleep hygiene, and community interventions) are mandatory and well-established but not easy to realize (2-4). One of the priorities is reducing the number of older and oldest persons who are or shall become dependent. According to the WHO model of Healthy Aging directed at increasing average healthy life span, preservation of active life longevity and achievement of the species-specific human life span limit, it is necessary to maintain functions and abilities at any age by increasing intrinsic capacity (IC) reserves in early aging and preserving cognitive and motorial abilities in late aging, restoring cognitive function when needed (if possible) (5-7). IC is the composite of an individual's major physiological and mental capacities that can be assessed in a day-to-day environment. Considering data from large cohort studies the WHO has suggested 5 key domains to maintain autonomy: sensorial (vision, audition), locomotor, cognitive, psychological and vitality. They influence each other and are influenced by environmental determinants (8-10).

Finally, timely identification of risk factors of frailty will be a tremendous goal, considering this multidimensional syndrome entails loss of energy, physical ability, cognition, and health in general, playing a significant role in morbidity, dependency and mortality. Frailty is a progressive age-related clinical condition characterized by a deterioration of physiological capacity leading to an increased vulnerability of the individual and a higher risk of having poor health as well as a faster entry into care dependence (11-13). Frailty occurs when the mobilization of the physiological reserve cannot overcome the challenge and maintain functional ability, which enables people to do

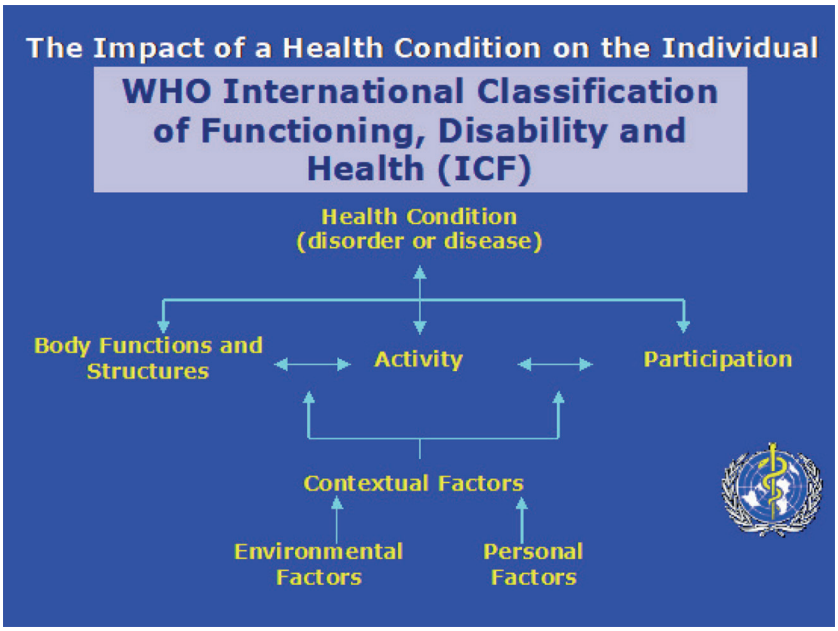

Figure 1. WHO – ICF

what they want. This ability comprises the individual's intrinsic capacity and interactions between the individual and the environment. For a function, handling stress depends on mobilising adaptive capacity. For an individual, reserves are her/his maximal adaptive capacity. To overcome these problems, older people should be maintained into the productive population group and taken into social development with a mobilization of all government, social services, mass media, and healthcare system efforts, maintaining the oldest robust and active (14-16) (Figure 1).

The competence indispensable for living a socially independent life is defined as the higher-level functional capacity. Great importance have social, ecological and psychological factors. A new kind of preventive medicine must be developed, considering the possibility of obtaining the maintenance of an independent and active life. Population aging brings challenges and opportunities, demanding enhanced health care, a skilled health and care workforce, age-friendly environments, and a collective effort to combat ageism across all sectors (17,18). Crucially, this should be coupled with ensuring that health systems are equipped to meet the needs of aged populations, especially in primary care settings, encompassing preventive, curative, rehabilitative, assistive, and palliative care, alongside sustainable long-term care.

Aging and senescence

Aging (A) is a complex process of accumulation of molecular, cellular, and organ damage, leading to loss of function and increased vulnerability to disease and death, and was defined as "increasing mortality with increasing chronological age in populations in the wild". A definition analogous to others is "actuarial senescence" and progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age (19,20). It is important to have full awareness that A exists, is well documented for humans, and is normal. Many theories explain the origin of the overall process, cause and effect including the immune system, inflammation, mineralization of connective tissue, wear and tear, and many others. In addition, genetic and epigenetic changes implicated in longevity and biochemical processes conserved in evolution are associated with A (21). Nine hallmarks represent common denominators in mammalian A: genomic instability, telomere attrition, epigenetic

alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. A major challenge is to dissect the interconnectedness between the cited hallmarks and their relative contributions to A (22).

Senescence (S) results from the balance between biological damage accumulation and compensatory mechanisms, an irreversible form of long-term cell-cycle arrest, caused by excessive intracellular or extracellular stress or damage. Senescent cells secrete a panel of molecules deleterious for the surrounding cells. As time passes, the compensatory mechanisms become less and less effective, which leads to more and more damage, a gradual decrease in physiological reserves and, phenotypically, this manifests as a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. This deterioration is the primary risk factor for major human pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Much literature is emerging that indicates the importance of cellular senescence in defining the aging phenotype (23). Potential interventions could be stem-cell-based therapy, anti-inflammatory drugs, blood borne-stem-cell-based therapy, anti-inflammatory drugs, blood-borne rejuvenation factors, elimination of damaged cells, telomerase activation, epigenetic drugs, activation of chaperons and proteolytic system, dietary restrictions, mTOR inhibition, mitohormetics, mitophagy, clearance of senescent cells. But until now no evidence-based result is available, and many strategies are unethical.

Classifying aging-senescence as a disease?

The recognition of A-S as a disease could be an important milestone for industry, academic community, healthcare and insurance companies, policymakers, and all individuals, as the presence of A-S in disease nomenclature and classification greatly impacts the way it could be treated, researched and reimbursed. To successfully evaluate the effect of any drug or treatment that could cure A-S disease, it is essential to have many measurable endpoints. With the advent of Big Data and Artificial Intelligence, it should become possible to track aging on the epigenetic level and measure accelerated aging and loss of functional abilities. There is a rapidly growing body of evidence that biomarkers of aging contribute to and are very similar to the many age-related diseases on all levels of organization, and it is possible to multiplex epigenetic, transcriptomic, proteomic, signalomic, metabolomic, metagenomic, and phenotypic biomarkers to track the progression of aging as a disease. Considering the WHO definition of health, it may be possible to establish an optimal set of biomarkers that would be characteristic to the "state of complete physical, mental and social well-being, not merely the absence of infirmity "and agree on the physiological threshold after which the net totality of deviation of these biomarkers from norm can be considered a disease. The idea that there may be common longevity-associated genes that affect many specific age-related conditions is gaining acceptance (24).

Anti-aging medicine (AAM) ad Healthy aging medicine (HAM)

Developing a cure for aging-disease might take a while: in the meantime, it is necessary to counteract the diseases of interest to the aging process. Interventional strategies have been shifting from an "enemy-oriented" approach to a "friend-oriented approach" based on the fact that aging is primarily a reduction in homeodynamic ability of self-maintenance and repair, and the best markers to monitoring the efficacy of any potential anti-aging interventions include stress response pathways, molecular damage regulatory pathways, and energy production and utilization. These basic molecular markers need to be incorporated into cellular and physiological level markers, such as cell type-specific functionality, intercellular communication networks, tissue and system robustness, and overall well-being of the individual (25-28). Only a combination of such multiple monitoring levels can provide evidence-based reliable data for screening, testing and developing effective antiaging interventions. AAM and HAM have to be based on assessment and management of adult, young old and old persons by means of screening tools for prevention,

evaluating vitality parameters, body composition, physical performance, cognition, affectivity, sensory functioning, along with social and biological aspects. Programs of evaluation and management designed to prevent functional decline have the potential of HAM when maintaining activities and fighting frailty. AAM and HAM have to improve quality of life and life satisfaction. Any biological, social, mental, physical or nutritional education program will be necessary to enable individuals to deal with their biological heritage. Data about AAM-HAM and a growing technological medicine and products market are proliferating. Tools aiming at preventing, arresting or reversing the age-related decline and functions of the old can become an irreversible worldwide phenomenon and may impact the quality, cost and accessibility of care, and the ability of citizens to remain healthy and active (29,30). Clinical controversies regarding AAM-HAM are overcome when quality of life and life satisfaction of population are improved. Interventions are needed to reduce the burden of disease and protect population productivity. Young people are the most attractive targets for therapies to extend health span (because it is still possible to prevent disease in the young). However, there is scepticism about whether ageing processes can be detected in young adults who do not yet have chronic diseases, but intervention to reverse or delay the march toward age-related diseases should be scheduled while people are still young. AAM-HAM have to be based on the multidimensional evaluation of different aspects and the dimensions that clinic global assessment (CGA) aims to measure are usually grouped into at least four domains: physical health, functional status (e.g., activities of daily living and instrumental activities of daily living], and other parameters such as mobility and quality of life), psychological health (e.g., cognitive and affective status), and socio-environmental parameters (social network, support needs, safety and adequacy of the living environment). Despite decades of CGA experience in clinical and research field, the culture on the CGA is still not robustly rooted in different geographical areas, settings and specialties, with substantial heterogeneity of approaches and implementations (31). A methodology based on CGA and behavioural social biological markers, named VIP (Valutazione Intensiva per la Prevenzione - Intensive /comprehensive assessment and clinical evaluation for healthy aging) was registered in 2007 (www.boneta.it). VIP was approved by un international advisory board, and consisted of three steps: the first to achieve the global index, the second a program of counselling and interventions; the third the follow up. VIP was strongly appreciated and effective but was costly (32,33).

Drugs and supplements that should delay many functional impairments of old age

To successfully evaluate the effect of any substance that could influence ageing, it is essential to have a measurable endpoint, such as biomarkers, tracking aging on the epigenetic level and measuring accelerated aging. There are promising studies of transcriptomic and multi-variate blood-based biomarkers that may lead to minimally invasive diagnostic tests. One approach to address this challenge is to assume a disease-free physiological state at a certain age, for example 25-30 years of age, and develop a set of interventions to keep the subjects as close to that state as possible, considering the WHO definition of health. For drugs to be approved for clinical use, developers must first identify the indication/condition that enables investigators to obtain authorization to carry on a trial in people. Discoveries about geroprotectors, chemotherapeutics, and similar factors, with the tendency to focus on the short term, and how researchers' performance is evaluated, must take a positive approach without forgetting ethical principles. In conclusion, many substances were studied and are under study, either to slow down the aging process or for prevention of age-related diseases, but no clear evidence was got until now. The impact of medication on aging trajectories is a major health issue because the tremendous developments in pharmacology and clinical therapeutics in recent years, with important opportunities for healthy ageing, but at the same time, drug misuse is the source of major health problems (34-37).

Looking at the near future

What is important is to work toward solutions and a concrete action plan not to be forever young, but to

maintain independence in late life, with the use of the global tech ecosystem, where visionaries investors and enterprise tech leaders come together in the right balance to accelerate the infinite cycle of tech innovation and artificial intelligence. Aging2.0 established these Grand Challenges : maintaining independence, empowering family caregivers, emerging older workforce, care coordination, engagement and social connection, generational inclusion, brain health and aging in place (38). It's time to embrace ecological management of longevity based on sociomedical and environmental prevention. Our health is a precious asset. Good health and well-being enable us to live happy, fulfilling lives and free us up to maintain our potential, not forgetting the most important component of a happy old age isn't health or wealth. It's having a solid social network.

References

1. Demontis L., Comparative analysis of medieval and modern scientific research on ageing reveals many conceptual similarities. J Gerontol Geriatr Res 2015; 4(3):216. doi:10.4172/2167-7182.1000216.
2. Thuault S. Reflections on aging research from within the National Institute on Aging. Nat Aging. 2021 Jan;1(1): 14-8. DOI: 10.1038/s43587-020-00009-z. PMID: 37117996.
3. Beard JR, Officer A, de Carvalho IA et al The World report on ageing and health: a policy framework for healthy ageing. Lancet. 2016 May 21;387(10033):2145-54. DOI: 10.1016 /S0140-6736(15)00516-4.
4. Donini LM, Poggiogalle E, Barbagallo M, Cucinotta D, et al. Anorexia and Eating Patterns in the Elderly. PLoS ONE,2013, 8(5): e63539. DOI: 10.1371/journal.pone.0063539
5. Edmondson, Ricca, and Hans-Joachim Von Kondratowitz (eds), *Valuing older people: A humanist approach to ageing* (Bristol, 2009; online edn, Policy Press Scholarship Online, 22 Mar. 2012). DOI: 10.1332/policypress/9781847422927 .001.0001, accessed 20 July 2024.
6. Cucinotta D. The Science of Choosing Wisely: should it be applied to any intervention for healthy and active longevity? Acta Biomed. 2019 May 23;90(2):357-8. doi: 10.23750/abm.v90i2.8459. PMID: 31125021; PMCID: PMC6776212.
7. At J, Bryce R, Prina M, et al. Frailty and the prediction of dependence and mortality in low- and middle-income countries: a 10/66 population-based cohort study. BMC Med. 2015 Jun 10;13:138. doi: 10.1186/s12916-015-0378-4. PMID: 26063168; PMCID: PMC4481121.
8. Global strategy and action plan on ageing and health. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
9. Cesari M, Araujo de Carvalho I, Amuthavalli Thiyagarajan J, et al Evidence for the Domains Supporting the Construct of Intrinsic Capacity. J Gerontol A Biol Sci Med Sci. 2018 Nov 10;73(12):1653-1660. doi: 10.1093/gerona/gly011. PMID: 29408961
10. Beard JR, Jotheeswaran AT, Cesari M, Araujo de Carvalho I. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. BMJ Open. 2019 Nov 2;9(11): e026119. doi: 10.1136/bmjopen-2018-026119. PMID: 31678933; PMCID: PMC6830681.
11. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013 Mar 2;381(9868):752-62. doi: 10.1016/S0140-6736(12)62167-9. Epub 2013 Feb 8. Erratum in: Lancet. 2013 Oct 19;382(9901):1328. PMID: 23395245; PMCID: PMC4098658
12. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019 Oct 12;394(10206): 1376-86. doi: 10.1016/S0140-6736(19)31785-4. PMID: 31609229
13. Polidori, M.C., Ferrucci, L. Frailty from conceptualization to action: the biopsychosocial model of frailty and resilience. Aging Clin Exp Res 2023;35: 725–7. DOI: 10.1007 /s40520-022-02337-z
14. van der Vorst A, Zijlstra GA, Witte N, Duppen D, et al D-SCOPE Consortium. Limitations in Activities of Daily Living in Community-Dwelling People Aged 75 and Over: A Systematic Literature Review of Risk and Protective Factors. PLoS One. 2016 Oct 19;11(10):e0165127. doi: 10.1371 /journal.pone.0165127. Erratum in: PLoS One. 2017 Jan 23;12(1):e0170849. doi: 10.1371/journal.pone.0170849. PMID: 27760234; PMCID: PMC5070862.
15. World Health Organization. How to use the ICF: A practical manual for using the International Classification of Functioning, Disability and Health (ICF). Exposure draft for comment. October 2013. Geneva: WHO
16. Sum G, Lau LK, Jabbar KA, et al . The World Health Organization (WHO) Integrated Care for Older People (ICOPE) Framework: A Narrative Review on Its Adoption Worldwide and Lessons Learnt. Int J Environ Res Public Health. 2022 Dec 22;20(1):154. doi: 10.3390/ijerph20010154.
17. Cucinotta D. Preparing for the Decade of Healthy Aging (2020-2030): prevention plus therapy? Acta Biomed. 2018 Jun 7;89(2):145-7. doi: 10.23750/abm.v89i2.7402. PMID: 29957744; PMCID: PMC6179028.
18. G. Libertini, G. Rengo, N. Ferrara, Aging and aging theories, Review. JGG, 2017;65:59-77
19. Barja G. Towards a unified mechanistic theory of aging. Exp Gerontol. 2019 Sep;124:110627. doi: 10.1016/j.exger .2019.05.016. Epub 2019 Jun 5. PMID: 31173843
20. Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat Med. 2015 Dec;21(12):1424-35. doi: 10.1038 /nm.4000. PMID: 26646499; PMCID: PMC4748967.
21. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol.

2007 Sep;8(9):729-40. doi: 10.1038/nrm2233. PMID: 17667954.
22. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013 Jun 6; 153(6):1194-217. doi: 10.1016/j.cell.2013.05.039. PMID: 23746838; PMCID: PMC3836174.
23. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. Proc Natl Acad Sci U S A. 2015 Jul 28;112(30):E4104-10. doi: 10.1073/pnas.1506264112. Epub 2015 Jul 6. PMID: 26150497; PMCID: PMC4522793
24. Zhavoronkov A, Bhullar B. Classifying aging as a disease in the context of ICD-11. Front Genet. 2015 Nov 4;6:326. doi: 10.3389/fgene.2015.00326. PMID: 26583032; PMCID: PMC4631811.
25. Ader I, Pénicaud L, Andrieu S, et al. Healthy Aging Biomarkers: The INSPIRE's Contribution. J Frailty Aging. 2021;10(4):313-9. doi: 10.14283/jfa.2021.15. PMID: 34549244; PMCID: PMC8081649.
26. Ferrucci L, Gonzalez-Freire M, Fabbri E, et al Measuring biological aging in humans: A quest. Aging Cell. 2020 Feb;19(2):e13080. doi: 10.1111/acel.13080. Epub 2019 Dec 12. PMID: 31833194; PMCID: PMC6996955.
27. Guyonnet S, Rolland Y, Takeda C, et al The INSPIRE Bio-Resource Research Platform for Healthy Aging and Geroscience: Focus on the Human Translational Research Cohort (The INSPIRE-T Cohort). J Frailty Aging. 2021;10(2): 110-20. doi: 10.14283/jfa.2020.38. PMID: 33575699; PMCID: PMC7352084.
28. Xu K, Guo Y, Li Z, Wang Z. Aging Biomarkers and Novel Targets for Anti-Aging Interventions. Adv Exp Med Biol. 2019;1178:39-56. doi: 10.1007/978-3-030-25650-0_3. PMID: 31493221.
29. Cucinotta D. Clinical Controversies in Antiaging Medicine, Aging Clin Exp Res 2011; 23 (suppl to n.1):67.
30. Rattan SI. Healthy ageing, but what is health? Biogerontology. 2013 Dec;14(6):673-7. doi: 10.1007/s10522-013-9442-7. PMID: 23852043.
31. Maggi S, Ferrucci L. The Italian guideline on comprehensive geriatric assessment (CGA) for the older persons. Aging Clin Exp Res. 2024 May 27;36(1):122. doi: 10.1007/s40520-024-02780-0. PMID: 38797795; PMCID: PMC11128381.
32. Cucinotta D. La valutazione funzionale intensiva per la prevenzione (how old is older?) Geriatria 2002; XIV (5): 265-68.
33. Cucinotta D. Prevention of pathological aging by comprehensive clinical, functional and biological assessment. Arch Gerontol Geriatr. 2007;44 Suppl 1:125-32. doi: 10.1016/j.archger.2007.01.019. PMID: 17317445
34. Bellantuono I. Find drugs that delay many diseases of old age. Nature. 2018 Feb 15;554(7692):293-295. doi: 10.1038/d41586-018-01668-0. PMID: 29446384.
35. Zhang Y. New frontiers of aging reversal and aging-related diseases reprogramming Adv Genet Eng 2012;1:e101
36. Cucinotta D., Mikhailova O. Active and Healthy Ageing: Therapy *versus* Prevention// Proceedings of the International Symposium "Experts' opinion on current approaches in anti-ageing medicine and gerontology. - Geneva, Switzerland, 27 May, 2017.- p. 27-30.
37. Mikhailova O., Cucinotta D., Popovich I. Towards Longer and Productive Life// Proceedings.International Symposium of Experts "Regenerative medicine and ageing". - Dubai, UAE, 01-02 February 2020.- p. 38-40.
38. Aging2.0 - Global Innovation Search, Grand Challenges. Optimize 2024 in http://www.aging2.com/global-innovation-search

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Received: 24 June 2024
Accepted: 27 August 2024
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