The future of treating aging

Krystle Kalafut¹,*, Morgan Janes², and Francesca Riccio-Ackerman³
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HIGHLIGHTS

• The number of individuals above the age of 65 is increasing around the world, and an estimated one in four Americans will be aged 65 years or older by 2060.
• The ongoing demographic shift presents a public health challenge due to the increased risk of chronic diseases in older adults, necessitating adaptations to the current healthcare system.
• Research in the field of geroscience has identified a set of core underlying biological features of the aging process, referred to as the “hallmarks of aging.”
• Several promising interventions targeting the hallmarks of aging, including dietary restriction, as well as drugs approved for other disease indications, have been successful in extending health in animal models.
• Efforts to identify reliable biomarkers of the aging process, define the indication for use of geroscience-guided therapies, and determine appropriate clinical trial design will be instrumental in the translation of novel therapies to improve healthy longevity in humans.

The number of adults aged 65 and older in the United States and globally is expected to nearly double in size by 2050. It will be necessary to devise strategies spanning the science, healthcare, and regulatory sectors to support the growing number of older adults and adapt to the changes of population aging. Given the greater disease risk in older individuals, this population shift also presents new opportunities for research and development of both preventive and therapeutic interventions that target a wide range of chronic conditions. Many previous articles have focused on the advantages and drawbacks of classifying aging as a disease, which we briefly summarize. Then, we focus on the discussion of actionable steps to adapt the healthcare system and clinical regulatory frameworks to support research in geroscience, develop novel therapeutics that delay the biological aging process, and promote the translation of these therapies to patients.

Aging is universal — it happens to everyone, everywhere — and this has always been the case. Yet, over the past 10 years, billions of dollars have been invested into longevity research companies, and advertisements for products or diets promising to reverse or prevent the signs of aging are almost as ubiquitous as aging itself. What is behind this renewed societal focus on healthy aging?

Due to increasing in life expectancy and declining fertility rates, the world's population is growing older. Older adults are more likely to develop chronic health conditions and, for many, aging is accompanied by a period of declining health — making population aging a pressing public health concern. In response, societal infrastructure must adapt to support the increasing number of older adults by remodeling healthcare systems to reflect the shifting demands and by fostering the development of novel therapies to treat diseases associated with older age. Recent scientific discoveries demonstrate the potential to target biological features of aging, with the promise of preventing or treating a long list of chronic diseases. However, there are barriers to translating these findings into treatments that can be used by the general public. This article will:

• Describe the healthcare demands associated with population aging and introduce the efforts to adapt the current healthcare system to better serve a growing number of older individuals.
• Review the current understanding of aging biology and promising therapeutic interventions.
• Outline steps to support the development and translation of novel therapies for age-associated diseases and to implement preventive measures to slow the biological aging process.

Adapting to longer lives

Incredible advances in medicine and public health have supported the near doubling of life expectancy across the world since the start of the 20th century [1]. Simultaneously, birth rates have fallen by about 50% both in the U.S. and globally since 1950 [2]. As a result, the number of

¹Department of Molecular Metabolism, Harvard T. H. Chan School of Public Health, Boston, MA, United States
²Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, United States
³Biomechatronics Group, MIT Media Lab, Massachusetts Institute of Technology, Cambridge, MA, United States
* Email: kkalafut@fas.harvard.edu

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older individuals and the average age of the population are increasing, a phenomenon referred to as population aging. Globally, the number of individuals aged 65 years or older is projected to nearly double by 2050, yielding an estimated 1.5 billion people [3]. This means that older individuals will make up a larger portion of the world’s population than ever before.

In the United States, the number of individuals above the age of 65 is expected to climb to 94.7 million by 2060, a 75% increase from 2019 [4]. An estimated one in four Americans will be in the 65 and older age bracket, and older adults are expected to outnumber children for the first time in U.S. history [4] (Figure 1).

Figure 1: Estimated and projected population distribution by age in the U.S. in 2020 and 2060. The number of Americans aged 65 and older is projected to increase from 49.2 million in 2020 to 94.7 million in 2060 [4]. As a result, older adults will make up almost one-quarter of the U.S. population.

However, the average number of years lived in “full health” has increased at a slower rate than overall life expectancy [2]. This key distinction between lifespan and healthy lifespan, or “healthspan”, is reflected in the fact that many older individuals spend a portion of their life in poor health. Thanks to progress in science and medicine that has alleviated the transmission and severity of acute, communicable diseases, chronic non-communicable diseases have now become the most common cause of morbidity and mortality. Notably, age has been recognized as a primary risk factor for many prominent chronic diseases, including cardiovascular disease and cancer (Figure 2), and the risk of accumulating more than one chronic illness increases with age [5]. In 2008, 85.6% of individuals aged 65 years or older had at least one chronic condition, and 56% had two or more [6]. Consequently, population aging presents a public health challenge characterized by a need to provide adequate and equitable care to a rising number of older adults [7], while supporting their health, independence, and quality of life.

Efforts to prepare and respond to this challenge are ongoing, as a result of the advocacy of patients, caregivers and experts in numerous domains. For instance, the FDA recently held a workshop titled Roadmap to 2030 for New Drug Evaluation in Older Adults, which discussed strategies for increasing the inclusion of older adults in clinical trials [9]. The workshop highlighted the under-representation of older adults in clinical trials, as the number of older adults included in clinical trials testing the safety and efficacy of a broad range of treatments does not reflect the size or disease prevalence rates of the older population. [10]. Given that older adults are more likely to have multiple comorbidities and to require multiple medications, they tend to make up the majority consumer base for many medications approved for long-term use, making the lack of safety and efficacy data for older adults particularly dangerous [5]. Thus, efforts by the FDA to address the discrepancy between the size and disease prevalence of the older population and the inclusion of older individuals in clinical trials will help lower the risk of adverse drug events among this growing portion of the population.

The population and epidemiological shift may require adaptations to the health system overall, specifically in response to the predicted rise in health expenditures and demand to serve the needs of people with chronic conditions and disabilities [11]–[13]. Experts predict a greater demand for geriatricians [13], physicians specializing in the treatment of complex and interconnected health conditions of older adults; The National Center for Health Workforce Analysis predicts there will be a geriatrician shortage of approximately 27,000 in 2025 [14]. Furthermore, older adults and those with chronic conditions may require additional support from a caregiver, increasing demand for both in-home and long-term care services. Alternatively, spouses, family members, and friends (women in particular) often act as unpaid caregivers to loved ones, which can entail unrecognized physical, emotional, and economic stress [15]. New monitoring and delivery platforms, such as remote patient monitoring technologies, wearable sensors (e.g. the ECG in the Apple Watch), telehealth services, and mobile health clinics, have begun to adapt our healthcare system to the needs of older or chronically ill individuals and to improve continuity of care [16]–[19], but much remains to be done to bridge the growing gap. Overall, prioritizing management of chronic conditions, disabilities, and other age-related changes can prevent severe health complications and maximize quality of life.

But what about preventing people from getting sick as they age in the first place? In addition to updating existing sectors of our healthcare system, a new area of research, called geroscience, aims to understand the biological drivers of aging in order to delay the onset of multiple diseases [7, 20].
The goal of geroscience research is not to increase human lifespan at all costs, but rather to compress the period of morbidity at the end of life, resulting in an extension of health
[7].

What causes aging and can we treat it?

The field of geroscience has emerged to investigate potential solutions to the health challenges of population aging. Geroscience aims to “understand how aging enables diseases and to exploit that knowledge to slow the appearance and progression of age-related diseases and disabilities” [21]. A network of collaborators across 20 NIH institutes belonging to the Trans-NIH Geroscience Interest Group is currently working to identify how aging biology intersects with the disease focus areas of each institution [21]. Investigators hope to not only improve our understanding of basic aging biology, but also to develop new tools and paradigms to treat age-related diseases.

Collectively, society has a common understanding of what it means to age on the exterior. However, is there a single, defined root cause? The idea of a “master regulator” is certainly appealing, yet the biological picture is much more complex. One way to begin to understand aging from a biological perspective is to examine its common manifestations at the molecular level. Scientists have identified a set of biological functions that deteriorate with age, which they termed the “hallmarks of aging.” These hallmarks generally meet three criteria: (i) decline in function is observed during normal aging, (ii) induction or acceleration of the process increases the pace of aging, and (iii) removal or dampening of the process slows the pace of aging [22]. Age-related decline occurs across all levels of biological function, including how genetic information is preserved, interpreted, and converted into the biological material that maintains our body’s healthy functioning; how that cellular machinery is controlled; how cells respond to varying environmental conditions; and how cells and tissues communicate with each other to coordinate whole-body health (Figure 3). These hallmarks are highly conserved across species and can be observed even amongst the most simple, single-celled organisms. Undoubtedly, the biological hallmarks are intimately connected, and parsing the potential causes of aging apart from one another has proven challenging. However, the unifying potential that these hallmarks underline the development of seemingly unrelated diseases across organism systems is what makes progress in this area so encouraging.

The natural first step to begin exploring the hallmarks of aging is at the core of our cells — our DNA. While certain gene variants are known to be associated with age and may in part underlie the average lifespan, our genetic makeup is estimated to only account for a small fraction of observed variations in biological aging and lifespan [23]. Instead, although a concrete theory remains elusive, it is widely accepted that the accumulation of damage to genetic material is a major factor in the process of aging (Figure 3). Changes to how the information in our genetic code is read and processed can also contribute to the aging process. Epigenetics, the field associated with this phenomenon, involves modifications that alter the way our DNA is packaged, determining which genes get read and which get ignored. Epigenetics is an exciting area because there is evidence that (i) defined epigenetic changes are associated with age, (ii) these changes can be clearly linked to pathology or other hallmarks of aging, and (iii) anti-aging interventions can restore healthy biological processes compromised by epigenetic changes [22]. The harmful genetic damage accrued throughout an individual’s lifespan confers susceptibility to broader cellular dysfunction, or even cell death.

In addition to genetic causes, biological processes involved in responding to nutrient availability may play a critical role in aging due to their ability to control metabolism [22]. Cellular metabolism includes processes that break down the nutrients we consume to generate energy for immediate use or storage, as well as those that use energy to assemble important complex molecules out of simple building blocks. It is important for cells to be able to appropriately sense and adapt to changing nutrient conditions, such as in response to daily meals and nighttime fasts, in order to maintain a balance between the utilization and storage of energy (Figure 3). Diminished sensitivity of these processes is thought to play a major role in aging and age-associated disease.

The decline in healthy functioning of these and other cellular processes, including the ability of cells to replicate normally and to maintain cellular protein machinery, impairs the ability of cells and tissues to respond to and overcome stress, leading to increased cellular dysfunction or cell death and, ultimately, age-related disease (Figure 3). These discoveries have encouraged scientists to rethink how we treat and prevent diseases in older individuals.

Treating aging as more than a risk factor

Progress in our understanding of the biology of aging demonstrates that age is more than just a risk factor for chronic conditions, but rather it is a continuous biological process that varies across individuals and that can be altered using a variety of interventions. Furthermore, the effects of age, such as neurodegeneration, cardiometabolic dysfunction, bone and muscle loss, and increased cancer risk, are observed across multiple organ systems. This set of pathologies jointly contribute to broad physical and cognitive decline, and scientists have proposed targeting the aging process itself in order to slow the onset of multiple diseases, instead of treating each pathology as a separate condition. Aging researchers discount the “one disease at a time approach” as an ineffective means to improve health in older populations since older individuals cured of one disease would still be at an increased risk for many other chronic conditions [7]. Thus, a central premise of geroscience is that targeting the hallmarks of aging has the potential to address multiple age-associated diseases [7, 21].

Many potential interventions are being evaluated for their ability to delay the aging process, and a few of these
Figure 3: Aging is characterized by broad loss of cellular and organismal homeostasis, including loss of quality control of the functional proteins in cells (top), impaired regulation of cellular energetics and coordination of metabolism with nutrient availability (right), genetic damage or altered epigenetics (bottom), weakened cellular stress response leading to cell death and altered ability to replicate (left), as well as additional alterations. Dietary restriction, metformin, and rapamycin have been shown to delay aging in animal models by affecting one or more of these processes [22].

interventions show efficacy in rodent models with some evidence to support that they may be effective in humans. Thus far, the most substantial investigations in humans have focused on the area of nutrient sensing and metabolism. Not surprisingly, adjustments in diet and exercise have been shown to promote healthy aging. Caloric restriction (CR), a reduction in total daily caloric intake without deprivation of essential micronutrients, is the most well-established intervention that has been demonstrated to extend lifespan in a variety of model organisms (flies, mice, and rats) and to promote metabolic health in humans [24,25]. One study found that CR decreased mortality and delayed the onset of age-related diseases in non-human primates [26]. CR has also been investigated in humans through the CALERIE trial, which tested the effects of a 25% reduction in caloric intake for two years [27]. Individuals on CR had improved metabolic health, including significant reductions in cholesterol, blood pressure, and insulin levels, when compared to control subjects, and demonstrated some of the same metabolic and hormonal adaptations as rodents on CR [27]. Other modes of dietary intervention, broadly termed dietary restriction (DR), are also being investigated to pinpoint the optimal macronutrient content and feeding regimen to extend health.

Broadly, it is hypothesized that CR promotes healthy aging by acting as a moderate (but not harmful) physiologic stress, forcing cells and tissues to turn to a protective state of self-preservation [22]. It has been shown that cells in this protective state are less vulnerable to age-promoting damage and respond better to future stressors. This beneficial effect of low-grade stress is termed hormesis. Scientists are hopeful that by understanding the biological processes underlying this phenomenon, we may be able to develop biological or pharmaceutical agents that can delay or reverse signs of aging – geroprotectors and gerotherapeutics, respectively – that do not necessitate the lifestyle change associated with CR, which may not be feasible for all.

There has been some progress in identifying compounds that mediate healthspan and lifespan in animal models. One of the central nutrient-sensing programs that is implicated in CR involves the regulatory protein mTOR. Activation of mTOR sets off a flood of signals that promote energy-consuming processes and block processes that conserve energy and recycle damaged cellular components, leading to cellular growth and division [28]. Rapamycin, a small molecule derived from soil bacteria that is used clinically as an immunosuppressant, is a potent inhibitor of mTOR and is associated with lifespan extension in a variety of model organisms [24]. Studies to test the ability of rapamycin and novel small molecules with similar functions to promote healthy longevity in humans are currently under development.

Metformin, one of the most popular and effective drugs used to treat diabetes, has also been studied in the context of aging and age-related disease. Studies show that metformin improves longevity across species, extending lifespan in
mice by 6% [29]. In addition to its glucose-lowering action, metformin has been demonstrated to act on numerous hallmarks of aging, improving health across multiple species [30]. Importantly, metformin is the subject of the first clinical trial focused on preventing age-associated disease, called the Targeting Aging with Metformin (TAME) trial, which is discussed in further detail below. Beyond the area of metabolism, epigenetic regulators are also potential therapeutic targets. Compounds that support the function of sirtuins, proteins that maintain a youthful epigenetic state and have also been associated with DR-mediated lifespan extension, are of particular interest [31].

While the above strategies are designed to slow biological aging, scientists also have their sights set on the futuristic concept of age reversal. One approach to reversing age is to reprogram cells in a way that restores a more youthful identity using a series of stem cell-associated factors that modify gene expression [32,33]. Early research in this area offers promise for late-life interventions [32].

Aging is a highly complex process regulated by a variety of interconnected biological pathways, and the identification of a single “fountain of youth” to slow or reverse aging remains elusive. However, current science suggests that a carefully tailored suite of interventions may be able to extend healthy lifespan by mediating the biological processes related to the established hallmarks of aging. With the demographic shift in population aging underway, it will be critical to harness our scientific discoveries in a way that propels us towards a future in which we may all be able to live healthier for longer.

Is aging a disease?

Progress in geroscience demonstrates that processes underlying biological aging can be therapeutically targeted to extend health, raising the question of whether aging itself should be classified as a disease. The World Health Organization (WHO) has included “old age” as a general symptom and “aging-related disease” as an extension code in the latest update of the International Classification of Diseases (ICD), a global system for categorizing and reporting mental and physical illnesses, [34], which is now in its 11th edition [35]. Although this latest update is yet to be adopted and integrated into the American healthcare system, there has been a myriad of responses from gerontology and geroscience experts in reaction to the decision.

The “aging as a disease” debate began in the geroscience community almost a decade ago, and the updates to ICD-11 have sparked renewed interest in defining the advantages and disadvantages to formally recognizing old age as a disease. In the literal sense, aging shares some attributes of a disease: it is characterized by specific signs or symptoms, is connected to functional limitations, and is associated with an increased risk of additional health limitations or death [20]. However, in a 2019 Public Policy and Aging Report published by the Gerontological Society of America (GSA), Wake Forest University Gerontology Professor Stephen Kritchevsky asks whether these shared attributes are “enough for old age to be considered a disease”; there are multiple conditions that, similar to aging, require specialized medical consideration, such as biological sex or pregnancy, yet these are not considered a disease. Kritchevsky argues that even considering old age as a disease in the metaphorical sense could have negative effects on how the public acts and feels about old age, envisioning that “old age would be something to be feared and avoided.” Despite warning of the negative implications of medicalizing a large and growing portion of the population, he acknowledges that more formally recognizing the aging-disease connection could improve access to new therapies for age-associated diseases.

Proponents of classifying aging as a disease have argued that this action would lead to increased well-being of older adults and provide economic and healthcare benefits for stakeholders by: (i) promoting allocation of funding for aging research and drug development, (ii) garnering increased attention from the medical field to foster a proactive approach to treating age-associated diseases, and (iii) expanding insurance coverage of new gerotherapeutics [36]. To support the disease classification, aging has been compared to obesity, which is now classified as a disease with multiple codes in ICD-10 (an earlier edition adopted for use by the U.S. in 2009, [37]) due to its association with a cluster of conditions, such as heart disease and diabetes [38]. In addition, accelerated aging syndromes in children, such as Progeria, are recognized as diseases. Butleris et al. highlight how “when the same changes happen to an individual 80 years older, they are considered normal and unworthy of medical attention” [36], arguing that this contradiction is detrimental to the care and treatment of older adults.

Some experts are less enthusiastic to recognize aging as a disease due to both the philosophical and practical implications. Dr. Peter A. Boling, a geriatrician at Virginia Commonwealth University, argues that “if aging is a disease, then by logical extension, as a result of simply staying alive, we are all ‘sick’” [39]. Furthermore, in a global call to action, experts argued that the codification of aging as a disease in ICD-11 is “detrimental and deleterious from clinical, research, and humanitarian points of view” [40]. According to this perspective, it is ethically dangerous to classify older adults as diseased because it presents the opportunity for these adults to be deprioritized for care (as occurred when care was rationed due to COVID-19 [41]) or written off as less valuable to society.

As recently as July 2022, experts in the fields of geroscience, geriatric medicine, and social gerontology contributed to a webinar discussion hosted by the Gerontological Society of America (GSA), titled “Insights and Implications of ICD-11 Codes Related to Aging”, to discuss the topic of old age being considered a disease [42]. During this discussion, Nancy Morrow-Howell, a Gerontology Professor and educator at Washington University in St. Louis, expressed concern that prevention and therapeutic intervention will be “much harder to achieve under an ‘aging as disease’ framework.” Morrow-Howell argues that
the vast variability in the manifestations of aging illustrates the opportunity for prevention and intervention, while a “fatalistic generalization” of all older adults under a disease classification ignores this variability and may lead to ageism, reduced efforts to prevent and treat morbidity in older adults, and a lack of attention to social determinants of health affecting the older population.

The American Association of Retired Persons (AARP) also stands against the classification of aging as a disease. The AARP Second Half of Life Study demonstrated that the proportion of adults who perceive themselves to be in “excellent” health increases rather than decreases with age [43]. Contrary to conventional perspectives on health and aging, the AARP survey revealed that many older adults consider themselves healthy if they are “independent, mobile, and of strong mind.” The CEO of AARP, Jo Ann Jenkins, subsequently expressed the need to adopt an evolving definition of good health that reflects age- and condition-sensitive goals [44].

Even some geroscientists who were once in support of considering biological aging a disease have come to recognize the nuances of the debate. In the GSA webinar, Matt Kaeberlein, a professor studying the biology of aging at the University of Washington, emphasized the need to distinguish between the questions of whether ICD-11 should reflect that biological aging is modifiable and whether aging is a disease [42]. While he states the importance of helping stakeholders and the public understand that biological aging can be therapeutically targeted, he expressed that “asking whether aging is a disease distracts in many ways from the point that biological aging is modifiable.” Similarly, Dr. Nir Barzilai, a longevity researcher who serves as the Scientific Director of AFAR and the principal investigator on the TAME trial, stated in a 2015 interview “In my mind, aging is not a disease,” clarifying, “I don’t care what they want to call it, if I can delay it.” [45]. In other words, if the common goal is improving the health and well-being of older adults, it may be more valuable to prioritize the development of a framework for treating aging like a disease, rather than debating whether it should be called one. Numerous alternative approaches, such as supporting scientific research to facilitate the development and translation of new technologies, have the potential to improve the health of older adults without the need to classify aging as a disease.

**Paving the path forward for gerotherapeutics**

There are several of key considerations affecting the implementation of novel therapies and preventive approaches proposed by geroscience research. These considerations include (i) identifying reliable biomarkers of the aging process, (ii) determining appropriate clinical trial outcomes to test the efficacy of interventions treating age-related disease, and (iii) defining the indication for use of gerotherapeutics [46]. These steps will assist with the translation of geroscience to clinical applications while adhering to the standards of FDA regulatory principles and setting new benchmarks for future gerotherapeutic development.

The scientific and economic status of promising gerotherapeutic and preventive strategies, as well as potential regulatory approval pathways, were highlighted in an article published in the Public Policy and Aging Report, called “A Regulatory Pathway for Medicines That Target Aging” [47]. The article negated the necessity of classifying aging as a disease. Authors made the case that it is possible to approve drugs targeting the aging process, citing other medications used for prevention, such as drugs that lower cholesterol to reduce the risk of cardiovascular disease and vaccines that protect against various infectious diseases [20, 47]. Thus, developing drugs that target risk factors of age-related diseases is a route to getting gerotherapeutics on the market without considering aging a disease. One major hurdle is the identification of reliable, widely accepted methods of tracking the aging process (i.e., biomarkers) that would be necessary both to assess the efficacy of new therapies and to determine the target population for safe usage.

Appropriate biomarkers of the aging process will indicate the degree to which the hallmarks of aging have begun to deteriorate and will likely be associated with the onset of chronic diseases, overt signs of aging, and may even predict lifespan. In order to be implemented broadly, biomarkers should be assayed using a non-invasive and cost-effective approach and will have to be verified in a diverse human population. Investigators across multiple institutions are working to develop and validate aging biomarkers through The Predictive Biomarkers Initiative, which was launched by the National Institute on Aging in 2019. This work involves identifying new biomarkers of processes spanning the hallmarks of aging, developing methods for non-invasive sample detection and analysis, and analyzing how biomarkers track with physical signs of aging [48]. New biomarkers must be evaluated by FDA’s Center for Drug Evaluation and Research Biomarker Qualification Program. This program is responsible for qualifying biomarkers for use in specific contexts, such as clinical trials or disease diagnosis, and provides a framework for the FDA to support scientists and clinicians in pursuit of new biomarkers [49].

An epigenetic process called DNA methylation, which involves the addition of a carbon-based chemical group directly to DNA, has garnered recent interest as an indicator of biological age. There is abundant evidence that epigenetic modification patterns are altered throughout the lifespan [50]. This feature has enabled the development of epigenetic clocks, algorithms that use information about the number and location of DNA modifications to estimate biological age [50]. This “DNA age” is a strong predictor of both lifespan and age-associated comorbidities and is a promising aging biomarker [51, 52]. In addition to epigenetic clocks, assays to quantify the presence of stressed cells that have stopped replicating in blood or tissue –another hallmark of aging– are soon expected to enter the clinical research stage [51]. Biomarkers monitoring DNA damage or repair capacity are also being studied, but the reliability and broad applicability
of these measures are not yet convincing enough for use in humans. While promising advances have been made in each of these areas, no single measure will provide insight into all hallmarks of aging. Thus, a composite readout of multiple biomarkers may provide more insight, especially considering the heterogeneity in the rate of aging [51].

A rational approach toward the treatment of age-related symptoms would be to track cellular or systemic deterioration prior to the onset of more severe signs of aging, such as frailty or memory loss. With reliable testing, we might be able to track relevant markers of the aging process starting early in life, just as eyesight and blood pressure are assessed regularly to monitor vision and cardiovascular health. When assessed throughout the lifespan, epigenetic clocks or other biomarkers may be able to identify individuals whose biological age is not aligned with their chronological age, opening the door to treat those who are aging at an accelerated pace. However, in order for this preventive approach to be applied to aging, scientists need to establish reliable biomarkers for the aging process that manifest prior to symptoms of disease. Furthermore, in addition to their utility in determining an individual’s biological age and disease risk, biomarkers can serve as surrogate endpoints to gauge the efficacy of a therapy in a clinical trial as benchmarks to measure the effectiveness of novel therapies in pre-clinical development.

Clinical trials will be an important step to better understand the effect of geroscience interventions on healthy aging in humans. Before gerotherapeutics can be used to treat age-associated diseases, a regulatory framework dictating the clinical testing of geroscience interventions must be established. Clinical trials are required to have pre-determined endpoints, metrics that allow investigators to determine drug efficacy in a certain disease context. In the context of aging, the purpose of a gerotherapeutic is to prevent the onset of a wide variety of age-associated diseases, complicating the choice around the most relevant outcome to evaluate. Within the current FDA framework, such trials could test the effect of an intervention on multiple individual outcomes, a composite taking into account multiple individual outcomes, or a single global outcome that could be affected by multiple parameters, such as all-cause mortality [46].

While a defined FDA framework does not yet exist for trials testing drugs with geroscience-related indications, there are pioneering clinical trials working toward this goal for the first time. The Targeting Aging with Metformin (TAME) trial will be a six-year clinical trial designed to assess the effect of metformin on age-associated comorbidities in older adults (ages 65-79) [29,47]. The trial aims to evaluate over 3,000 participants at 14 institutions across the United States. Primary investigators for the TAME trial, including Dr. Nir Barzilai, consulted the FDA on the trial design and were advised on how to best comply with current regulations. The primary endpoint for TAME is the time to onset of any major disease, including myocardial infarction, stroke, congestive heart failure, cancer, mild cognitive impairment/dementia, or death [47]. In other words, this trial aims to repurpose metformin, which has already been shown to be safe for use in humans and is approved for the treatment of diabetes, for a healthspan indication. TAME is unique in that the composite endpoint includes outcomes that cut across multiple previously unrelated disease categories with age being the unifying risk factor. While data about age-related biomarkers will be collected, the FDA denied the usage of this information as the primary basis upon which drug approval may be conferred [47]. The TAME trial is a critical first step towards the adoption of gerotherapeutics and will provide a path for more clinical trials testing existing and future gerotherapeutics with promising results in animal models.

However, because the onset of disease must be observed within the duration of a reasonably timed clinical trial, a framework based on the TAME design would not enable the assessment of drugs that could be used early in life as prophylactics. This is an important distinction, as prophylactic treatment with safe geroprotectives over a long period of time is most likely to allow patients to reap the benefits of treatment prior to potential disease onset. To test the benefit of such preventive therapies, the FDA must be convinced that biomarkers are highly reliable predictors of future health and longevity and approve their use as surrogate endpoints. Furthermore, clinical trials would have to demonstrate not only that geroprotective therapies provide clinically meaningful benefits for patients, but that they are safe enough to administer broadly to a healthy population [47].

As mentioned in the first section, it is imperative to include older individuals in clinical trials testing new therapies, especially those targeting the aging process. Analogously, it will be important to test pre-clinical aging interventions in aged animal models to improve the likelihood that any beneficial effects are mirrored in human trials.

Another challenge of adopting gerotherapeutics is determining the appropriate indication or target population. Since aging is a steady process and observable symptoms arise on a continuous scale across life, it will be challenging to determine benchmarks for disease diagnosis, and age or symptom cut-offs are likely to be arbitrary and to trigger ongoing debate among clinicians, scientists, and the public. In addition, defining aging as a disease based on such determined benchmarks or age groups may limit opportunities for the prevention of disease in younger individuals experiencing accelerated aging. Additionally, although aging is a universal phenomenon, the rate at which it occurs is not uniform. Genetic, environmental, and social determinants of health affect the biological aging process [53], rendering chronological age alone a weak delimiter of “disease” status and progression. Ultimately, the current lack of consensus about how to define the context of use for geroscience-guided therapies further complicates the regulatory landscape.

An additional regulatory consideration is the distinction between approved drugs that can be repurposed for healthspan indications, unapproved gerotherapies with
rigorous scientific support, and “anti-aging” supplements. Drugs like rapamycin and metformin have a long history of safe usage for other FDA-approved indications, and require a prescription. Other putative gerotherapeutics are not currently approved to treat any indication and therefore not regulated by the FDA. However, some of these compounds are widely available on the market as dietary supplements. Treatments or supplements that are not under the purview of the FDA are not subjected to the same scientific burden of proof [54] or long-term use studies [55] for safety and efficacy. Consequently, at best, the lack of oversight allows for easier development and translation of safe products not requiring FDA approval, but in numerous cases, companies have made exaggerated [56], untrue [57], [58] or misleading claims [59] about the efficacy of their products. Ultimately, it will become increasingly difficult for the general public to differentiate between safe and effective treatments, and those that could introduce harm and lasting damage to their health, thus adding a deserved degree of caution to potential beneficiaries of the fruits of geroscience.

Given the potential for a new drug market, the biotechnology sector will also play a role in developing new gerotherapies, and a clinical trial framework that streamlines the process of testing these therapies will benefit both investors and patients. Companies aimed at developing gerotherapeutics have garnered considerable attention as of late, with large technology and venture firms excited about investing in the potential to overcome the limits of human lifespan. Calico Life Sciences LLC, launched by Google in 2013, is focused on understanding the biology of aging and collaborates with AbbVie for late-stage clinical development and commercialization [60]. The prominent Harvard investigator, Dr. David Sinclair, launched Life Biosciences, Inc. in 2017 to develop gene therapy techniques to restore youthful function to old cells [60]. Life Biosciences has raised $158 million thus far. Most recently, Allos Labs, Inc. announced its launch in January 2022, with an impressive $3 billion in initial funding from prominent investors, including Jeff Bezos of Amazon [60]. New venture capital firms, such as the Longevity Fund [61], also emphasize the growth in industry-sponsored aging research and provide additional funding opportunities. Continued investment in research aimed at preventing or treating aging will likely foster the development of innovative drugs and better patient outcomes, in addition to boosting jobs and economic development in this field.

Progress reflected in the efforts from academia, government, and biotechnology sectors make a case that classifying aging as a disease may not be necessary for science and society to prioritize healthy aging. Addressing the key remaining barriers outlined above will prepare society to enter a new era of treating aging.

Conclusion

Population aging is expected to yield a greater proportion of older adults in the United States than ever before. Therefore, the health of this age group, and that of the U.S. population more broadly, will depend greatly on improved prevention and management of chronic diseases. While age is known to be a risk factor for many conditions that affect healthspan and lifespan, age has been considered largely immutable, and the increased risk of disease has been accepted as a fact of life. However, recent developments in geroscience research suggest that the biological processes underlying aging may be more plastic. The potential of this finding is significant in that appropriate interventions may enable a paradigm shift from the management of diseases associated with advanced age to broad prevention of many illnesses through which individuals may increase the number of years they live in good health. In terms of both humanistic and economic factors, there is an emerging incentive to develop treatments and monitoring techniques that can properly assess and treat the hallmarks of aging. While classifying aging as a disease could be detrimental to older adults, treating the underlying biological processes that occur in every individual may provide a means to broadly improve health, given the strong links between these processes and the development of chronic disease.

However, without key scientific evidence to clinically define biological aging, measure its progress and effects, and produce an appropriate indication for geroscientific treatments, regulatory approval ensuring the safety and efficacy of products will continue to be an obstacle. The development of gerotherapeutics that can be administered across the lifespan will require an in-depth assessment of biomarkers for the aging process, and the acceptance of these biomarkers by scientific communities as well as by the FDA.

This challenge has drawn the interest of clinicians, patients, caretakers, entrepreneurs, sociologists, and government officials alike. Through deliberate collaboration among these important stakeholders, we will be able to pave a path forward to improve the healthspan of older adults and the population at large.

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