

# Geroscience

## A Translational Review

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**IMPORTANCE** The incidence of stroke, heart failure, dementia, many cancers, coronary artery disease, and physical disability rise exponentially with age. Geroscience is a relatively new discipline that aims to define and modify aging-related biologic pathways, slow age-related disability, prevent age-related diseases, and increase disability-free survival.

**OBSERVATIONS** Medical therapies typically alter biologic pathways to treat or prevent specific diseases. For example, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are cholesterol-lowering medications used to prevent development and progression of atherosclerosis. However, disease-focused treatments do not alter aging's effects on disease and declining function (eg, statins do not significantly reduce noncardiovascular mortality or cancer). In animal models, treatments can alter aging's effect on disease. For example, in mice, caloric restriction increases mean lifespan from 10% to 40% compared with mice fed ad libitum and favorably affects multiple cellular pathways implicated in aging including nutrient sensing, protein synthesis, autophagy, and inflammation. In adults with obesity and diabetes, compared with non-caloric restriction intervention groups, randomization to receive caloric restriction was associated with a 15% reduction in all-cause mortality and a lower incidence of weight-related chronic diseases. Rapamycin, a drug approved to suppress posttransplant organ rejection, increased mouse median lifespan by 249 days in females and 154 days in males. A rapamycin analogue, everolimus, improved antibody titers to influenza vaccine in older adults. In humans, senescent cells increase in abundance with age and are characterized by growth arrest, apoptosis resistance, and an altered secretome (the set of proteins secreted by a cell into the extracellular space). A greater abundance of senescent cells is associated with more physical impairments and increased mortality. Reducing the number of these cells in animal models extends lifespan and improves physical function, such as grip strength and mobility, and cardiac ejection fraction. However, potential health benefits of reducing senescent cells in humans remain unclear.

**CONCLUSIONS AND RELEVANCE** Therapies that inhibit aging biology, such as caloric restriction, metformin, senolytics, or rapalogs, may slow the development and progression of disease and functional decline in humans.

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Between 2020 and 2050, the number of US adults older than age 65 years is projected to increase by approximately 33 million, which is expected to be associated with an increase in age-related disease.<sup>1</sup> Typically, medical therapies are developed to treat specific diseases by altering biologic pathways specific to that disease. For example, in a pooled analysis of 15 randomized primary or mixed primary and secondary prevention trials (N = 74 390), compared with placebo or no therapy, statin therapy was associated with a 28% lower risk of composite cardiovascular outcomes (3.5% to 4.9%; RR, 0.72 [95% CI, 0.64-0.81]).<sup>2</sup> Translational geroscience evaluates therapies that alter specific cellular pathways related to aging, such as autophagy and free radical generation, to prevent diseases such as stroke, heart failure, many cancers, coronary artery disease, dementia, and physical disability, for which older age is the strongest risk factor (Box). Geroscience

posits that successfully altering aging-related pathways would benefit multiple age-related health outcomes simultaneously, including age-related diseases, mobility function, and health span, ie, disability-free survival.<sup>3-6</sup> This translational review summarizes current evidence regarding geroscience (Table 1).<sup>7-9</sup>

### Disease-Specific Approach to Prevention and Treatment

Disease-specific approaches for preventing and treating disease have limitations.<sup>10</sup> For example, a disease-specific focus does not address age-related health conditions that are common even when overt disease is absent, such as fatigue, mobility limitation, frailty (a condition of increased susceptibility to physiologic stressors such

as infection), and physical disability. In the Cardiovascular Health Study, a longitudinal epidemiologic study with more than 30 years of follow-up that enrolled 5201 adults aged 65 years or older, 16% of participants were more frail (a classification based on weakness, walking speed, weight loss, exhaustion, and low energy) than predicted from their number of medical conditions. Adjusting for number of comorbidities, the more frail group experienced 2 to 3 fewer years of life free from difficulties carrying out activities of daily living, compared to those without frailty.<sup>11</sup> Older age is strongly associated with adverse disease outcomes. For example, in the US, the death rate from COVID-19 was 7 times higher in those aged 85 years or older (1.6%) compared with those aged 65 to 74 years (0.2%).<sup>12</sup>

Disease-specific paradigms do not account for age as the strongest determinant of risk for many diseases including coronary heart diseases, many cancers, chronic obstructive pulmonary disease, stroke, dementia, and chronic kidney disease. Furthermore, worldwide, more than 50% of adults 60 years or older have more than 1 chronic medical condition, and the incidence of developing a third disease among those with 2 chronic medical conditions is 5.2% among those aged 50 to 59 years and 16% in those aged 70 to 79 years.<sup>13,14</sup> Preventing additional diseases could reduce Medicare expenditures; in 2011 for beneficiaries with 4 or more health conditions expenditures were \$17 000 more than in those with 0 or 1 condition.<sup>15</sup> The limitations of the disease-specific approach could be addressed if it were possible to favorably alter aging-related biologic changes that increase susceptibility to disease.

## Geroscience and Clinical Applications

Directly altering the biological process of aging could affect medical practice in several ways (Table 2<sup>16-23</sup> and Box). Older age is associated with worse outcomes for most illnesses, and older adults are more likely to experience treatment-related complications. For example, among 59 633 US patients 65 years or older undergoing an emergency general surgical procedure, 30-day mortality was 6.8%. Compared with those aged 65 to 70 years, those aged 71 to 80 years had a higher odds of 30-day mortality (odds ratio, 1.51 [95% CI, 1.36-1.67]; absolute rates not available) adjusting for multiple covariates.<sup>24</sup> Vaccine efficacy is also lower in older adults. For example, among 50 people aged 21 to 82 years who received the COVID-19 vaccine, age was inversely associated with levels of COVID-19 vaccine-elicited neutralizing antibody titers ( $r = -0.44$ ;  $P = .002$ ).<sup>25</sup> Some conditions or their treatments appear to accelerate the aging process. HIV is associated with the development of age-related health conditions at younger ages. In the US National Health and Nutrition Examination Survey, persons with HIV aged 18 to 59 years had a higher covariate-adjusted prevalence of frailty (28.9% vs 10.4%) and more difficulty carrying out activities of daily living (59.7% vs 36.3%) compared with HIV-negative participants.<sup>26</sup> Both HIV and HIV treatments, such as nucleoside-analogue reverse transcriptase inhibitors and protease inhibitors, can adversely affect mitochondrial function.<sup>27</sup> Whether these effects impact frailty and functional impairment is unclear. Radiation and some chemotherapeutic agents, such as cisplatin, cause genomic instability and telomere attrition, induce cellular senescence, and are associated with the aging process.<sup>28</sup> In the St Jude Lifetime Cohort study of 4117 patients who survived childhood cancer, at age 50 years

### Box. Common Questions About Geroscience

#### What is geroscience?

Geroscience studies therapies that alter aging-related biologic pathways to prevent diseases for which age is the strongest risk factor, such as stroke, heart failure, most cancers, coronary artery disease, dementia, and physical disability. Targeting aging biology directly may simultaneously benefit many age-related health outcomes including slowing age-related diseases and mobility impairment and increasing disability-free survival.

#### Are there interventions that change the aging process?

Experiments in mice, fruit flies, nematodes, and other models show that targeting aging biology through reducing energy intake or through certain drugs, such as rapamycin, can extend lifespan by up to 40% and delay the emergence of age-related diseases. Whether these strategies will benefit humans remains unclear.

#### What are potential clinical benefits of directly intervening on the aging process?

Intervening on the aging process may ameliorate age-related health issues that are not related diseases per se, such as surgical complications, resilience to infection, declining mobility, and fatigue. It may mitigate the effect of diseases and treatments that appear to accelerate phenotypic aging such as HIV, adverse effects of cancer chemotherapy, and Down syndrome.

individuals who survived childhood cancers had a mean of 17.1 conditions compared with 9.2 in age-matched controls.<sup>29</sup>

## Biologic Age

The geroscience hypothesis maintains that biologic aging is a process that is distinguishable from chronologic aging. Biologic age is a concept that quantifies the extent to which a person's physiology differs from what would be expected based on chronologic age. For example, a 50-year-old woman with a maximal oxygen consumption of 32 mL/kg/min (typical of women 10 years younger) would have a biologic age of 40 years. Biologic age estimates are typically scores based on multiple measurements and may include routine clinical tests such as red blood cell distribution width or serum creatinine levels, physiologic assessments (eg, forced vital capacity or maximal oxygen consumption), the pattern of methylated DNA base pairs, radiologic assessments such as brain magnetic resonance imaging (MRI), or panels of circulating proteins (eg, GDF-15 and cystatin C).<sup>29-33</sup> There is currently no consensus regarding the optimal measure of biologic age. Age advancement, the difference between biologic age and chronologic age, predicts mortality and other age-related outcomes independent of chronologic age. For example, a person with a biologic age 8.3 years older than their chronologic age, based on DNA methylation, had a hazard rate of death 2.2 times higher than a person with similar biologic age.<sup>34,35</sup> The Saint Jude's cohort of 4117 adult survivors of childhood cancer calculated biologic age based on physiologic measurements and DNA methylation. At a mean age of 35 years, cancer survivors were 2.2 to 6.5 years older biologically than age- and sex-matched controls using 7 different approaches based on physiologic measures or DNA methylation.<sup>36</sup> "Ages" of specific organs and physiologic systems (eg, brain age or immunologic age) have also been developed.<sup>37,38</sup>

Table 1. Select Interventions Hypothesized to Have Benefits Related to Effects on the Biology of Aging in Humans

Pathways/targets	Aging-related pathways affected	Observations from preclinical models	Potential interventions	Summary of human data
Caloric restriction	Increased autophagy Decreased reactive oxygen species Decreased inflammation Decreased cellular senescence Increased DNA repair Preserved mitochondrial function	Lifespan extension in multiple animal species Delay in onset of age-related disease	Voluntary caloric restriction GLP-1 receptor agonists (eg, semaglutide, tirzepatide, liraglutide) Other pharmacologic interventions to decrease caloric intake Bariatric surgery	Meta-analysis of weight loss trials showed a reduction in all-cause mortality Caloric restriction slowed aging according to various measures of biologic age
Metformin	Increased autophagy Decreased reactive oxygen species Decreased inflammation Increased DNA repair Decreased mammalian target of rapamycin	Lifespan extension in some animal species and mouse strains Preserved physical function	Metformin	Observational data were consistent with multiple health benefits such as neurodegenerative disease and COVID-19 infection severity; Clinical trial data are mixed
Rapamycin/rapalogs	Decreased mammalian target of rapamycin Increased autophagy	Lifespan extension in multiple animal species Delay in onset of age-related disease	Sirolimus Everolimus Temozolomide RTB101	Evidence of improved vaccine efficacy; improved symptoms in patients with rheumatoid arthritis
Senolytics	Decreased burden of senescent cells targeting p16 and p53/p21 Decreased inflammation	Lifespan extension Reduction of age-related organ dysfunction	Dasatinib plus quercetin Fisetin	Early-phase studies indicate that treatments are well-tolerated

Table 2. Lifespan Effects of Select Compounds Evaluated by the Interventions Testing Program Evaluation in Genetically Heterogeneous Mice (UM-HET3)

Compound (age started)	Mode of action	Maximal lifespan extension, %	Human indications and adverse effects	Adverse effects
Acarbose	Inhibits $\alpha$ -glucosidase, which breaks down ingested carbohydrates	8% Female 11% Male	Type 2 diabetes	Diarrhea and flatulence
Metformin (9 mo)	Multiple; inhibition of mitochondrial complex I, activation of adenosine monophosphate protein kinase, decreased liver gluconeogenesis, increased insulin sensitivity	No significant effect in either sex	Type 2 diabetes, ovary syndrome	Diarrhea, nausea, bloating, decreased vitamin B <sub>12</sub> absorption, lactic acidosis (rare)
Rapamycin (9 mo)	Inhibition of mammalian target of rapamycin complex 1 signaling	16% Female 11% Male	Prevention of organ transplant rejection Multiple, decreased glucose tolerance, peripheral edema, dyslipidemia, stomatitis, infection	Multiple, including decreased glucose tolerance, peripheral edema, dyslipidemia, stomatitis, infection
Rapamycin (20 mo)	See above	14% Female 9% Male	See above	See above
Metformin and rapamycin (16 mo)	See above	17% Female 14% Male	See above	See above
Acarbose and rapamycin	See above	15% Female 18% Male	See above	See above
Canagliflozin	Sodium-glucose cotransporter-2 inhibitor Increased glucose excretion	No significant effect on females 10% Male	Type 2 diabetes, cardiovascular disease prevention	Multiple, including urinary tract infection, limb amputation, acute kidney injury dehydration, yeast infection, hypoglycemia, bone fractures

For example, in 1771 participants in the Atherosclerosis Risk in Communities study (mean age, 76.4 years), a difference between MRI-based brain age and chronologic age more than 1.75 years was associated with a 2.6-fold higher adjusted total mortality rate over the subsequent 8 years (absolute rates not available).<sup>37</sup> In clinical and public health settings, older biologic age is associated with earlier presentation of age-related diseases and syndromes such as falls and frailty and increased number of chronic diseases.

## Altering Biologic Pathways to Reduce Susceptibility to Age-Related Diseases

Biologists specializing in aging have identified cellular pathways that can affect lifespan (the total length of life) or health span (the length of life spent free from disease).<sup>3-6</sup> These cellular pathways involve many aspects of cellular physiology such as the accumulation of

somatic DNA variations and the regulation and accuracy of DNA transcription. Regulation includes the maintenance of telomeres, which are regions of repetitive DNA sequences at the end of a chromosome that shorten after replication. If telomeres are too short, DNA does not replicate. The methylation of DNA bases and other epigenetic changes can alter gene transcription with age. Maintaining cellular protein structure and function (protein homeostasis) is related to aging. In particular, autophagy involves removal of damaged intracellular proteins. Other pathways involve sensing the nutrient environment (eg, signaling induced by amino acids, insulin, or IGF-1); maintaining stem cell populations; and preserving mitochondrial function. For example, mitochondrial DNA variations accumulate with age. A genetic variant (m.3243A>G) is associated with the inherited mitochondrial encephalomyopathy lactic acidosis and stroke-like episode syndrome, which may affect as many as 0.24% of adults 49 years and older, but the variant can occur spontaneously.<sup>39</sup> Among 789 adults aged 70 to 80 years, approximately 33% carried this genetic variant in 6% to 19% of their leukocyte mitochondrial DNA. These individuals had slower cognitive speed (Digit Symbol Substitution Test score: 33.1 vs 35.3;  $P = .04$ ), stiffer arteries (976 vs 890 cm/s;  $P = .008$ ), and less grip strength (30.4 vs 31.8 kg;  $P = .02$ ).<sup>40</sup> Participants with greater abundance of this variant had higher 17-year death rates from dementia (27% vs 15%; hazard ratio, 1.25 [95% CI, 1.01-1.56]), and stroke (14% vs 6%; HR, 2.43 [95% CI, 1.00-5.97]) than those with the lowest abundance of this variant, adjusting for age, sex, race, and clinic site.

Biologic processes are closely interlinked. Altering one biologic pathway would likely affect others; for example, mitochondrial dysfunction can lead to inflammation and cellular senescence. Aging is characterized by accumulating damage to these pathways and can lead to altered intercellular communication, intracellular proteins and lipids and cell matrices, accumulation of protein aggregates, cellular senescence, and a chronic low-grade inflammatory state.<sup>41</sup>

Both genetic and environmental factors can alter these biologic pathways. It is estimated that smoking a pack of cigarettes a day for 1 year generates 150 variants to lung tissue DNA.<sup>42</sup> Chronic psychosocial stress is associated with systemic inflammation and telomere shortening.<sup>43</sup> Pathways can be affected by damage resulting from normal metabolic processes such as the generation of oxygen radicals and other reactive molecules, which can damage nearby proteins, posttranslational modifications to proteins, or spontaneous molecular rearrangements such as isomerization and epimerization.<sup>41</sup> All enzymatic reactions can generate byproducts, and some of these contribute to cellular and tissue dysfunction. For example, L-2-hydroxyglutarate, a side product of lactate dehydrogenase, has neurotoxic effects.

## Interventions That May Alter Age-Related Disease Susceptibility

Many age-related biological pathways are conserved in evolution; therefore, organisms such as nematodes, fruit flies, and mice can be studied to evaluate the potential effects of altering these pathways to reduce susceptibility to disease. The National Institute on Aging's Interventions Testing Program (ITP) has evaluated more than 45 candidate compounds in studies involving large numbers of male

and female mice.<sup>44</sup> Interventions typically are administered beginning at age 4 or 12 months and continue until 90% of the mice have died. The strongest benefit was observed for the mammalian target of rapamycin (mTOR) inhibitor rapamycin, which extended lifespan from 1077 days to 1246 days in females and 1060 days in males.<sup>45</sup> Combining rapamycin with metformin or acarbose—an  $\alpha$ -glucosidase inhibitor and treatment for type 2 diabetes—showed greater lifespan extension (lifespan extension of the treated mice compared with control mice: metformin: 17% and 14%; acarbose: 21% and 24% in females and males, respectively).<sup>44</sup> Although motor function was not assessed in the ITP, Bitto et al<sup>46</sup> showed that in mice aged 20 months, 3 months of rapamycin preserved physical function, measured by forelimb grip strength and Rotarod performance, compared with control mice. Seven tested compounds showed effects only in male mice. More than 35 other compounds showed no benefit, including many commonly marketed supplements such as fish oil, nicotinamide riboside, and mitochondrial supplements. However, the mouse is an imperfect model of human aging. Most mouse studies use survival as the primary outcome, whereas in humans, the preservation and restoration of mobility and prevention of disease are relevant outcomes in addition to survival. Mice live approximately 3 years and develop different diseases than humans, with fibrosarcomas and lymphomas as common causes of death in the strain used by the ITP.<sup>47</sup> In addition, unless genetically modified, mice do not develop many diseases that are common in humans such as atherosclerosis and Alzheimer disease.

## Caloric Restriction

Caloric restriction, ie, reducing energy intake below what would be voluntarily consumed while providing all essential nutrients, is likely the most studied intervention to prevent adverse effects of aging in animals. At a constant energy expenditure, caloric restriction reduces body mass. In one strain of mice, a 20% caloric restriction increased median survival from 785 to 1096 days in females (40%) and from 807 to 999 days (24%) in males.<sup>48</sup> In these same mice, caloric restriction delayed the onset of lymphoma and induced cellular changes relevant to aging biology including increased autophagy and reduced insulin, glucose, and insulin-like growth factor 1. In F344 male rats, a 10% caloric restriction increased mean lifespan from 796 to 1090 days.<sup>49</sup>

In humans, caloric restriction induces similar cellular changes to those observed in mice. The CALERIE trial randomized 218 adults without obesity aged 21 to 51 years to receive a 2-year intervention that compared caloric restriction vs no caloric restriction. Participants randomized to caloric restriction reduced their caloric intake from a mean of 2467 kcal/d to a mean of approximately 2210 kcal/d.<sup>50</sup> Gene enrichment pathway analysis using RNA sequencing of muscle biopsies showed that caloric restriction upregulated autophagy and DNA repair and downregulated the inflammatory response, measured using rank-based pathway enrichment analysis.<sup>51</sup> Participants in the restriction group aged 0.6 years less over the 24 months of the study compared with control participants based on a biologic age measure derived from routine clinical laboratory tests (ie, blood cell count, lipid and metabolic panels).<sup>52</sup>

Because most randomized clinical trials of weight loss last less than 2 years and are conducted in middle-aged adults, the effects of caloric restriction on age-related functional decline and disease are unclear. Trials have almost exclusively enrolled people with



obesity or type 2 diabetes, making it difficult to distinguish the effects of caloric restriction on aging vs benefits from treating obesity or type 2 diabetes. The Look AHEAD trial randomized 5145 persons with type 2 diabetes to either an intensive lifestyle intervention with caloric restriction and increased physical activity group or a control group that attended group sessions providing education and social support. At 8 years of follow-up, compared with the control group, the lifestyle intervention group had 9% fewer new chronic diseases (0.89 vs 0.98 [95% CI, 3%-15%]) from a list of 10 diseases.<sup>53</sup> A meta-analysis of 15 randomized clinical trials with 17 186 participants that compared a behavioral weight loss intervention vs a non-weight loss control group reported that weight loss was associated with a 15% reduction in all-cause mortality (3.1% vs 3.5%; odds ratio, 0.85 [95% CI, 0.73-1.00]).<sup>54</sup> Involuntary weight loss is a poor prognostic sign, and caloric restriction is rarely recommended as a strategy to improve therapeutic outcomes in patients. However, in mice injected with human breast and ovarian cancer cells, fasting protected the mice from adverse effects of chemotherapy and slowed tumor progression.<sup>55</sup>

Incretin-based therapies, such as semaglutide and tirzepatide, will facilitate study of the effects of caloric restriction because the potency and durability of caloric restriction associated with these medications is greater than that achieved with behavioral interventions.<sup>56</sup> In adults ( $n = 1961$ ) with body mass index greater than 30 or at least 27 and 1 or more weight-related condition, administration of semaglutide, 2.4 mg/wk, resulted in a 14.9% reduction in body weight over 68 weeks.<sup>57</sup> In people with or without type 2 diabetes, incretin-based therapies are associated with a 20% decrease in cardiovascular events (absolute rates not available), a 20% decrease in worsening kidney function, a 19% reduction in all-cause mortality, and a 23% reduction in non-cardiovascular disease mortality.<sup>58-60</sup> Establishing the effect of incretin-based therapies on age-related conditions, independently of obesity-related conditions, will require longer-term studies that include aging-related outcomes, such as mobility disability and cognitive impairment.

Short periods of fasting induce cellular responses similar to persistent caloric restriction, and animal models suggest that intermittent reductions in energy intake may achieve similar benefits as continual caloric restriction.<sup>61</sup> However, further study is needed.

### Metformin

Metformin, a biguanide medication and first-line treatment for type 2 diabetes, may slow age-related adverse biologic processes due to its effects on multiple aging pathways. Metformin inhibits mitochondrial complex I, which increases AMPK activity, thereby inhibiting mTOR complex 1 (mTORC1) and activating peroxisome proliferator-activated receptor gamma coactivator 1- $\alpha$ . These actions upregulate autophagy and mitochondrial biogenesis. Other effects of metformin include reductions in reactive oxygen species and proinflammatory cytokines.<sup>62,63</sup> In one study, 12 male cynomolgus monkeys aged 13 to 16 years (equivalent to 40-50 human years) were randomized to receive either 20 mg/kg of metformin orally or a vehicle control for 40 months.<sup>64</sup> Compared with control animals, the treated animals had better memory and reduced thinning of the lateral, prefrontal cortex, anterior cingulate cortex, and other brain regions. Metformin slowed other age-related changes, such as preserved fast twitch muscle fibers and reduced accumulation of p21-positive cells, an indicator of cellular senescence.

In humans, observational studies suggest that metformin has health benefits in persons with type 2 diabetes compared with other diabetes treatments. Among 5528 Veterans Affairs patients with type 2 diabetes, metformin users had a lower rate of incident neurodegenerative disease (dementia, Parkinson disease, Huntington disease, and mild cognitive impairment) compared with nonusers (11.48 vs 25.45 per 1000 person-years).<sup>65</sup> Among patients with type 2 diabetes hospitalized with COVID-19 infection, metformin use was associated with a lower 28-day mortality rate (16.0% vs 23.6%), a difference that was maintained after propensity score matching (odds ratio after propensity matching, 0.71;  $P < .05$ ).<sup>66</sup> Metformin may also reduce dry age-related macular degeneration, frailty, and heart disease.<sup>67-69</sup>

Studies of the effects of metformin on patients with diabetes and prediabetes have had inconsistent results. The UK Prospective Diabetes Study (UKPDS) compared metformin vs a diet intervention to treat diabetes. The UKPDS randomized 1704 patients with newly diagnosed fasting plasma glucose greater than 6.0 mmol/L and body weight greater than 120% of ideal to undergo glucose control by diet alone ( $n = 411$ ), metformin ( $n = 342$ ), chlorpropamide ( $n = 265$ ), glibenclamide ( $n = 277$ ), or insulin ( $n = 409$ ). Compared with the diet intervention, metformin reduced all-cause mortality by 36% over a median follow-up of 10.7 years (13.5 vs 20.6 per 1000 person-years;  $P = .01$ ). Metformin improved survival compared with the other medical treatments (13.5 vs 18.9 per 1000 person-years;  $P = .02$ ).<sup>70</sup> Also, a 2025 preliminary study showed a benefit of metformin for knee osteoarthritis.<sup>71</sup>

The Diabetes Prevention Program (DPP) compared metformin vs a diet and physical activity intervention to prevent type 2 diabetes.<sup>72</sup> The DPP randomized 3234 persons with prediabetes to receiving placebo, metformin (850 mg twice daily), or a lifestyle modification program that included caloric restriction sufficient to achieve at least 7% weight loss and increased physical activity and moderate physical activity for at least 150 minutes per week. Individuals randomized to either metformin or lifestyle were less likely to develop diabetes after a mean follow-up of 2.8 years. The DPP continued as an observational study in which all participants were offered the lifestyle intervention, and metformin was continued in the original metformin group. Metformin showed no comparative benefit for frailty prevention, mortality, age-related macular degeneration, or cognition, compared with the lifestyle intervention 10 to 20 years after initial randomization, depending on the outcome.<sup>73-76</sup> The UKPDS and DPP clinical trials were not designed to address aging-related outcomes. Ongoing clinical trials were designed to test the effects of metformin on treating frailty, cognitive impairment, and sarcopenia.

### Rapamycin/Rapalogs

mTOR is a regulatory element of the cellular nutrient sensing pathway that forms the core of 2 protein complexes, mTORC1 and mTORC2. mTORC1 is regulated by nutrient signals from amino acids and stimulates anabolic processes such as protein synthesis. Reducing mTOR activity increases cellular autophagy. mTORC2 inhibition adversely affects glucose metabolism and has immunosuppressive effects.<sup>77</sup> The inhibition of mTORC1 by rapamycin increased the lifespan of many model organisms, including mice (Table 2), even when initiated in mice 20 months of age.<sup>45,78</sup>

Rapamycin (sirolimus) and its derivatives (everolimus, temsirolimus) are approved by the US Food and Drug Administration (FDA)

to prevent posttransplant organ rejection (sirolimus) and to treat some forms of cancer. In humans, sirolimus at FDA-approved dose levels has immunosuppressive effects and other adverse effects that include mouth sores and impaired wound healing.<sup>79</sup> However, lower intermittent doses may improve aging-related biologic pathways with fewer adverse effects.<sup>80,81</sup> In a clinical trial of 218 persons aged 65 years and older, compared with placebo, 6 weeks of everolimus at 0.5 mg daily or 5 mg weekly was safe and significantly improved the response to influenza vaccination, as measured by the geometric mean increase in hemagglutination inhibition titers to influenza A strains vaccination, which correlates with the ability of the vaccine to protect against infection.<sup>82,83</sup> A randomized trial evaluating the combination of everolimus and the catalytic site mTOR inhibitor RTB101 (10 mg/daily) demonstrated that self-reported infections were lower in the intervention group compared with placebo (1.49 vs 2.41 per person-year;  $P = .001$ ).<sup>84</sup> However, in a trial of 1024 older adults, this dose of RTB101 did not affect rates of clinically symptomatic respiratory illness.<sup>85</sup>

### Senolytics

Senescence is a cell state that occurs after many cell divisions or in response to damage such as radiation. Senescent cells no longer divide, are resistance to apoptosis, and can secrete inflammatory cytokines (such as IL-6 and IL-1 $\alpha$ ), chemokines (such as CXCL-1 and eotaxin), proteases (such as MMP-1, MMP-10), and other substances referred to as the senescence associated secretory phenotype.<sup>86</sup> The senescence-associated secretory phenotype can induce a DNA damage response and induce senescence in neighboring cells.<sup>87</sup> Senescence pathways involve the 2 cyclin-dependent kinase inhibitors CDKN2A (p16) and CDKN1A (p21).

Senescent cells accumulate with age. In an analysis of human tissue arrays, the concentration of kidney cells producing the senescence marker p21 was 1% in 5 older donors (aged 71-79 years) compared with less than 0.2% in 5 young donors (aged 19-30 years).<sup>88,89</sup> In mice, eliminating p16-positive cells with AP20187, which induced apoptosis in genetically modified mice expressing p16, was associated with increased median lifespan up to 27% (from 624 to 793 days) and reduced cancer mortality, delayed cataract formation, and increased spontaneous physical activity.<sup>90</sup> In a separate study, mice were genetically modified to allow the modulation of transcription of the p21 promoter with tamoxifen. When initiated monthly at 20 months of age, removing cells that highly expressed p21 was associated with a 9% increase in median lifespan (from 898 to 977 days), better grip strength and movement speed (Rotarod test), and improved ejection fraction.<sup>91</sup>

Cells expressing p16 and p21 expression are present in fibroblastic foci in human idiopathic pulmonary fibrosis lung tissue.<sup>92</sup> The expression of p16 in cardiac progenitor cells increases linearly with donor age ( $r = 0.85$ ).<sup>93</sup> Other conditions linked to higher senescence burden include Down syndrome, diabetic retinopathy, preeclampsia, ischemic kidney disease, diabetes, and obesity.<sup>94</sup> In humans, the percentage of thigh adipose cells expressing p16 was inversely associated with grip strength ( $r = -0.74$ ) and walking speed ( $r = -0.73$ ).<sup>95</sup> Higher levels of circulating senescence-associated secretory phenotype were associated with poorer physical function and an increased mortality risk.<sup>96,97</sup> In the Mayo Clinic biobank study, 14 senescence biomarkers were associated with increased risk of

death, the strongest being GDF-15 (hazard ratio, 1.79;  $P < .05$  per SD of the natural log-transformed value).

The deleterious effects of senescent cells relate to the absolute number of these cells in tissues.<sup>97</sup> Senolytics are drugs that target pathways that confer apoptosis resistance, causing senescent cell death. This can happen after just a few high doses of the drug, so dosing is intermittent rather than chronic. Most randomized clinical trials, typically lasting less than 3 months, have used either the combination of the tyrosine kinase inhibitor dasatinib and the flavanol quercetin or the flavanol fisetin. Early-phase studies established the safety of this therapy in patients with mild cognitive impairment, idiopathic pulmonary fibrosis, diabetic macular edema, or kidney disease.<sup>98-101</sup> These studies showed that senolytic treatment (usually dasatinib plus quercetin) reduced the number of cells expressing p16 and p21. In a phase 2 clinical trial, Farr and colleagues randomized 60 postmenopausal women to receive dasatinib plus quercetin or placebo on 2 consecutive days once monthly for 5 consecutive months to evaluate the effect on biomarkers of bone turnover.<sup>102</sup> At 20 weeks of follow-up, levels of the bone resorption marker C-terminal telopeptide of type 1 collagen did not differ between the groups. The bone formation marker procollagen type 1 N-terminal propeptide (P1NP) was significantly higher in the dasatinib plus quercetin group at weeks 2 (+16%;  $P = .02$ ) and 4 (+16%  $P = .02$ ), but not at week 20. In a post hoc analysis, women in the highest third of senescence burden based on T-cell mRNA levels of p16 had an increase in procollagen type 1 N-terminal propeptide after 2 weeks in the high dasatinib plus quercetin group (relative to control, +34%;  $P = .04$ ). Similarly, serum C-terminal telopeptide of type 1 collagen decreased at 2 weeks in the high dasatinib plus quercetin group (relative to control, -11%;  $P = .049$ ).

### Testing and Approval for Use

Most therapies currently undergoing evaluation to affect aging biology are either FDA-approved drugs for disease-specific indications or dietary supplements and nutrients that are not regulated by the FDA. The FDA does not recognize the indication of slowing aging or reducing aging-related conditions (eg, sarcopenia or mobility limitation). Appropriate evaluations of approved drugs for their age-modifying effects will require broad inclusion criteria, possibly different dosing regimens, and longer study durations than those used to establish therapeutic efficacy for the condition for which they were developed. Studies evaluating therapies to reduce susceptibility to age-related diseases should collect data on relevant aging outcomes including physical and cognitive function. If multiple clinical trials, including those evaluating potential indications for specific diseases such as peripheral artery disease, heart failure, or osteoporosis, collect these outcomes, it may be possible to identify response patterns that can guide the development of future studies with measures that are better linked to specific aging-related biologic targets. Adverse outcomes should also be collected and compared across studies.

### Limitations

This review has several limitations. First, this was not a systematic review, and quality of included evidence was not formally evaluated. Second, geroscience is a rapidly developing field and relevant references may have been missed. Third, the review focuses on the most widely evaluated approaches in clinical research.

Other FDA-approved therapies that might also alter the biology of aging such as sodium-glucose cotransporter-2 or angiotensin-converting enzyme inhibition were not discussed here. Fourth, therapies in early stages of development such as mitochondrial and stem cell transplantation, gene editing, and epigenetic reprogramming were not discussed in this review.<sup>97</sup>

## Conclusions

Therapies that inhibit aging biology, such as caloric restriction, metformin, senolytics, or rapalogs, may slow the development and progression of disease and functional decline in humans.

### ARTICLE INFORMATION

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**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at [kristin.walter@jamanetwork.org](mailto:kristin.walter@jamanetwork.org).

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