MAYO CLINIC

Exceptional Human Longevity

Robert J. Pignolo, MD, PhD

Abstract

Exceptional longevity represents an extreme phenotype. Current centenarians are survivors of a cohort who display delayed onset of age-related diseases and/or resistance to otherwise lethal illnesses occurring earlier in life. Characteristics of aging are heterogeneous, even among long-lived individuals. Associations between specific clinical or genetic biomarkers exist, but there is unlikely to be a single biomarker predictive of long life. Careful observations in the oldest old offer some empirical strategies that favor increased health span and life span, with implications for compression of disability, identification and implementation of lifestyle behaviors that promote independence, identification and measurement of more reliable markers associated with longevity, better guidance for appropriate health screenings, and promotion of anticipatory health discussions in the setting of more accurate prognostication. Comprehensive PubMed literature searches were performed, with an unbiased focus on mechanisms of longevity. Overall, the aggregate literature supports that the basis for exceptional longevity is multifactorial and involves disparate combinations of genes, environment, resiliency, and chance, all of which are influenced by culture and geography.

 ■ Mayo Clin Proc. 2019;94(1):110-124

From the Division of Geriatric Medicine and Gerontology, Mayo Clinic, Rochester, MN.

Although the definition of exceptional longevity must at some level be arbitrary, major criteria should likely include the concepts of chronological vs biological age, as well as preservation of function. For successful aging, 2 assumptions exist: (1) that biological age, however determined, is less than chronological age and (2) functional status is maintained or the decline in functional status is relatively slowed or delayed. These assumptions are not unreasonable given that individuals who are exceptionally long-lived would necessarily tend to meet both criteria, or at least would have had to meet these criteria during some period leading up to their extreme longevity. For this review, comprehensive PubMed literature (1980-2018) searches were performed, with an unbiased focus on mechanisms of longevity.

Evidence to date suggests that exceptional longevity involves interacting mechanisms that may be genetic, environmental, cultural, or geographic in origin. This review will examine the heterogeneous nature of exceptional longevity and how studying the oldest old may substantiate the involvement of the aforementioned mechanisms on the pace of aging, elucidate homeostatic responses characteristic of resiliency, suggest interventions in the aging process, and inform measurements of successful aging.

CENTENARIANS

In 1995, it was estimated that during the span of human history the likelihood of living from birth to age 100 rose from 1 in 20 million to 1 in 50 for females in low-mortality nations such as Japan and Sweden[1]; subsequent analyses published in 2009 indicated that this probability increased to approximately 1 in 2.[2] About 1 in 5000 persons in the United States is a centenarian or older,[3] and this prevalence is predicted to markedly increase in the United States and other developed nations. Human longevity exceeds 115 years, with reliably reported ages of 122 years for Jeanne Calment who died in France in 1996[4] and 116 years for Jiroemon Kimura who died in Japan in 2013.[5]

Although human life expectancy and median length of life rose dramatically over the past century, maximum life span has remained largely unchanged (Figure 1).[6] Although the debate is ongoing, the weight

of evidence suggests that there is a limit to human longevity, and indeed, over the past 2 decades, the ages at death of the longest surviving individuals have not significantly risen.[7] Conversely, arguments have been made that this lack of increase does not rule out the possibility that maximum human life span in years may quite gradually increase in the future.[8]

In centenarians, the age at onset of common age-associated diseases, with the exception of cognitive impairment, is variable, with one or more diagnoses being made in 24% of males and 43% of females before 80 years of age. Approximately 43% of both male and female centenarians reach the age of 80 years before experiencing age-associated illness. Remarkably, there is an absence of any disease diagnosis in some 15% and 30% of female and male centenarians, respectively, at the age of 100 years. These results suggest that the onset of age-related conditions, regardless of sex differences, is heterogeneous and that their earlier manifestation (before 80) may still allow exceptional longevity.[9]

As many as 25% of centenarians are cognitively intact, and among those who reach 100 years of age and are not cognitively intact, the vast majority have delayed clinical onset of impairment until the average age of 92 years.[10] Neurodegenerative disease and dementia do not occur in significant subsets of centenarians, and even in centenarians who exhibit neuropathologic markers of Alzheimer disease, criteria for dementia may be absent.[10] Cancer is diagnosed at a substantially later age in centenarians.[11] Supercentenarians (>110 years of age) may have development of vascular disease relatively late in life or not at all, and many are functionally independent or require minimal assistance.[4,5,12]

GEOGRAPHIC CLUSTERING OF EXCEPTIONALLY LONG-LIVED INDIVIDUALS

Human subpopulations that display exceptionally long life spans illustrate the profound effects of environmental prolongevity factors. Long-lived Okinawans subscribe to the nutritional behavior of "hara haci bu" or "eat until you are only 80% full." Their "rainbow diet" is based on diverse fruits and vegetables, with soy providing the bulk of protein intake.[13,14] Their daily caloric intake is substantially reduced compared with other diets, accounting for their low body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) ($\sim$20 kg/m^2) and suggesting that caloric restriction may contribute to their longevity. The association of lean body mass with exceptional longevity is also corroborated by studies in US centenarians born in the 1880s.[15] Levels of dehydroepiandrosterone, the endogenous hormone secreted by the adrenal gland and a surrogate marker of life span extension, decline more slowly in Okinawans and mimic the trend seen in animal experiments of controlled caloric restriction.[16]

Compared with men elsewhere, men in Ovodda, Sardinia, tend to live longer.[17] Sardinians who emigrated in early adulthood or middle age are still capable of extreme longevity; their longevity may reflect their lineage from a select number of original settlers and that they remained isolated and interbred.[18] The basis for this male exceptional longevity may be related to as yet incompletely defined genetic traits.[19] Although Jiroemon Kimura had long-lived (nonagenarian) siblings, suggesting a

ARTICLE HIGHLIGHTS

- The mechanisms of extreme long life appear to be multifactorial and can be accomplished by disparate combinations of genes, environment, resiliency, and chance that vary with culture and geography.
- Characteristics of aging are heterogeneous, even among long-lived individuals.
- Associations between specific clinical or genetic biomarkers exist, but there is unlikely to be a single biomarker predictive of long life.
- Careful observations in the oldest old offer some empirical strategies that favor increased health span and life span, including eating in moderation, regular exercise, purposeful living, and strong social support systems.

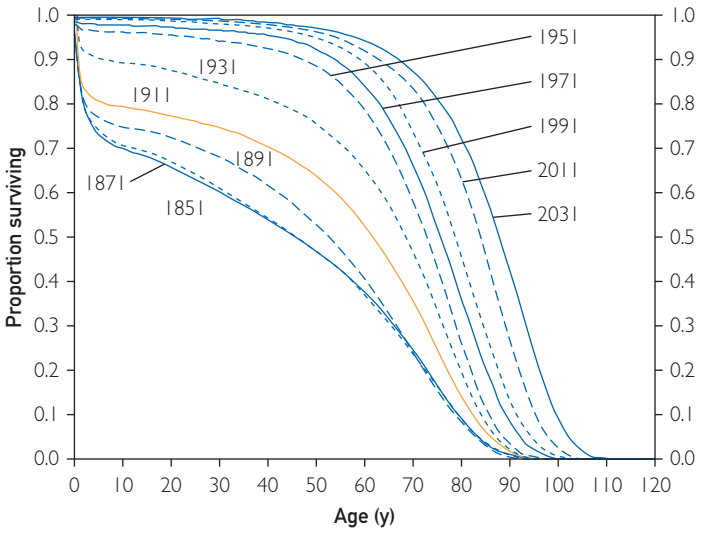

FIGURE 1. Survivorship according to mortality rates experienced or projected in persons born 1851-2031 in England and Wales. Although mean life span has increased, maximum life span has remained essentially unchanged. From the UK Office for National Statistics,[6] with permission granted by the United Kingdom Licensing Framework, Open Government License.

possible genetic component to his longevity, he attributed his long life to several health practices including small apportioned meals.[20]

Seventh Day Adventists, largely residing in Loma Linda, California, outlive their fellow citizens by 5 to 10 years.[21,22] Their religious faith requires abstinence from alcohol and tobacco, and recommends a vegetarian diet that is followed by many. Spirituality informs their daily living; indeed, life span is increased in regular churchgoers, whatever their faith.[23-25] Seventh Day Adventists exhibit significantly lower levels of measured stress hormones.[26]

Other geographic clustering of long-lived individuals occurs in Costa Rica (Nicoya Peninsula), in Ikaria, Greece, and perhaps elsewhere.[27,28] There are several generalizations that can be made on the basis of common behavioral and environmental influences that may contribute to longevity in these areas (Table 1). These factors include eating in moderation and mostly plant-based diets, exercise that is incorporated into daily routines, purposeful living, maintaining social support systems, and other nutritional or behavioral factors that may underpin or reinforce healthy living.

TABLE 1. Longevity Factors Associated With Geographic Clustering of Long-Lived Populations

Eating in moderation (small- or moderate-portioned "regular" meals), mostly plant-based diets, with lighter meals at the end of the day
Purposeful living (eg, life philosophy, volunteerism, "hard work" or "work ethic")
Social support systems: interactions with family/friends, laughter/humor
Exercise, especially walking, gardening
Other nutritional factors: goat's milk, red wine, herbal teas
Spirituality
Maintenance of a healthy body mass index
Other possible factors: sunshine, adequate hydration, naps

TRENDS IN LONGEVITY

Insights into trends and consequences of longer life can be gained through an understanding of human survivorship, demographics of longevity, and models of predicted morbidity as populations become long-lived. Japan remains one of the best examples of exceptional trends in increased longevity. However, regardless of location, concerns exist that enhanced longevity will be accompanied by more years of disability rather than more years of healthy life.

Safeguarding against premature death, as opposed to variations in primary aging processes, underlies the survival benefit reflected by median life span and life expectancy (Figure 1). Reduction in the high rate of infant deaths (due to improved sanitation, nutrition, and immunization) largely accounts for protection from premature death by environmental hazards and infectious diseases seen early in the twentieth century.[29]

Demographics of Longevity

Japan, followed by Germany, Italy, Greece, Finland, and Sweden, had the world's oldest populations in 2015, with a longevity shift toward Asian populations expected by 2050, including Japan, South Korea, Hong Kong, and Taiwan.[30] In 2015, countries with the longest life expectancy at age 65 were Japan, Macau, Singapore, Australia, and Switzerland, with an additional 25.2 and 20.0 years of life expected for Japanese

Mayo Clin Proc. ■ January 2019;94(1):110-124 ■ https://doi.org/10.1016/j.mayocp.2018.10.005
www.mayoclinicproceedings.org

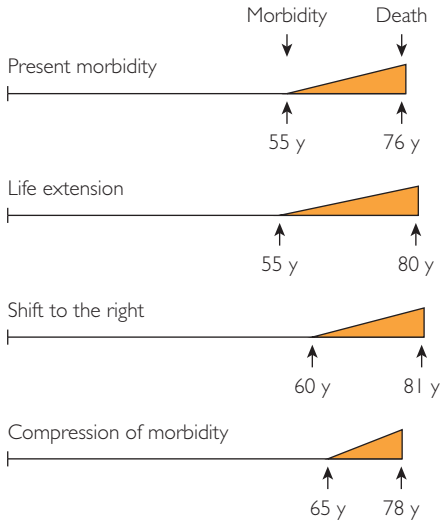

FIGURE 2. Possible scenarios for future morbidity and longevity. From *Ann Intern Med*, Fries JF, Measuring and monitoring success in compressing morbidity, Volume No. 139, Issue No. 5 (Part 2), Pages 455-459.[32] Copyright © 2003 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

females and males, respectively.[30] In fact, in 2002, Japanese female life expectancy rose at a consistent rate of about 3 months per year for the preceding 160 years.[31]

In countries with the highest life expectancy, healthy life years vary between 25% and 75% of the predicted life expectancy at age 65 years.[30] Norway, Sweden, and Iceland have the greatest number of expected healthy years at age 65.[30]

Compression of Morbidity

There are several models of predicted morbidity proposed on the basis of extended longevity (Figure 2).[32] In one model of life extension, the age at initiation of morbidity remains constant and life years gained are accompanied by increased morbidity. In a second model, both the initiation of morbidity and the life years accrued are shifted to the right, with no gain or loss of morbidity. In a third model, initiation of morbidity is delayed and accompanied by added years accrued, resulting in the compression of morbidity.

Fries' "compression of morbidity" hypothesis puts forth the possibility that chronic morbidity begins at a later age and that the delay of onset would exceed the increase in life expectancy.[33] In essence, for these longer-living individuals, the duration of chronic diseases and associated disability is diminished, with the attendant reduction in cumulative morbidity.

Evidence that a reduction in disability trends of about 2% per year, accompanied by a 1% per year decline in mortality during the same period of time, supports this hypothesis.[34] However, because the cohort of individuals 85 years or older comprises the most rapidly increasing sector of the American population, it is possible that compression of morbidity may not apply to individuals surviving to very old age. Delays in morbidity from age-onset diseases occur in many surviving to very old age; for others who survive to extreme old age, delay in disabilities alone is the essential requirement.[35]

With some exceptions, estimated rates for the need for help in activities of daily living (ADLs) for aged individuals decreased during the 1980s and 1990s.[36-40] Some studies that covered the early years of the 21st century suggest a continued decline in rates of assistance needed by the elderly for ADLs, but others suggested a possible leveling off of these rates.[41-43] Data gathered from noninstitutionalized working-age adults and elderly individuals from 1984 to 2010 found that impairments in mobility and mental health decreased in the latter group.[44] As supercentenarians attain the current limit of human longevity, a later age at onset is increasingly seen for physical and cognitive impairment, age-related diseases, and overall age-dependent morbidity.[45]

WHY ARE SOME INDIVIDUALS LONG-LIVED?

Insights into possible mechanisms of human longevity point to genetic and environmental influences, sex differences, and resiliency. Twin studies have been important in differentiating genetic from environmental contributions to long life, and several theories have been put forward to explain increased

longevity for women compared with men, including the role of reproduction and child-rearing. Resiliency, the capacity to adequately respond to stressors or resist typical age-related physiologic system-based changes, has also been implicated in conferring protection against insults that shorten life and health span.

Genetic and Environmental Influences

The genetic basis of longevity is supported by several lines of evidence: maximum life span is highly conserved in specific species; the age reached by monozygotic twins is remarkably similar, as compared with ages attained by dizygotic twins or by nontwin siblings; exceptional longevity is often observed within families; and premature aging syndromes, such as seen in syndromes of faulty DNA repair, among others, are genetically based. Centenarians' offspring have an increased likelihood of surviving to 100 years and exhibit a diminished prevalence of age-associated diseases.[46] Considering the ancestry of Jeanne Calment, a remarkable group of long-lived relatives existed in her family's preceding 5 generations, especially in her father's lineage, suggesting a largely genetic origin for her extreme longevity from paternal inheritance.[4]

Polymorphisms involving the *APOE* gene, the latter required in catabolizing triglyceride-rich lipoprotein constituents, may influence life span.[47] Additionally, the apolipoprotein E ε4 allele occurs more frequently in middle-aged individuals compared with centenarians.[48] Polymorphisms in other genes and their associated pathways implicated as imparting prolongevity effects include insulin/insulin-like growth factor 1, cholesteryl ester transfer protein, anti-inflammatory cytokines such as interleukin 10, RNA editing genes and stress response genes such as the heat shock protein 70 genes.[49-53] Genome-wide association studies continue to identify new genetic variants for longevity.[54-56]

Longevity-associated genes are postulated to be more conserved among long-lived species, to promote life span, and to be functionally enhanced in longer-lived species based on conservation of DNA or protein sequence information. Genes for breast cancer 1, early onset, and growth hormone (GH) receptor strongly associate with maximum life span across mammalian species.[57,58] The breast cancer 1, early onset, gene occurs with different genotype frequencies in centenarian populations compared with controls.[59] A GH receptor gene exon 3 deletion alters GH sensitivity, and the prevalence of homozygosity for the exon 3 deletion increases with age in long-lived individuals.[60] In fact, exon 3 homozygosity adds approximately 10 years to life span and exhibits sexual dimorphism by positively affecting male longevity.[60]

Polymorphisms in genes protective against oxidative stress such as superoxide dismutase have not been found to be associated with long life. The GenAge database provides a comprehensive catalog of genes that may associate with human longevity.[61]

Despite substantive evidence that genetic influences can positively affect longevity, environmental factors exert even greater effects. Indeed, as indicated by twin studies, no more than approximately 25% of the variance in adult human life span can be traced back to genetic differences.[62-64] This finding strongly suggests that behavior, environment, and health practices can profoundly affect the potential for long life.

Sex Differences

Universally, women live longer than men.[65,66] Female babies also have better survival. In the United States, beginning at about age 55 years, the difference between the number of females and males roughly doubles by age 75 years and then doubles again by age 85 years and over.[30]

Evolutionary pressure to extend human life span may also be closely linked to increasing the number of childbearing years for women.[67] Middle-aged mothers appear to live longer, and older maternal age at birth of the last child is associated with women's longevity.[68-70] There are conflicting results regarding the relationship between fecundity and longevity.[71-73]

Mayo Clin Proc. ■ January 2019;94(1):110-124 ■ https://doi.org/10.1016/j.mayocp.2018.10.005
www.mayoclinicproceedings.org

The duration of a female's postreproductive life span may influence the reproductive success of her offspring and her grandchildren's survival; this "grandmother hypothesis" may more likely involve maternal grandmothers.[71,74] Length of postreproductive life in women may be related to their predominant role as caregivers, given that the caregiver role, at least in nonhuman primates, appears to be associated with greater longevity regardless of sex.[75]

The likelihood of living to be 100 years appears to be greater for offspring of younger vs older mothers, whereas paternal age does not exert a significant effect on longevity.[76] Sex differences are also seen in terms of longevity determinants, in which occupation history as well as relatedness to male centenarians are important factors for men and environmental conditions in the home or marriage to male centenarians (who share the same living conditions) are important to women.[76,77] To the extent that women tend to be shorter than men, a possible explanation for both greater longevity and lower height is diminished GH secretion.[78-80]

Despite the greater longevity of women, functional status is better in older men compared with older women.[65,81]

Resiliency

There is growing evidence to suggest that resiliency, or the ability to adequately respond to or resist various stressors, plays a key role in conferring successful aging.[82] Although the mechanism(s) are poorly defined and may be tissue- or system-specific, examples of resiliency across multiple domains indicate that it contributes to health benefits in later life. Despite the paucity of human studies that address interventions that promote resiliency, animal investigations suggest that exercise (compared with calorie restriction) promotes resilience more effectively against diverse types of stress.[83]

Resistance to stressors and disease that contributes to healthy aging is often described in the context of psychological resiliency, such as reduction of depression.[84,85] In fact, much work has been initiated describing the framework to study the effects of psychological and social factors on resistance to behavioral stressors that are common with aging.[86,87] However, this aspect is different from physical and physiologic stressors and the homeostatic responses driven by resistance mechanisms against aging-related, system-specific declines and against multisystem insults, including loss of muscle strength,[88] impaired sleep quality and susceptibility to sleep disorders,[89] frailty,[90] skeletal aging,[91] dementia (including Alzheimer disease),[92-100] and multimorbidity.[101] There are likely direct relationships among resiliency against physical and physiologic stressors, homeostatic resistance mechanisms against aging-related, system-specific dysfunction, and longevity.[91,102] Resiliency is a plausible mechanism by which some centenarians, despite onset of chronic disease before the age of 80 years, live exceptionally long.

HOW IS EXCEPTIONAL LONGEVITY ACHIEVED?

Empirical and other evidence suggest that several strategies can be employed to positively influence health and life span, including dietary modification (eg, moderate caloric restriction) to achieve and maintain ideal weight, exercise, healthy behaviors, avoidance of smoking and excessive drinking, active engagement, and development of social networks and support systems. It is widely accepted that poor health behaviors account for a large proportion of disease burden and contribute to premature death, with 40% of preventable deaths in the United States attributable to behavioral patterns.[103,104]

Caloric restriction effectively retards the aging phenotype in mammals, as shown by abundant studies.[105] Reduced caloric intake ranging from 30% to 60% extends mean and maximum life span. This effect has been reproduced in controlled studies in numerous species including worms, flies, fish, rodents, and nonhuman primates. A 20-year longitudinal adult-onset caloric restriction study in rhesus monkeys found that moderate reduction in dietary intake reduced age-associated deaths and delayed the onset of diabetes,

cancer, cardiovascular disease, and brain atrophy.[106] However, in a second study in nonhuman primates in which the control group was fed an apportioned diet to prevent obesity (as opposed to ad libitum feeding), there was no survival advantage with caloric restriction.[107] There were, however, delays in cancer and diabetes in the dietary restriction groups in both studies.

Short-term caloric restriction in humans improves surrogate markers of delayed aging such as serum glucose and insulin levels.[108,109] The Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy-2 study, a 2-year randomized controlled trial of calorie restriction in humans, randomized nonobese adults to 25% caloric restriction (11.7% restriction was achieved) or to maintenance of current diet for 2 years.[110-112] Biomarker data were applied to 2 biological age algorithms, both of which revealed that reduced caloric intake retarded aging independent of weight reduction.[113]

Although reduced intake of calories in adults improves metabolic and hormonal profiles as well as functional capability, the specific reduction in caloric intake or the requisite body fat mass that improves human health and maximizes life span remains unknown.[114,115] Fontana et al[116] found that calorie restriction (20% decrease in calories) substantially improved the main risk factors for coronary artery disease in normal-weight and overweight middle-aged adults, and these benefits were similar to the effects of a 20% augmentation in energy expenditure achieved by physical activity.

Reduced calorie intake retards aging and its processes only when such reduction, in all likelihood, is quite substantial. As such, this strategy may not be a feasible regimen in all but a very small fraction of the population who, like Okinawans, have incorporated dietary moderation as one of several cultural mores of health living. Therefore, it will become necessary to define the mechanism(s) by which caloric restriction alters age-dependent processes that cause functional decline. Thus far, studies in aging models do not demonstrate a beneficial effect of dietary enrichment with antioxidants on median or maximum life span. The longevity benefits of dietary restriction in those with normal BMI are unclear, as are the benefits of supplemental antioxidants or other dietary interventions.

Regular physical activity promotes healthy human life span, but it is still uncertain whether such activity increases maximum longevity.[117,118] Normal body weight confers the most protection from mortality. All-cause mortality is increased in white adults who are overweight and obese (and possibly underweight)[119] and is usually at its lowest when BMI ranges between 20.0 to 24.9 kg/m^2.[119]

Increased physical activity is associated with improved life expectancy, with a benefit of 4.5 years at the highest activity level of 22.5 metabolic equivalent hours per week or more, equal to vigorous walking for at least 450 minutes per week.[120] Continual activity (>7.5 metabolic equivalent h/wk) and a normal weight (BMI, 18.5-24.9 kg/m^2) are associated with an added 7.2 years of life compared with inactivity and obesity (BMI, ≥35.0 kg/m^2).[120] Increased physical activity promotes life expectancy irrespective of BMI and is a dominant factor in benefiting survival and healthy life in adults over the age of 74 years.[121]

Studies also suggest that active engagement and development of social networks and support systems confer longevity benefits. For example, lack of strong social relations is associated with a mortality risk roughly equivalent to smoking.[122] Conversely, a high purpose in life is attended by less impairment in cognitive function and less disability.[123,124] Productive engagement, even when targeted as a short-term intervention, can lead to a significant improvement in episodic memory.[125]

These interventions, including dietary modification, exercise, active engagement, and purposeful living, appear to be well-represented among the exceptionally long-lived (Table 1), confirming their relevance in practical application to daily life.

Mayo Clin Proc. ■ January 2019;94(1):110-124 ■ https://doi.org/10.1016/j.mayocp.2018.10.005
www.mayoclinicproceedings.org

MEASURING SUCCESSFUL AGING

Valid aging biomarkers, when delineated, would enable the assessment of biological age and life expectancy, the evaluation of strategies intended to retard aging, and the standardization of studies in aging research. Minimal criteria for a biomarker of aging would include (1) existence of a quantitative correlation between the biomarker and the age of individuals, (2) evidence suggesting the parameter is not altered with a disease process, (3) evidence that an age-associated change in the putative biomarker is not due to confounding effects of metabolic or nutritional changes, and (4) demonstration that factors that influence the aging rate also alter the putative biomarker.[126]

However, the development of these minimal criteria for validation of biomarkers must be further refined to account for the role of primary aging in chronic disease processes and the use of dietary or other manipulations that may affect primary aging. For example, a biomarker of aging could also be altered with, predict, or even be implicated in specific chronic diseases for which aging represents a major risk factor. Also, given that many nutritional interventions can alter biological aging processes, such biomarkers of aging would also be altered. Moreover, alterations in such biomarkers with caloric restriction, and with drugs that affect senescence mechanisms, could provide additional support that a given biomarker is reflective of aging.

Diverse structural and physiologic alterations occur with age, some of which may be deleterious and cause functional decline. These alterations may be due to aging itself, superimposed diseases, the effect of toxicants, adaptive and maladaptive responses, physiologic deficits, or some combination of these influences. A challenge of basic gerontological research is to delineate those phenotypic features and processes in aged individuals that, directly or indirectly, reflect aging per se and constitute primary aging phenomena.

Some characteristics proposed as being common to human aging include increase in postmaturation mortality (eg, steep drop-off in survival with age), altered chemical constituents in tissues (eg, increased amounts of lipofuscin and cross-linked extracellular matrix proteins), impaired organ function (eg, glomerular filtration rate), impaired organ adaptation to diverse stress (eg, impaired "first-pass" metabolism by the liver, reduced hemodynamic responses to exercise), and rising incidence of assorted diseases (eg, osteoporosis, Alzheimer disease).[127]

These "characteristics" of aging, although widely found, have exceptions that call into question their relevance to primary aging processes and their use as biomarkers for aging.[127] For example, alterations in chemical constituents of tissues, impaired physiologic function, and maladaptive responses to stress vary among organs in a given individual as well as among individuals. Although disease-specific mortality increases with age, it has been estimated that the abrogation of mortality caused by atherosclerosis and cancer would lengthen average life span by no more than a decade and would not increase maximum life span. In addition, recent evidence suggests that mortality risk continues to rise even at extremely advanced old age, findings that oppose the conventional view that mortality rates flatten at very advanced ages.[128]

Putative biomarkers of primary aging may also represent possible predictors of longevity[46,129-179] (Table 2). Each measurement has its limitations as a reliable biomarker for aging and longevity. Some biomarkers have relevance to both biological and functional aspects of exceptional longevity, including gait speed and preservation of ability to perform ADLs. Other biomarkers are biochemical measurements used in clinical practice that in combination have value in estimating biological age. Some are system-specific measurements that are likely surrogates for overall health. Many are more speculative and require further investigation.

Inclusion of centenarians in biomarker studies offers the possibility of developing

TABLE 2. Putative Biomarkers of Primary Aging Processes and Longevity

Biomarker	Reference
Disease-free survival or disability-free survival at 6-month intervals	159
Time to impairment in the next activity of daily living	159
Length of stay after hospitalization	142
Height, especially in men	145, 153, 172
Facial features	131
Gait speed, grip strength, muscle mass, mobility stress test	158, 167, 168, 171, 175
Daily and instrumental activities of daily living	138, 162, 173
Cognitive tests such as the Digit Symbol Substitution Test or Montreal Cognitive Test	148, 151, 163, 169
Blood glucose or hemoglobin A_{1c}, hypertension and elevated lipids, interleukin 6, insulin-like growth factor 1, and insulin-like growth factor binding proteins	136, 157, 163, 178
$CD4^+$, $CD28^-$ and $CD8^+$, $CD28^-$ T cells; percentage of T cells that are naive vs memory (CD4 cells, CD8 cells)	132, 137, 164, 170, 179
Antibody response to annual influenza vaccination; delayed hypersensitivity skin test	140, 144, 152, 166
Cataracts	135, 146, 155, 160
Threshold for hearing high-pitched tones; tests of taste and smell	134, 141, 143, 149, 165
Tests of proprioception and balance	150
Forced expiratory volume in 1 second	129, 174
Number of remaining teeth	147, 154
One or two parents reaching 90 years of age	46, 130, 139
Educational attainment	133, 156
More speculative: DNA methylation indices; senescent cell burden	161, 176, 177

measurements that can identify successful (biological) aging even before extreme longevity is reached. These studies may also implicate pathways that help to define mechanisms that link current health status to exceptional long life.[180-184] There are multiple pathways to exceptional longevity (Figure 3). Based on existing data, possible relationships among factors associated with extremely long life likely account for both the attainment of long life and the heterogeneity of centenarians (Figure 3). For example, an individual who achieves exceptional longevity by escaping from age-onset disease may do so through genetic mechanism(s), dietary practices and exercise, or through some combination of these influences. Conversely, an individual who achieves exceptional longevity through survival from age-onset disease may do so through as yet poorly understood resiliency pathways.

Measuring biomarkers of aging in younger cohorts obviates the confounders of chronic disease. In the Dunedin Study (New Zealand) that follows a 1972-1973 birth cohort, assessment of balance, grip strength, motor function, physical disability, cognitive function, facial aging, clinical laboratory tests, cognitive decline, and self-rated health was undertaken.[131] The rate of functional decline in diverse organs was used to determine biological aging in young individuals in whom age-related diseases were not present. Interestingly, "biological aging" varied in a normal distribution among similarly aged individuals in this cohort.[131]

IMPLICATIONS OF EXCEPTIONAL LONGEVITY

Individuals with extended life expectancy, and especially those with exceptional longevity, demonstrate compression of disability and support that trends of increasing life expectancy need not be associated with greater morbidity. Observations in long-lived individuals suggest lifestyle strategies that promote independence, health span extension, and perhaps even life span extension. Identification and measurement

Mayo Clin Proc. ■ January 2019;94(1):110-124 ■ https://doi.org/10.1016/j.mayocp.2018.10.005
www.mayoclinicproceedings.org

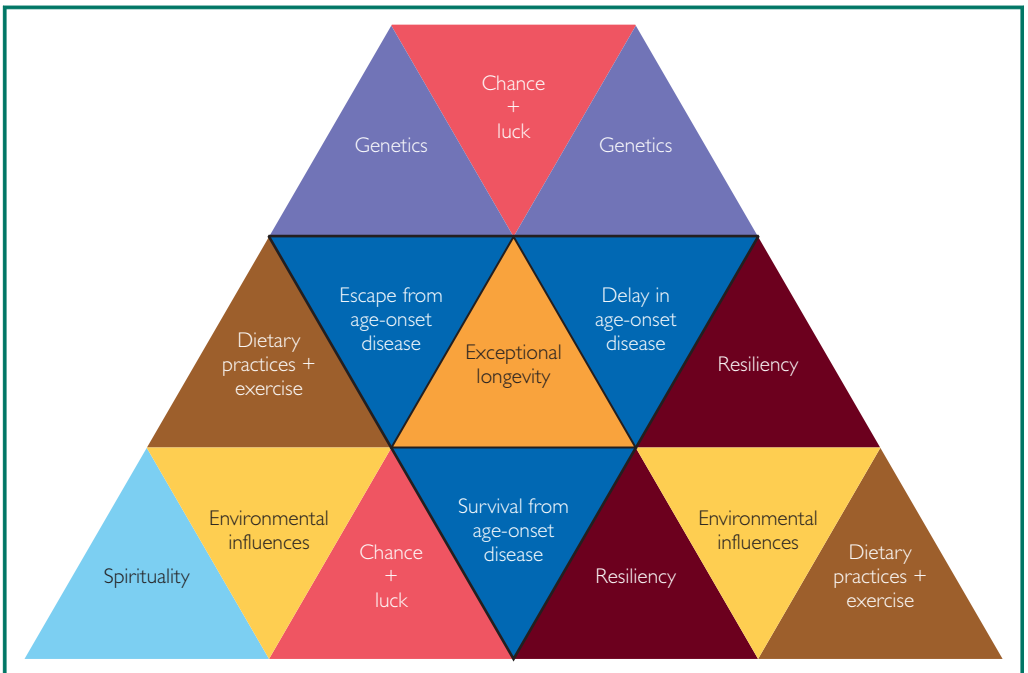

FIGURE 3. Multiple pathways to exceptional longevity. Shown are putative relationships among factors associated with extreme long life.

of biomarkers associated with longevity will permit more accurate estimates of biological age that will inform better guidance for appropriate health screening as well as guidance for anticipatory health discussions.

Several algorithms have been proposed to estimate biological age.[178,185-187] Those based on functional as well as biochemical and other measurements may be more likely to capture key elements associated with prediction of extreme longevity. An unresolved issue relates to disagreement between person-level vs population-level measures, and better resolution of person-level changes awaits further investigations.

Historically, guidance on appropriate health screening has not accounted for differences between chronological and biological age, and thus screening may be overlooked for individuals with predicted longer life or pursued in those with shorter expected life spans.

The utility and role of screening tests in older adults are currently unresolved. There is a need for guidelines regarding individualized screening decisions in older people, which may have greater utility than those based on age alone. A framework that takes into account estimates of life expectancy, risk of cause-specific mortality, and recognized screening outcomes would yield potential benefits to screening. Walter and Covinsky[188] found that with respect to cancer screening, potential benefits to screening varied substantially for similarly aged patients with different life expectancies. One conclusion drawn by this approach is that cancer screening fails to confer any benefit when life expectancy is less than 5 years.

Better estimates of individualized life expectancy through clinical and other measures of biological aging would thus contribute to screening decisions in older adults. For example, a validated mortality index has been used to create a life expectancy calculator that incorporates patient-level risk factors. Such a calculator may aid clinicians in deciding on relevant preventive interventions for their older patients.[189]

CONCLUSION

The bases of extreme long life are multifactorial and are contributed to by genetic disposition and especially environmental influences that vary with culture and geography. Characteristics of aging are heterogeneous, even among long-lived individuals. Associations between specific clinical or genetic biomarkers exist, but thus far there is no single biomarker predictive of long life. Careful observations in the oldest old offer empirical strategies that favor increased health span and life span, with implications for compression of disability, identification and implementation of lifestyle behaviors that promote independence, and better clinical decision making by assessment of biological age.

ACKNOWLEDGMENTS

I thank Dr Karl Nath for his careful review of the submitted manuscript and thoughtful editorial suggestions.

Abbreviations and Acronyms: **ADLs** = activities of daily living; **BMI** = body mass index; **GH** = growth hormone

Grant Support: Dr Pignolo is supported by the Robert and Arlene Kogod Professorship in Geriatric Medicine.

Potential Competing Interests: The author reports no competing interests.

Correspondence: Address to Robert J. Pignolo, MD, PhD, Division of Geriatric Medicine and Gerontology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (pignolo.robert@mayo.edu).

REFERENCES

1. Vaupel JW, Jeune B. The emergence and proliferation of centenarians. In: Vaupel JW, Jeune B, eds. *Exceptional Longevity: From Prehistory to the Present*. Rostock, Germany: Odense University Press; 1995. https://www.demogr.mpg.de/Papers/Books/Monograph2/start.htm. Accessed February 1, 2018.
2. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet*. 2009;374(9696):1196-1208.
3. Meyer J. *Centenarians: 2010*. US Census Bureau, 2010 Census Special Reports, C2010SR-03. Washington, DC: US Government Printing Office; 2012.
4. Robine JM, Allard M. The oldest human. *Science*. 1998;279(5358):1834-1835.
5. Gondo Y, Hirose N, Yasumoto S, Arai Y, Saito Y. Age verification of the longest lived man in the world. *Exp Gerontol*. 2017;99:7-17.
6. UK Office for National Statistics. Chapter 4: Mortality, 2010-based NPP reference volume. In: *National Population Projections*. London, UK: United Kingdom Statistics Authority; 2012. chap 4; 1-28.
7. Dong X, Milholland B, Vijg J. Evidence for a limit to human lifespan. *Nature*. 2016;538(7624):257-259.
8. Gavrilov LA, Krut'ko VN, Gavrilova NS. The future of human longevity. *Gerontology*. 2017;63(6):524-526.
9. Evert J, Lawler E, Bogan H, Perls T. Morbidity profiles of centenarians: survivors, delayers, and escapers. *J Gerontol A Biol Sci Med Sci*. 2003;58(3):232-237.
10. Perls T. Dementia-free centenarians. *Exp Gerontol*. 2004;39(11-12):1587-1593.
11. Andersen SL, Terry DF, Wilcox MA, Babineau T, Malek K, Perls TT. Cancer in the oldest old. *Mech Ageing Dev*. 2005;126(2):263-267.
12. Schoenhofen EA, Wyszynski DF, Andersen S, et al. Characteristics of 32 supercentenarians. *J Am Geriatr Soc*. 2006;54(8):1237-1240.
13. Willcox DC, Willcox BJ, Todoriki H, Curb JD, Suzuki M. Caloric restriction and human longevity: what can we learn from the Okinawans? *Biogerontology*. 2006;7(3):173-177.
14. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28(suppl):500S-516S.
15. Gavrilova NS, Gavrilov LA. Search for mechanisms of exceptional human longevity. *Rejuvenation Res*. 2010;13(2-3):262-264.
16. Suzuki M, Wilcox BJ, Wilcox CD. Implications from and for food cultures for cardiovascular disease: longevity. *Asia Pac J Clin Nutr*. 2001;10(2):165-171.
17. Franceschi C, Motta L, Valensin S, et al. Do men and women follow different trajectories to reach extreme longevity? Italian Multicenter Study on Centenarians (IMUSCE). *Aging (Milano)*. 2000;12(2):77-84.
18. Passarino G, Underhill PA, Cavalli-Sforza LL, et al. Y chromosome binary markers to study the high prevalence of males in Sardinian centenarians and the genetic structure of the Sardinian population. *Hum Hered*. 2001;52(3):136-139.
19. Koenig R. Sardinia's mysterious male Methuselahs. *Science*. 2001;291(5511):2074-2076.
20. Kimura J. Japan's century club swells to more than 40,000. 2009. Available at: https://www.webcitation.org/5rWEU7TEb?url=http://abcnews.go.com/International/wireStory?id=8544037. Accessed January 30, 2018.
21. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645-1652.
22. Lee JW, Morton KR, Walters J, et al. Cohort profile: the Biopsychosocial Religion and Health Study (BRHS). *Int J Epidemiol*. 2009;38(6):1470-1478.
23. Hall DE. Religious attendance: more cost-effective than Lipitor? *J Am Board Fam Med*. 2006;19(2):103-109.
24. McCullough ME, Hoyt WT, Larson DB, Koenig HG, Thoresen C. Religious involvement and mortality: a meta-analytic review. *Health Psychol*. 2000;19(3):211-222.
25. Musick MA, House JS, Williams DR. Attendance at religious services and mortality in a national sample. *J Health Soc Behav*. 2004;45(2):198-213.
26. Fraser GE. *Diet, Life Expectancy, and Chronic Disease: Studies of Seventh-day Adventists and Other Vegetarians*. New York, NY: Oxford University Press; 2003.
27. Azofeifa J, Ruiz-Narváez EA, Leal A, Gerlovin H, Rosero-Bixby L. Amerindian ancestry and extended longevity in Nicoya, Costa Rica [published online ahead of print September 8, 2017]. *Am J Hum Biol*. https://doi.org/10.1002/ajhb.23055.
28. Stefanadis CI. Unveiling the secrets of longevity: the Ikaria study. *Hellenic J Cardiol*. 2011;52(5):479-480.
29. Masoro EJ. Aging: current concepts. In: Masoro EJ, ed. *Handbook of Physiology*. Section 11. New York, NY: Oxford University Press; 1995:3-21.
30. He W, Goodkind D, Kowal P. *An Aging World: 2015*. Washington, DC: US Government Publishing Office; 2016. US Census Bureau International Population Reports P95/16-1.

31. Oeppen J, Vaupel JW. Broken limits to life expectancy. *Science*. 2002;296(5570):1029-1031.
32. Fries JF. Measuring and monitoring success in compressing morbidity. *Ann Intern Med*. 2003;139(5, pt 2):455-459.
33. Fries JF. Aging, natural death, and the compression of morbidity. *N Engl J Med*. 1980;303(3):130-135.
34. Fries JF. Frailty, heart disease, and stroke: the Compression of Morbidity paradigm. *Am J Prev Med*. 2005;29(5, suppl 1): 164-168.
35. Terry DF, Sebastiani P, Andersen SL, Perls TT. Disentangling the roles of disability and morbidity in survival to exceptional old age. *Arch Intern Med*. 2008;168(3):277-283.
36. Schoeni RF, Freedman VA, Wallace RB. Persistent, consistent, widespread, and robust? another look at recent trends in old-age disability. *J Gerontol B Psychol Sci Soc Sci*. 2001; 56(4):S206-S218.
37. Waidmann TA, Liu K. Disability trends among elderly persons and implications for the future. *J Gerontol B Psychol Sci Soc Sci*. 2000;55(5):S298-S307.
38. Cutler DM. Declining disability among the elderly. *Health Aff (Millwood)*. 2001;20(6):11-27.
39. Freedman VA, Agree EM, Martin LG, Comman JC. Trends in the use of assistive technology and personal care for late-life disability, 1992-2001. *Gerontologist*. 2006;46(1):124-127.
40. Schoeni RF, Freedman VA, Martin LG. Why is late-life disability declining? *Milbank Q*. 2008;86(1):47-89.
41. Cai L, Lubitz J. Was there compression of disability for older Americans from 1992 to 2003? *Demography*. 2007;44(3): 479-495.
42. Fuller-Thomson E, Yu B, Nuru-Jeter A, Guralnik JM, Minkler M. Basic ADL disability and functional limitation rates among older Americans from 2000-2005: the end of the decline? *J Gerontol A Biol Sci Med Sci*. 2009;64(12):1333-1336.
43. Martin LG, Schoeni RF, Andreski PM. Trends in health of older adults in the United States: past, present, future. *Demography*. 2010;47(suppl):S17-S40.
44. Kaye HS. Disability rates for working-age adults and for the elderly have stabilized, but trends for each mean different results for costs. *Health Aff (Millwood)*. 2013;32(1):127-134.
45. Andersen SL, Sebastiani P, Dworkis DA, Feldman L, Perls TT. Health span approximates life span among many supercentenarians: compression of morbidity at the approximate limit of life span. *J Gerontol A Biol Sci Med Sci*. 2012;67(4):395-405.
46. Terry DF, Wilcox MA, McCormick MA, et al. Lower all-cause, cardiovascular, and cancer mortality in centenarians' offspring. *J Am Geriatr Soc*. 2004;52(12):2074-2076.
47. Eggertsen G, Tegelman R, Ericsson S, Angelin B, Berglund L. Apolipoprotein E polymorphism in a healthy Swedish population: variation of allele frequency with age and relation to serum lipid concentrations. *Clin Chem*. 1993;39(10):2125-2129.
48. Louhija J, Miettinen HE, Kontula K, Tikkanen MJ, Miettinen TA, Tilvis RS. Aging and genetic variation of plasma apolipoproteins: relative loss of the apolipoprotein E4 phenotype in centenarians. *Arterioscler Thromb*. 1994;14(7):1084-1089.
49. Bonafè M, Barbieri M, Marchegiani F, et al. Polymorphic variants of insulin-like growth factor I (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for an evolutionarily conserved mechanism of life span control. *J Clin Endocrinol Metab*. 2003;88(7): 3299-3304.
50. Lio D, Scola L, Crivello A, et al. Gender-specific association between -1082 IL-10 promoter polymorphism and longevity. *Genes Immun*. 2002;3(1):30-33.
51. Singh R, Kølvraa S, Bross P, et al. Heat-shock protein 70 genes and human longevity: a view from Denmark. *Ann N Y Acad Sci*. 2006;1067:301-308.
52. Barzilai N, Atzmon G, Schechter C, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA*. 2003;290(15):2030-2040.
53. Sebastiani P, Montano M, Puca A, et al. RNA editing genes associated with extreme old age in humans and with lifespan in *C. elegans* [published correction appears in *PLoS One*. 2009; 4(12). doi: 10.1371/annotation/387f8074-5f80-4bdd-bb0b-b36d49a16ac0]. *PLoS One*. 2009;4(12):e8210.
54. Pilling LC, Kuo CL, Sicinski K, et al. Human longevity: 25 genetic loci associated in 389,166 UK biobank participants. *Aging (Albany NY)*. 2017;9(12):2504-2520.
55. Sebastiani P, Gurinovich A, Bae H, et al. Four genome-wide association studies identify new extreme longevity variants. *J Gerontol A Biol Sci Med Sci*. 2017;72(11):1453-1464.
56. Murabito JM, Yuan R, Lunetta KL. The search for longevity and healthy aging genes: insights from epidemiological studies and samples of long-lived individuals. *J Gerontol A Biol Sci Med Sci*. 2012;67(5):470-479.
57. Lindborg CM, Propert KJ, Pignolo RJ. Conservation of pro-longevity genes among mammals. *Mech Ageing Dev*. 2015; 146-148:23-27.
58. Semeiks J, Grishin NV. A method to find longevity-selected positions in the mammalian proteome. *PLoS One*. 2012;7(6): e38595.
59. Vijg J, Perls T, Franceschi C, van Orsouw NJ. *BRCA1* gene sequence variation in centenarians. *Ann N Y Acad Sci*. 2001; 928:85-96.
60. Ben-Avraham D, Govindaraju DR, Budagov T, et al. The GH receptor exon 3 deletion is a marker of male-specific exceptional longevity associated with increased GH sensitivity and taller stature. *Sci Adv*. 2017;3(6):e1602025.
61. Gene Database (GenAge). Human Ageing Genomic Resources website, http://genomics.senescence.info/genes/longevity.html. Accessed October 28, 2018.
62. Christensen K, Johnson TE, Vaupel JW. The quest for genetic determinants of human longevity: challenges and insights. *Nat Rev Genet*. 2006;7(6):436-448.
63. Herskind AM, McGue M, Holm NV, Sørensen TI, Harvald B, Vaupel JW. The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870-1900. *Hum Genet*. 1996;97(3):319-323.
64. Herskind AM, McGue M, Iachine IA, et al. Untangling genetic influences on smoking, body mass index and longevity: a multivariate study of 2464 Danish twins followed for 28 years. *Hum Genet*. 1996;98(4):467-475.
65. Austad SN, Bartke A. Sex differences in longevity and in responses to anti-aging interventions: a mini-review. *Gerontology*. 2015;62(1):40-46.
66. Austad SN, Fischer KE. Sex differences in lifespan. *Cell Metab*. 2016;23(6):1022-1033.
67. Perls TT, Alpert L, Fretts RC. Middle-aged mothers live longer. *Nature*. 1997;389(6647):133.
68. Smith KR, Mineau GP, Bean LL. Fertility and post-reproductive longevity. *Soc Biol*. 2002;49(3-4):185-205.
69. Müller HG, Chiou JM, Carey JR, Wang JL. Fertility and life span: late children enhance female longevity. *J Gerontol A Biol Sci Med Sci*. 2002;57(5):B202-B206.
70. Sun F, Sebastiani P, Schupf N, et al. Extended maternal age at birth of last child and women's longevity in the Long Life Family Study. *Menopause*. 2015;22(1):26-31.
71. Lahdenperä M, Lummaa V, Helle S, Tremblay M, Russell AF. Fitness benefits of prolonged post-reproductive lifespan in women. *Nature*. 2004;428(6979):178-181.
72. Lockhart PA, Martin P, Johnson MA, Shirtcliff E, Poon LW. The relationship of fertility, lifestyle, and longevity among women. *J Gerontol A Biol Sci Med Sci*. 2017;72(6):754-759.
73. Tabatabaie V, Atzmon G, Rajpathak SN, Freeman R, Barzilai N, Crandall J. Exceptional longevity is associated with decreased reproduction. *Aging (Albany NY)*. 2011;3(12):1202-1205.
74. Jamison CS, Cornell LL, Jamison PL, Nakazato H. Are all grandmothers equal? a review and a preliminary test of the "grandmother hypothesis" in Tokugawa Japan. *Am J Phys Anthropol*. 2002;119(1):67-76.

75. Allman J, Rosin A, Kumar R, Hasenstaub A. Parenting and survival in anthropoid primates: caretakers live longer. *Proc Natl Acad Sci U S A*. 1998;95(12):6866-6869.
76. Gavrilov LA, Gavrilova NS. Biodemography of exceptional longevity: early-life and mid-life predictors of human longevity. *Biodemography Soc Biol*. 2012;58(1):14-39.
77. Gavrilov LA, Gavrilova NS. Predictors of exceptional longevity: effects of early-life and midlife conditions, and familial longevity. *N Am Actuar J*. 2015;19(3):174-186.
78. Bartke A. Growth hormone and aging: a challenging controversy. *Clin Interv Aging*. 2008;3(4):659-665.
79. Bartke A, Sun LY, Longo V. Somatotropic signaling: trade-offs between growth, reproductive development, and longevity. *Physiol Rev*. 2013;93(2):571-598.
80. van der Spoel E, Jansen SW, Akintola AA, et al. Growth hormone secretion is diminished and tightly controlled in humans enriched for familial longevity. *Aging Cell*. 2016;15(6):1126-1131.
81. Nakamura E, Miyao K. Sex differences in human biological aging. *J Gerontol A Biol Sci Med Sci*. 2008;63(9):936-944.
82. Hadley EC, Kuchel GA, Newman AB, et al. Report: NIA Workshop on Measures of Physiologic Resiliencies in Human Aging. *J Gerontol A Biol Sci Med Sci*. 2017;72(7):980-990.
83. Huffman DM, Schafer MJ, LeBrasseur NK. Energetic interventions for healthspan and resiliency with aging. *Exp Gerontol*. 2016;86:73-83.
84. Jeste DV, Savla GN, Thompson WK, et al. Association between older age and more successful aging: critical role of resilience and depression. *Am J Psychiatry*. 2013;170(2):188-196.
85. Puterman E, Epel ES, Lin J, et al. Multisystem resiliency moderates the major depression-telomere length association: findings from the Heart and Soul Study. *Brain Behav Immun*. 2013;33:65-73.
86. Luthar SS, Cicchetti D, Becker B. The construct of resilience: a critical evaluation and guidelines for future work. *Child Dev*. 2000;71(3):543-562.
87. Wagnild GM, Collins JA. Assessing resilience. *J Psychosoc Nurs Ment Health Serv*. 2009;47(12):28-33.
88. Rantanen T, Masaki K, He Q, Ross GW, Willcox BJ, White L. Midlife muscle strength and human longevity up to age 100 years: a 44-year prospective study among a decedent cohort. *Age (Dordr)*. 2012;34(3):563-570.
89. Parrino L, Vaudano AE. The resilient brain and the guardians of sleep: new perspectives on old assumptions. *Sleep Med Rev*. 2018;39:98-107.
90. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: systematic review and development of an emerging construct. *J Gerontol A Biol Sci Med Sci*. 2016;71(4):489-495.
91. Cauley JA, Lui LY, Barnes D, et al. Successful skeletal aging: a marker of low fracture risk and longevity; the Study of Osteoporotic Fractures (SOF). *J Bone Miner Res*. 2009;24(1):134-143.
92. Boyle PA, Yu L, Wilson RS, Schneider JA, Bennett DA. Relation of neuropathology with cognitive decline among older persons without dementia. *Front Aging Neurosci*. 2013;5:50.
93. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol*. 2003;62(11):1087-1095.
94. Latimer CS, Keene CD, Flanagan ME, et al. Resistance to Alzheimer disease neuropathologic changes and apparent cognitive resilience in the Nun and Honolulu-Asia Aging studies. *J Neuropathol Exp Neurol*. 2017;76(6):458-466.
95. Mufson EJ, Malek-Ahmadi M, Perez SE, Chen K. Braak staging, plaque pathology, and APOE status in elderly persons without cognitive impairment. *Neurobiol Aging*. 2016;37:147-153.
96. Riley KP, Snowdon DA, Markesbery WR. Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. *Ann Neurol*. 2002;51(5):567-577.
97. SantaCruz KS, Sonnen JA, Pezhouh MK, Desrosiers MF, Nelson PT, Tyas SL. Alzheimer disease pathology in subjects without dementia in 2 studies of aging: the Nun Study and the Adult Changes in Thought Study. *J Neuropathol Exp Neurol*. 2011;70(10):832-840.
98. Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J Alzheimers Dis*. 2009;18(3):691-701.
99. Snowdon DA. Healthy aging and dementia: findings from the Nun Study. *Ann Intern Med*. 2003;139(5, pt 2):450-454.
100. Sonnen JA, Santa Cruz K, Hemmy LS, et al. Ecology of the aging human brain. *Arch Neurol*. 2011;68(8):1049-1056.
101. Wister AV, Coatta KL, Schuurman N, Lear SA, Rosin M, MacKey D. A lifecourse model of multimorbidity resilience: theoretical and research developments. *Int J Aging Hum Dev*. 2016;82(4):290-313.
102. Ash AS, Kroll-Desrosiers AR, Hoaglin DC, Christensen K, Fang H, Perls TT. Are members of long-lived families healthier than their equally long-lived peers? evidence from the Long Life Family Study. *J Gerontol A Biol Sci Med Sci*. 2015;70(8):971-976.
103. Schroeder SA. Shattuck Lecture: We can do better—improving the health of the American people. *N Engl J Med*. 2007;357(12):1221-1228.
104. McGinnis JM, Foege WH. Actual causes of death in the United States. *JAMA*. 1993;270(18):2207-2212.
105. Masoro EJ. Caloric restriction and aging: controversial issues. *J Gerontol A Biol Sci Med Sci*. 2006;61(1):14-19.
106. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*. 2009;325(5937):201-204.
107. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature*. 2012;489(7415):318-321.
108. Ingram DK, Anson RM, de Cabo R, et al. Development of calorie restriction mimetics as a prolongevity strategy. *Ann N Y Acad Sci*. 2004;1019:412-423.
109. Lane MA, de Cabo R, Mattison J, Anson RM, Roth GS, Ingram DK. The Roy Walford legacy: diet restriction from molecules to mice to monkeys to man and onto mimetics. *Exp Gerontol*. 2004;39(6):897-902.
110. Das SK, Roberts SB, Bhapkar MV, et al; CALERIE-2 Study Group. Body-composition changes in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)-2 study: a 2-y randomized controlled trial of calorie restriction in nonobese humans. *Am J Clin Nutr*. 2017;105(4):913-927.
111. Rickman AD, Williamson DA, Martin CK, et al. The CALERIE Study: design and methods of an innovative 25% caloric restriction intervention. *Contemp Clin Trials*. 2011;32(6):874-881.
112. Rochon J, Bales CW, Ravussin E, et al; CALERIE Study Group. Design and conduct of the CALERIE study: comprehensive assessment of the long-term effects of reducing intake of energy. *J Gerontol A Biol Sci Med Sci*. 2011;66(1):97-108.
113. Belsky DW, Huffman KM, Pieper CF, Shalev I, Kraus WE. Change in the rate of biological aging in response to caloric restriction: CALERIE Biobank analysis. *J Gerontol A Biol Sci Med Sci*. 2017;73(1):4-10.
114. Fontana L, Klein S. Aging, adiposity, and calorie restriction. *JAMA*. 2007;297(9):986-994.
115. Heilbronn LK, de Jonge L, Frisard MI, et al; Pennington CALERIE Team. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial [published correction appears in *JAMA*. 2006;295(21):2482]. *JAMA*. 2006;295(13):1539-1548.
116. Fontana L, Villareal DT, Weiss EP, et al; Washington University School of Medicine CALERIE Group. Calorie restriction or exercise: effects on coronary heart disease risk factors; a

randomized, controlled trial. *Am J Physiol Endocrinol Metab*. 2007;293(1):E197-E202.
117. Stessman J, Hammerman-Rozenberg R, Cohen A, Ein-Mor E, Jacobs JM. Physical activity, function, and longevity among the very old. *Arch Intern Med*. 2009;169(16):1476-1483.
118. van Saase JL, Noteboom WM, Vandenbroucke JP. Longevity of men capable of prolonged vigorous physical exercise: a 32 year follow up of 2259 participants in the Dutch eleven cities ice skating tour. *BMJ*. 1990;301(6766):1409-1411.
119. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults [published correction appears in *N Engl J Med*. 2011;365(9):869]. *N Engl J Med*. 2010;363(23):2211-2219.
120. Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*. 2012;9(11):e1001335.
121. Hirsch CH, Diehr P, Newman AB, et al. Physical activity and years of healthy life in older adults: results from the Cardiovascular Health Study. *J Aging Phys Act*. 2010;18(3):313-334.
122. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS Med*. 2010;7(7):e1000316.
123. Boyle PA, Buchman AS, Bennett DA. Purpose in life is associated with a reduced risk of incident disability among community-dwelling older persons. *Am J Geriatr Psychiatry*. 2010;18(12):1093-1102.
124. Boyle PA, Buchman AS, Barnes LL, Bennett DA. Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling older persons. *Arch Gen Psychiatry*. 2010;67(3):304-310.
125. Park DC, Lodi-Smith J, Drew L, et al. The impact of sustained engagement on cognitive function in older adults: the Synapse Project. *Psychol Sci*. 2014;25(1):103-112.
126. Mooradian AD. Biomarkers of aging: do we know what to look for? *J Gerontol*. 1990;45(6):B183-B186.
127. Cristofalo VJ, Gerhard GS, Pignolo RJ. Molecular biology of aging. *Surg Clin North Am*. 1994;74(1):1-21.
128. Gavrilov LA, Gavrilova NS. New developments in the biodemography of aging and longevity. *Gerontology*. 2015;61(4):364-371.
129. Amara CE, Koval JJ, Paterson DH, Cunningham DA. Lung function in older humans: the contribution of body composition, physical activity and smoking. *Ann Hum Biol*. 2001;28(5):522-536.
130. Atkins JL, Pilling LC, Ble A, et al. Longer-lived parents and cardiovascular outcomes: 8-year follow-up in 186,000 U.K. Biobank participants. *J Am Coll Cardiol*. 2016;68(8):874-875.
131. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. *Proc Natl Acad Sci U S A*. 2015;112(30):E4104-E4110.
132. Boucher N, Dufeu-Duchesne T, Vicaut E, Farge D, Effros RB, Schachter F. CD28 expression in T cell aging and human longevity. *Exp Gerontol*. 1998;33(3):267-282.
133. Brown DC, Hayward MD, Montez JK, Hummer RA, Chiu CT, Hidajat MM. The significance of education for mortality compression in the United States. *Demography*. 2012;49(3):819-840.
134. Campa D, De Rango F, Carrai M, et al. Bitter taste receptor polymorphisms and human aging. *PLoS One*. 2012;7(11):e45232.
135. Cypel MC, Salomão SR, Dantas PEC, et al. Vision status, ophthalmic assessment, and quality of life in the very old. *Arq Bras Oftalmol*. 2017;80(3):159-164.
136. Deelen J, van den Akker EB, Trompet S, et al. Employing biomarkers of healthy ageing for leveraging genetic studies into human longevity. *Exp Gerontol*. 2016;82:166-174.
137. Derhovanessian E, Maier AB, Hähnel K, et al. Lower proportion of naive peripheral CD8+ T cells and an unopposed pro-inflammatory response to human Cytomegalovirus proteins in vitro are associated with longer survival in very elderly people. *Age (Dordr)*. 2013;35(4):1387-1399.
138. Diehr P, Diehr M, Arnold A, et al. Predicting future years of life, health, and functional ability: a healthy life calculator for older adults. *Gerontol Geriatr Med*. 2015;1:2333721415605989.
139. Dutta A, Henley W, Robine JM, Langa KM, Wallace RB, Melzer D. Longer lived parents: protective associations with cancer incidence and overall mortality. *J Gerontol A Biol Sci Med Sci*. 2013;68(11):1409-1418.
140. Frasca D, Diaz A, Romero M, Blomberg BB. The generation of memory B cells is maintained, but the antibody response is not, in the elderly after repeated influenza immunizations. *Vaccine*. 2016;34(25):2834-2840.
141. Genther DJ, Betz J, Pratt S, et al; Health ABC Study. Association of hearing impairment and mortality in older adults. *J Gerontol A Biol Sci Med Sci*. 2015;70(1):85-90.
142. Gill TM, Allore HG, Holford TR, Guo Z. Hospitalization, restricted activity, and the development of disability among older persons. *JAMA*. 2004;292(17):2115-2124.
143. Grzegorczyk PB, Jones SW, Mistretta CM. Age-related differences in salt taste acuity. *J Gerontol*. 1979;34(6):834-840.
144. Hays NP, Bathalon GP, Meydani SN, et al. Metabolic aging and predicted longevity: results of a cross-sectional study in postmenopausal women. *Aging Clin Exp Res*. 2002;14(6):465-473.
145. He Q, Morris BJ, Grove JS, et al. Shorter men live longer: association of height with longevity and *FOXO3* genotype in American men of Japanese ancestry. *PLoS One*. 2014;9(5):e94385.
146. Hennis A, Wu SY, Li X, Nemesure B, Leske MC; the Barbados Eye Study Group. Lens opacities and mortality: the Barbados Eye Studies. *Ophthalmology*. 2001;108(3):498-504.
147. Hirotomi T, Yoshihara A, Ogawa H, Miyazaki H. Number of teeth and 5-year mortality in an elderly population. *Community Dent Oral Epidemiol*. 2015;43(3):226-231.
148. Holtzer R, Wang C, Lipton R, Verghese J. The protective effects of executive functions and episodic memory on gait speed decline in aging defined in the context of cognitive reserve. *J Am Geriatr Soc*. 2012;60(11):2093-2098.
149. Humes LE, Kewley-Port D, Fogerty D, Kinney D. Measures of hearing threshold and temporal processing across the adult lifespan. *Hear Res*. 2010;264(1-2):30-40.
150. Kaye JA, Oken BS, Howieson DB, Howieson J, Holm LA, Dennison K. Neurologic evaluation of the optimally healthy oldest old. *Arch Neurol*. 1994;51(12):1205-1211.
151. Kopecek M, Bezdicek O, Sulc Z, Lukavsky J, Stepankova H. Montreal Cognitive Assessment and Mini-Mental State Examination reliable change indices in healthy older adults. *Int J Geriatr Psychiatry*. 2017;32(8):868-875.
152. Lambert ND, Ovsyannikova IG, Pankratz VS, Jacobson RM, Poland GA. Understanding the immune response to seasonal influenza vaccination in older adults: a systems biology approach. *Expert Rev Vaccines*. 2012;11(8):985-994.
153. Lemez S, Wattie N, Baker J. Do "big guys" really die younger? an examination of height and lifespan in former professional basketball players. *PLoS One*. 2017;12(10):e0185617.
154. Matsuyama Y, Aida J, Watt RG, et al. Dental status and compression of life expectancy with disability. *J Dent Res*. 2017;96(9):1006-1013.
155. McKibbin M, Mohammed M, James TE, Atkinson PL. Short-term mortality among middle-aged cataract surgery patients. *Eye (Lond)*. 2001;15(pt 2):209-212.
156. Montez JK, Hayward MD. Cumulative childhood adversity, educational attainment, and active life expectancy among U. S. adults. *Demography*. 2014;51(2):413-435.
157. Morrisette-Thomas V, Cohen AA, Fülöp T, et al. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. *Mech Ageing Dev*. 2014;139:49-57.
158. Nakamoto M, Otsuka R, Yuki A, et al. Higher gait speed and smaller sway area decrease the risk for decline in higher-level

functional capacity among middle-aged and elderly women. *Arch Gerontol Geriatr*. 2015;61(3):429-436.
159. Newman JC, Milman S, Hashmi SK, et al. Strategies and challenges in clinical trials targeting human aging. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1424-1434.
160. Nucci C, Cedrone C, Culasso F, et al. Association between lens opacities and mortality in the Priverno Eye Study. *Graefes Arch Clin Exp Ophthalmol*. 2004;242(4):289-294.
161. Peters MJ, Joehanes R, Pilling LC, et al. The transcriptional landscape of age in human peripheral blood. *Nat Commun*. 2015;6:8570.
162. Rasmussen SH, Thinggaard M, Højgaard MB, Jeune B, Christensen K, Andersen-Ranberg K. Improvement in activities of daily living among Danish centenarians? a comparative study of two centenarian cohorts born 20 years apart. *J Gerontol A Biol Sci Med Sci*. 2018;73(8):1125-1131.
163. Sanders JL, Ding V, Arnold AM, et al. Do changes in circulating biomarkers track with each other and with functional changes in older adults? *J Gerontol A Biol Sci Med Sci*. 2014;69(2):174-181.
164. Sansoni P, Vescovini R, Fagnoni F, et al. The immune system in extreme longevity. *Exp Gerontol*. 2008;43(2):61-65.
165. Seow YX, Ong PK, Huang D. Odor-specific loss of smell sensitivity with age as revealed by the Specific Sensitivity test. *Chem Senses*. 2016;41(6):487-495.
166. Sridhar S, Begom S, Hoschler K, et al. Longevity and determinants of protective humoral immunity after pandemic influenza infection. *Am J Respir Crit Care Med*. 2015;191(3):325-332.
167. Srikanthan P, Karlamangla AS. Muscle mass index as a predictor of longevity in older adults. *Am J Med*. 2014;127(6):547-553.
168. Stessman J, Rottenberg Y, Fischer M, Hammerman-Rozenberg A, Jacobs JM. Handgrip strength in old and very old adults: mood, cognition, function, and mortality. *J Am Geriatr Soc*. 2017;65(3):526-532.
169. Stijntjes M, de Craen AJ, van Heemst D, et al. Familial longevity is marked by better cognitive performance at middle age: the Leiden Longevity Study. *PLoS One*. 2013;8(3):e57962.
170. Strindhall J, Nilsson BO, Löfgren S, et al. No Immune Risk Profile among individuals who reach 100 years of age: findings from the Swedish NONA immune longitudinal study. *Exp Gerontol*. 2007;42(8):753-761.
171. Taekema DG, Gussekloo J, Westendorp RG, de Craen AJ, Maier AB. Predicting survival in oldest old people. *Am J Med*. 2012;125(12):1188-1194.e1.
172. Tanisawa K, Hirose N, Arai Y, et al. Inverse association between height-increasing alleles and extreme longevity in Japanese women. *J Gerontol A Biol Sci Med Sci*. 2018;73(5):588-595.
173. Tomioka K, Kurumatani N, Hosoi H. Relationship of having hobbies and a purpose in life with mortality, activities of daily living, and instrumental activities of daily living among community-dwelling elderly adults. *J Epidemiol*. 2016;26(7):361-370.
174. Venturelli M, Schena F, Scarsini R, Muti E, Richardson RS. Limitations to exercise in female centenarians: evidence that muscular efficiency tempers the impact of failing lungs. *Age (Dordr)*. 2013;35(3):861-870.
175. Verghese J, Holtzer R, Lipton RB, Wang C. Mobility stress test approach to predicting frailty, disability, and mortality in high-functioning older adults. *J Am Geriatr Soc*. 2012;60(10):1901-1905.
176. Waaijer ME, Gunn DA, Adams PD, et al. p16INK4a Positive cells in human skin are indicative of local elastic fiber morphology, facial wrinkling, and perceived age. *J Gerontol A Biol Sci Med Sci*. 2016;71(8):1022-1028.
177. Waaijer ME, Parish WE, Strongitharm BH, et al. The number of p16INK4a positive cells in human skin reflects biological age. *Aging Cell*. 2012;11(4):722-725.
178. Waaijer ME, Westendorp RG, Goldeck D, et al. Assessment of health status by molecular measures in adults ranging from middle-aged to old: ready for clinical use? *Exp Gerontol*. 2017;87(pt B):175-181.
179. Wikby A, Månsson IA, Johansson B, Strindhall J, Nilsson SE. The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age. *Biogerontology*. 2008;9(5):299-308.
180. Arai Y, Martin-Ruiz CM, Takayama M, et al. Inflammation, but not telomere length, predicts successful ageing at extreme old age: a longitudinal study of semi-supercentenarians. *EBioMedicine*. 2015;2(10):1549-1558.
181. Collino S, Montoliu I, Martin FP, et al. Metabolic signatures of extreme longevity in northern Italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism [published correction appears in *PLoS One*. 2013;8(8). doi:10.1371/annotation/5fb9fa6f-4889-4407-8430-6dfc7ecdfbdd]. *PLoS One*. 2013;8(3):e56564.
182. Hausman DB, Fischer JG, Johnson MA. Protein, lipid, and hematological biomarkers in centenarians: definitions, interpretation and relationships with health. *Maturitas*. 2012;71(3):205-212.
183. Horvath S, Pirazzini C, Bacalini MG, et al. Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring. *Aging (Albany NY)*. 2015;7(12):1159-1170.
184. Sanchis-Gomar F, Pareja-Galeano H, Santos-Lozano A, et al. A preliminary candidate approach identifies the combination of chemerin, fetuin-A, and fibroblast growth factors 19 and 21 as a potential biomarker panel of successful aging. *Age (Dordr)*. 2015;37(3):9776.
185. Belsky DW, Moffitt TE, Cohen AA, et al. Eleven telomere, epigenetic clock, and biomarker-composite quantifications of biological aging: do they measure the same thing? *Am J Epidemiol*. 2018;187(6):1220-1230.
186. Arbeev KG, Cohen AA, Arbeeva LS, et al. Optimal versus realized trajectories of physiological dysregulation in aging and their relation to sex-specific mortality risk. *Front Public Health*. 2016;4:3.
187. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? *J Gerontol A Biol Sci Med Sci*. 2013;68(6):667-674.
188. Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. *JAMA*. 2001;285(21):2750-2756.
189. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. *PLoS One*. 2014;9(9):e108540.