WHAT'S NEW WITH OLD? RECENT ADVANCES IN THE SCIENCE OF AGING

Abstract

The last decade has seen rising interest in and research efforts into the underlying drivers and mechanisms of aging. The incentive for this enthusiasm is much more than an academic exercise. If these drivers and mechanisms can be elucidated, then perhaps they can also be leveraged to prevent, slow, or even reverse aging processes. While no appreciable therapeutic interventions for aging are currently available (at least for humans), there is great hope that eventually human healthspans and possibly lifespans can be extended by population-wide implementation of material advances in anti-aging therapies. While certainly of great interest to society, these advances, if realized, could impact insurers' fundamental morbidity and mortality actuarial assumptions and overall business models.

This article will review recent controversies and developments in aging research and update what to anticipate in the coming years.

Introduction

Globally, people are living longer. According to the World Health Organization (WHO), every country in the world has experienced growth in both the number and size of the elder cohort in their populations. By 2030, the WHO estimates that one in every six people in the world will be age 60 or older, and the population age 60 and older will increase from one billion (as of 2020) to 1.4 billion. By 2050, the world's population of people age 60 and older will neary double to 2.1 billion.[1]

Despite recent reductions in life expectancy due to COVID-19, much of the observed increase in life expectancy during the 20th century was attributable to improvements in public health, sanitation, and nutrition, as well as reduced deaths due to more effective preventative measures and treatments for communicable diseases. Additionally, medical advances and primary and secondary prevention for non-communicable diseases (such as coronary artery disease) have contributed significantly to mortality improvement trends.[2, 3]

What will be needed to ensure long-term mortality rates continue to improve? Is "what got us here, will get us there" a viable strategy? While it will remain important to continue to study the social, economic, and medical factors impacting life expectancy, it is now also imperative to dive deeper into the fundamental biological mechanisms and drivers of aging. Through further understanding and research in this area of

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science, material increases in healthspans – the length of life lived without significant disease or impairment – and lifespans – the total time between birth and death – may be achieved.

Aging Defined

Many have attempted to define aging, and most definitions have similar and common verbiage. The WHO, for example, defines aging as follows:

> *"At the biological level, aging results from the impact of the accumulation of a wide variety of molecular and cellular damage over time. This leads to a gradual decrease in physical and mental capacity, a growing risk of disease and ultimately death. These changes are neither linear nor consistent, and they are only loosely associated with a person's age in years. The diversity seen in older age is not random."*[1]

World-renowned nutrition and aging researcher Dr. Luigi Fontana has defined aging similarly:

> *"Aging is a fascinating but complex and dynamic biological process. It is characterized by progressive functional and structural deterioration of multiple cells, tissues, and organ systems."*[4]

Both of these definitions are descriptive in nature, but do not provide specifics about the underlying mechanisms *per se* or explain why aging processes occur (or must occur). The WHO's definition is particularly interesting, as it states that aging is not a linear process and is only loosely associated with chronological age. The non-randomness of aging's diversity of expression seen at older ages indicates that multiple factors, both potentially modifiable and non-modifiable, are driving variations in aging. Nonetheless, aging ultimately and unequivocably results in death.

Is Aging a Disease?

Historically, aging has been considered a "natural" process – one that is immutable and inevitable and thus does not technically meet the criteria of a disease. On the other hand, aging has been and is a well-recognized risk factor and contributor to particular age-related diseases. Even the very definition of disease has been debated in the philosophical context. In these terms, "disease" has been defined as a state that has been medically described and evaluated as a "bad thing to have." One recent paper examining whether aging is a disease noted, "from the pragmatist perspective, it can be seen that the notion of aging is going through a conceptual change, and aging can today be understood as a not radically different process from any other condition that is usually considered a disease."[5]

There is strong evidence that by focusing research on aging pathways (and considering those pathways pathological processes), multiple seemingly unrelated diseases could be addressed simultaneously. According to a recent Lancet editorial, "if aging can be viewed as a pathological process, then it allows researchers to look at

the pathophysiological mechanisms of aging itself with a view to finding targetable mechanisms of action that slow the rate of aging." This approach could also result in improving healthspans as well as overall lifespans.[6]

Nonetheless, categorizing aging as a disease *per se* remains controversial. As noted above, some argue that aging is a normal, natural process experienced by everyone, whereas diseases only affect some of the population. Additionally, the processes of aging are also not always directly related to chronological age and are heterogeneous. Characterizing aging as a disease *per se* risks worsening age-related discrimination which already exists.[6]

The most recent WHO International Classification of Diseases (ICD-11), published January 2022, had proposed adding the term "old age" under the MG2A diagnostic category (that of symptoms, signs, or clinical findings not elsewhere classified). Additionally, an extension code was initially included in the category's causality section, which defined "aging-related" as "caused by pathological processes which persistently lead to the loss of [an] organism's adaptation and progress in older ages." This action was, however, met with much opposition by clinicians who stated that "referring to people by an undefined chronological age led to very serious real-world challenges for being used inappropriately and erroneously." After formal consultation with and feedback to the WHO, the term "old age" was retracted and replaced by "aging associated decline in intrinsic capacity" and in the extension code, "pathological" was changed to "biological." Thus, although the ICD-11 issue is settled for the time being, debate persists.[7]

From an economic standpoint, there may be value in targeting aging as a disease. One analysis demonstrated that targeting aging may offer greater economic gains in the U.S. than eradicating specific diseases and showed that slowing down aging enough to achieve one year of increased life expectancy could have a general economic value of $38 trillion. The authors noted the costs of any treatments which target aging must be low and have widespread population access to realize the full value of social gains.[8]

Aging is a complex process and must be considered as a whole.

Major Hallmarks of Aging

Significant effort and research have gone into elucidating the mechanisms and drivers (often termed "hallmarks"), whether considered normal or pathological, which cause aging. Since 2013, nearly 300,000 articles addressing the subject have been published, which is as many as published on the topic during the preceding century.

Hallmarks of aging have been described as needing to fulfill three criteria:

- Age-associated manifestation(s)
- Acceleration of aging by experimentally accentuating them
- Opportunity to decelerate, stop, or reverse aging by therapeutic interventions

Carlos Lopez-Otin *et al*. recently published an extensive literature review on the hallmarks of aging, which updates a similar review performed a decade earlier.[9] The authors have identified 12 specific

hallmarks of aging, some of which are interconnected, and have focused on the molecular, cellular, and systemic processes that mechanistically account for their manifestations. This supports the hypothesis that aging is a complex process and must be considered as a whole. They also noted that the 12 hallmarks of aging can be sorted into three categories: primary, antagonistic, and integrative. While prior research validated evidence for anti-aging intervention effectiveness in non-mammalian model organisms, more recent findings are beginning to corroborate their effectiveness for mammals, increasing their relevance for humans.

Table 1: Hallmarks of Aging

Primary – reflect damage affecting the genome, telomeres, epigenome, proteome, and organelles	
Hallmark	**Description**
Genomic instability	Genome integrity constantly threatened and damaged by endogenous and exogenous stressors
Telomere attrition	DNA damage occurring at the ends of chromosomes (telomeres) after multiple cell divisions
Epigenetic alterations	Epigenetic changes include DNA methylation patterns, abnormal modification of histones, chromatin remodeling, and deregulated function of non-coding RNAs
Loss of proteostasis	Impaired protein homeostasis leading to accumulation of misfolded, oxidized, or glycated protein, often forming aggregates
Disabled macroautophagy	Impaired sequestration and digestion of cytoplasmic material
Antagonistic – reflect responses to primary factors	
Hallmark	**Description**
Deregulated nutrient-sensing	Dysfunction of mechanisms in innate evolutionary nutrient-sensing capabilities
Mitochondrial dysfunction	Mitochondria are the energy "powerhouses" of the cell and can trigger inflammation Functional deterioration due to mitochondrial DNA mutations, deficient proteostasis, reduced turnover of the organelle
Cellular senescence	Characterized by stable proliferative arrest in the cell cycle resulting from multiple mechanisms
Integrative – reflect failure of compensation for primary and antagonistic processes	
Hallmark	**Description**
Stem cell exhaustion	Causes reduction of tissue renewal at steady state and with injury
Altered intercellular communication	Causes increased "noise" in the system and compromises homeostatic and hormetic (phased response to stress) regulation
Chronic inflammation	Aging-associated inflammation – "inflammaging"
Dysbiosis	Dysfunctional gut microbiome negatively impacts overall maintenance of health

Source: https://pubmed.ncbi.nlm.nih.gov/36599349/

The identification of the hallmarks of aging is enabling a basic understanding of their drivers and mechanisms and is forming a basis for research into anti-aging therapies. While each hallmark can be targeted, yielding potential tangible benefits for both healthspans and lifespans, it will be important to develop rational strategies for intervening in human aging.[9]

Notably, aging as a therapeutic target is not recognized by the U.S. Food and Drug Administration, thus drugs intended to treat aging must target a specific disease that often results from the aging process in order to demonstrate efficacy and gain approval.[10]

Conclusion

The understanding of the (patho)physiological processes that comprise aging in humans has experienced many significant advances in the last decade. Not only are the fundamental hallmarks of aging being elucidated, great effort is also being undertaken to develop therapies which might decelerate, stop, or reverse the aging process. Insurers would benefit from following these developments closely and considering their potential impact on morbidity and mortality actuarial assumptions and projections for both in force and new business modeling.

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